To: CTEP Protocol and Information Office

From: Aaron Mansfield, M.D.

Date: October 25, 2021

Re: Amendment #16 (PVD 25Oct21) for P10107: "Phase 1 Safety Run-In and Phase 2 Randomized Clinical Trial of Anetumab Ravtansine and MK-3475 (Pembrolizumab) Compared to MK-3475 (Pembrolizumab) Alone for Mesothelin-Positive Malignant Pleural Mesothelioma"

SUMMARY OF CHANGES:
Protocol (PVD 10/25/2021)

I. Response to Request for Rapid Amendment (dated October 4, 2021):

#	Section	Comments
1.	7.1.2	Version 2.5 of CAEPR for pembrolizumab replaced with Version 2.6 (July 15, 2021). Changes include: Added New Risk: ○ Rare but Serious: Hepatobiliary disorders - Other (sclerosing cholangitis) • Decrease in Risk Attribution: ○ Changed to Rare but Serious from Less Likely: Blood and lymphatic system disorders - Other (immune thrombocytopenic purpura) • Provided Further Clarification: ○ Thrombotic thrombocytopenic purpura is now reported as Blood and lymphatic system disorders - Other (immune thrombocytopenic purpura).

Phase 1 Safety Run-In and Phase 2 Randomized Clinical Trial of Anetumab Ravtansine and Pembrolizumab (MK-3475) Compared to Pembrolizumab Alone for Mesothelin-Positive Malignant Pleural Mesothelioma

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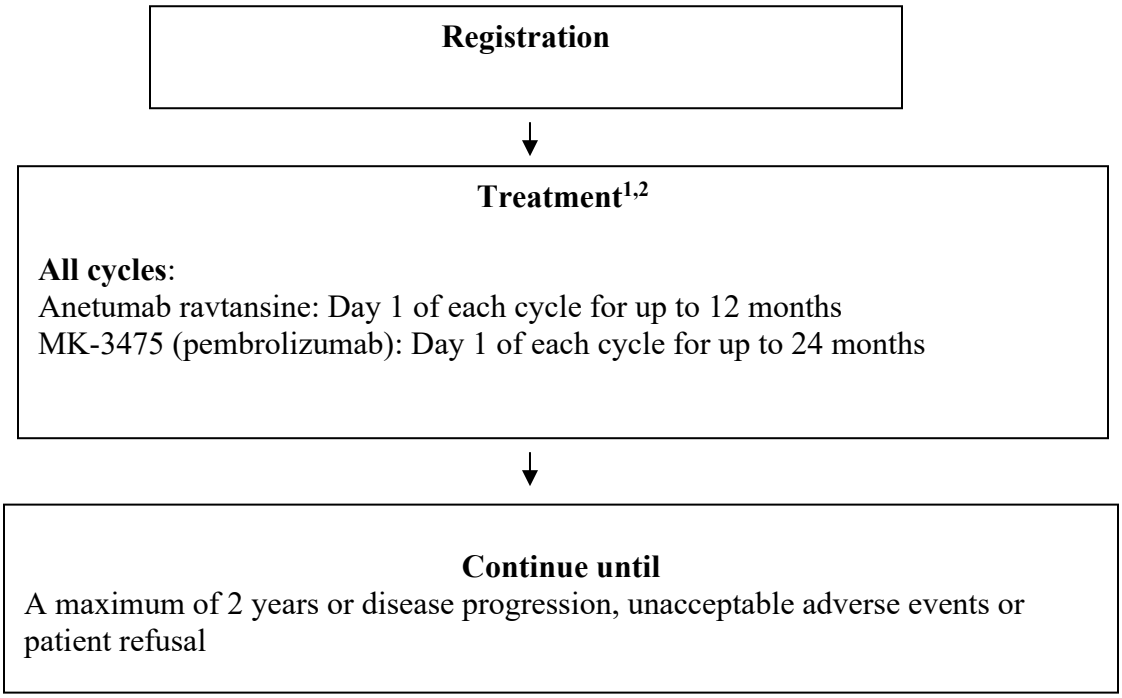
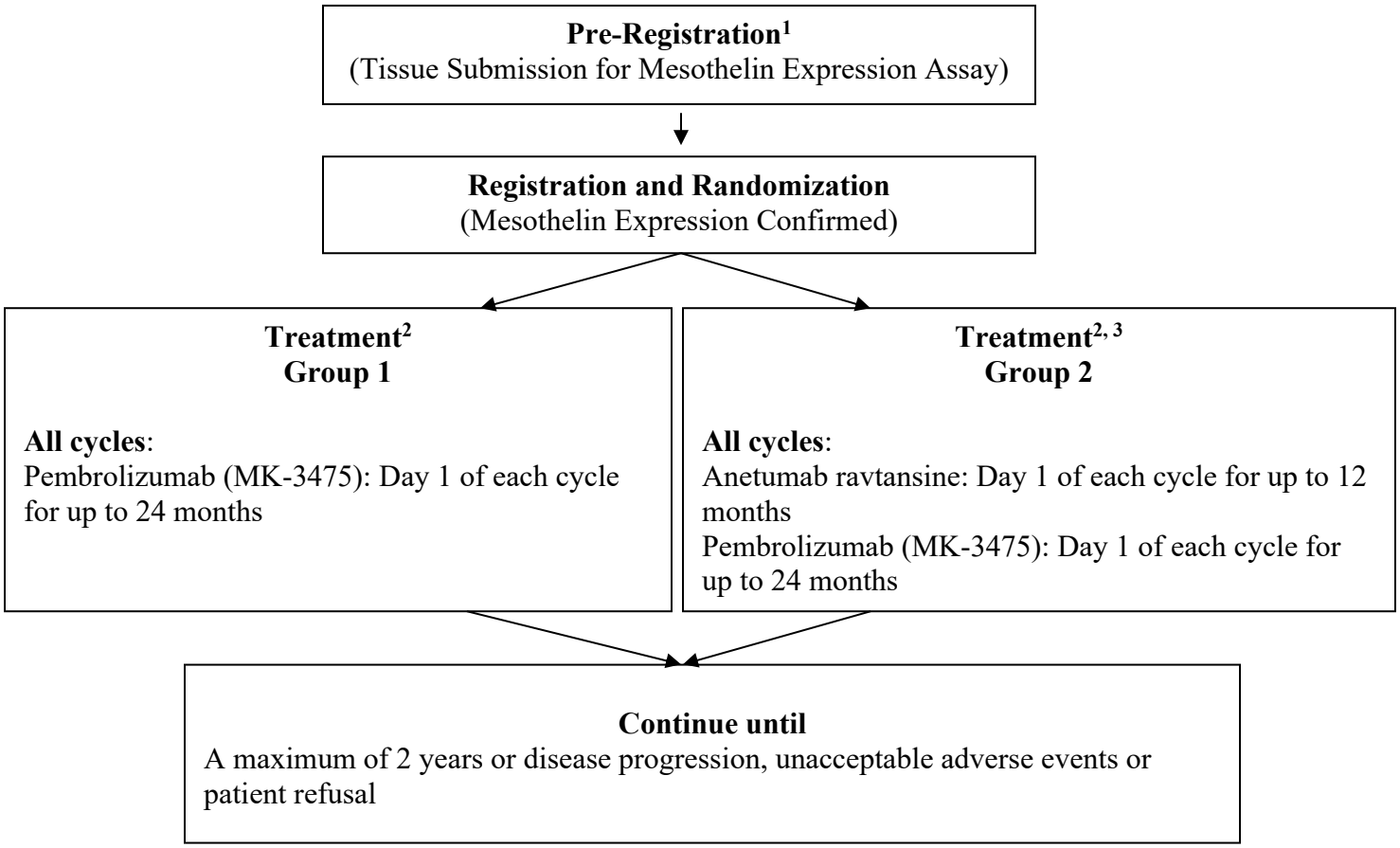
SCHEMA – Phase 1 Study



1. Cycle length = 21 days

2. Anetumab ravtansine is to be administered prior to pembrolizumab (MK-3475) when given in combination

SCHEMA – Randomized Phase 2 Study



1. Mesothelin expression may be determined while a patient is receiving frontline therapy and registration may occur at time of progression. Submitted tissue must show moderate or stronger mesothelin expression in ≥ 30% of the tumor cells for the patient to be eligible for and registered to the study. Submit slides or a tissue block to the central laboratory for the mesothelin expression assay as per Section 9.2.1.

2. Cycle length = 21 days

3. Anetumab ravtansine is to be administered prior to pembrolizumab when given in combination

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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 Phase 1 Safety Lead-In

- Determine the dose of anetumab ravtansine that is safe in combination with pembrolizumab to be used in the randomized phase 2 study.

1.1.2 Randomized Phase 2

- Determine if the overall response rate of the combination of anetumab ravtansine and pembrolizumab is superior to pembrolizumab alone.

1.2 Secondary Objectives

1.2.1 To determine the progression free survival of anetumab ravtansine and pembrolizumab compared to pembrolizumab alone.

1.2.2 To evaluate the pharmacodynamic effects of anetumab ravtansine and pembrolizumab on soluble megakaryocyte potentiating factor (MPF).

1.2.3 To evaluate the pharmacokinetics of anetumab ravtansine and pembrolizumab.

1.2.4 To evaluate mononuclear phagocyte system (MPS) function, FcγRs, hormone and chemokine mediators as methods to evaluate factors affecting the pharmacokinetics and pharmacodynamics of these agents.

1.2.5 To determine the incidence of antibodies directed against anetumab ravtansine.

1.3 Correlative Study Objectives

1.3.1 To determine whether elevations in Bim in T_{TR} predict responses to treatment and whether its detection is dynamic with treatment.

1.3.2 To determine whether soluble PD-L1 predicts responses to treatment and whether its detection is dynamic with treatment.

1.3.3 To evaluate PD-L1 expression in archival tissue as a predictive marker of response to pembrolizumab-based therapy.

1.3.4 To explore the symptomatic adverse events (AE) for tolerability of each treatment group using PRO-CTCAE.

2. BACKGROUND

2.1 Malignant Pleural Mesothelioma

Malignant pleural mesothelioma (MPM) is an inexorably progressive and almost universally fatal malignancy. The vast majority of cases are associated with exposure to fibrous minerals, specifically asbestos or erionite fibers. In addition, prior thoracic radiation therapy (1) and germline loss of function *BAP1* mutations have been linked to the development of MPM (2). With the continued use of asbestos products in many countries, the incidence of MPM continues to rise worldwide causing an estimated 43,000 deaths annually (3).

Effective treatment options are largely lacking for MPM. In fact, there is currently no United States Food and Drug Administration (FDA) approved second-line therapy for MPM. The roles of surgery and multi-modality therapy (i.e., chemotherapy followed by surgery and radiation) remain controversial and may only benefit highly selected patients (4). Folate antimetabolite based chemotherapy, the current standard of care, has modest benefits and has been shown to improve overall survival by approximately three months (5). The addition of bevacizumab to this regimen may further improve survival, but is not yet approved by the FDA (6). Chemotherapy provides even less of a benefit for patients with sarcomatoid subtypes of MPM (7).

2.2 CTEP IND Agents

2.2.1 Anetumab Ravtansine

Anetumab ravtansine is an IgG1 antibody-drug conjugate that recognizes mesothelin and is bound to a potent microtubule inhibitor, DM4. Mesothelin is a cell surface glycoprotein that is exclusively expressed by mesothelial cells under normal homeostasis. Mesothelin results from the cleavage of a precursor protein by the protease furin that releases megakaryocyte potentiating factor (MPF) from the amino terminus. Mesothelin is also expressed by MPM, pancreatic adenocarcinomas, ovarian adenocarcinomas and other malignancies. In fact, all epithelioid MPMs have been shown to express mesothelin to some extent (8). In a recent phase 1 clinical trial, anetumab ravantansine was administered to patients with MPM who had 2+/3+ mesothelin expression by immunohistochemistry. Five of 16 patients (31%) treated at the maximum tolerated dose (MTD) experienced a durable partial response to treatment. For four of these five patients the response lasted more than 600 days. Anetumab ravtansine appears to have a very steep dose-response as very few patients with MPM responded at doses lower than the MTD. Some drug-related adverse events included fatigue, nausea, vomiting and uniquely, corneal epitheliopathy.

2.2.2 Pembrolizumab (MK-3475)

Pembrolizumab has high affinity and potent receptor-blocking activity for the programmed cell death 1 (PD-1) receptor, based on preclinical *in vitro* data (9). Pembrolizumab has an acceptable preclinical safety profile and is being advanced for clinical development as an intravenous (IV) immunotherapy for advanced malignancies.

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (10). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded *ex vivo* and re-infused, inducing durable objective tumor responses in cancers such as melanoma (11, 12).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (programmed cell death ligand 1 [PD-L1] and/or programmed cell death ligand 2 [PD-L2]) (13, 14).

The structure of murine PD-1 has been resolved (15). PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP 1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (16-18). The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (19, 20). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in mesothelioma.

Programmed cell death 1 ligand 1 (PD-L1, aka B7-H1 and CD274) is a critical mediator of peripheral immune tolerance (21). PD-L1 is expressed by many components of the immune system including antigen presenting cells and T cells (21). PD-L1 is also constitutively expressed in immunologically privileged sites such as the eyes and placenta. Many tumors, including mesothelioma also express PD-L1 (22) and its expression is a poor prognostic marker in this disease (23). T cells that express PD-1, the receptor for PD-L1, undergo apoptosis when PD-1 and PD-L1 bind and tumors that express PD-L1 blunt anti-tumor immunity through T cell apoptosis (24). Pembrolizumab is approved by the FDA for the treatment of non-small cell lung cancer (NSCLC) in the first or second line, melanoma and head and neck cancer. There are many other ongoing clinical trials testing its efficacy in many malignancies. The first preliminary report of the activity of pembrolizumab in MPM was presented at the Annual Meeting of the

American Association for Cancer Research in 2015. Patients with MPM whose tumor cells had 1% or greater expression of PD-L1 were included as a cohort in a larger phase 1 clinical. Responses were measured by standard Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 every eight weeks. PD-L1 expression was detected in 38 patients of 84 who were screened (45%), and 25 of these patients were treated. There were three moderate to severe (grade 3 or higher) drug-related adverse events. There were six responders (24%, including unconfirmed responses) and 13 patients with stable disease (52%) for an impressive disease control rate of 76% (25). An update of this trial was presented at the 2016 International Association for the Study of Lung Cancer (IASLC) World Conference on Lung Cancer (WCLC) and the confirmed, clinical benefit rate (complete responses, partial responses and stable disease for six months or greater) was 40%, and the median overall survival was 18 months in this pretreated population (26).

Pembrolizumab has also been used in MPM in a larger phase 2 clinical trial with a two-stage design. The interim results from this trial were also presented at the 2016 IASLC WCLC meeting. There were important differences between these two trial designs to consider, including the eligibility of patients without detectable PD-L1 expression, the flat dosing of pembrolizumab, less frequent imaging assessments, and the use of the modified pleural RECIST (27). There were 35 patients who enrolled but one subject withdrew. Two patients died on study because of autoimmune hepatitis and an unknown cause. At the time of the presentation, the median progression free survival (PFS) was 6.2 months and the median overall survival (OS) had not been reached. There were seven partial responses (21%) and 19 patients with stable disease (56%). Over half of the patients did not have detectable PD-L1 expression yet responses to pembrolizumab were seen regardless (28). Similarly, in the largest trial of PD-1/PD-L1 axis inhibition to date in MPM, avelumab, an anti-PD-L1 antibody, demonstrated an overall response rate of 9.4%, regardless of tumor cell PD-L1 expression (29). Both pembrolizumab and avelumab have been relatively well tolerated by patients with MPM or other cancers; however, they are commonly associated with rash and auto-immune-like conditions affecting the endocrine system. Most of these toxicities do not overlap with those of anetumab ravtansine. In contrast to PD-1/PD-L1 axis inhibitors, the CTLA-4 inhibitor tremelimumab showed no benefit compared to best supportive care in patients with MPM and was poorly tolerated (30). Overall, inhibition of PD-1/PD-L1 interaction is a promising therapeutic strategy in MPM that needs further validation as a single agent, and may be synergistic in combination with chemotherapy.

2.2.2.1 Pembrolizumab Background and Clinical Trials

Pembrolizumab (Keytruda®), a humanized monoclonal antibody against the PD-1 protein, has been developed by Merck & Co. for the treatment of cancer. Pembrolizumab is approved for treatment of melanoma in several countries; in the United States (US) and European Union, it is approved for the treatment of advanced (unresectable or metastatic) melanoma in adults. Pembrolizumab has also been approved for treatment of NSCLC in several countries; in the US it is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by a Food and Drug Administration (FDA)-approved test and who have

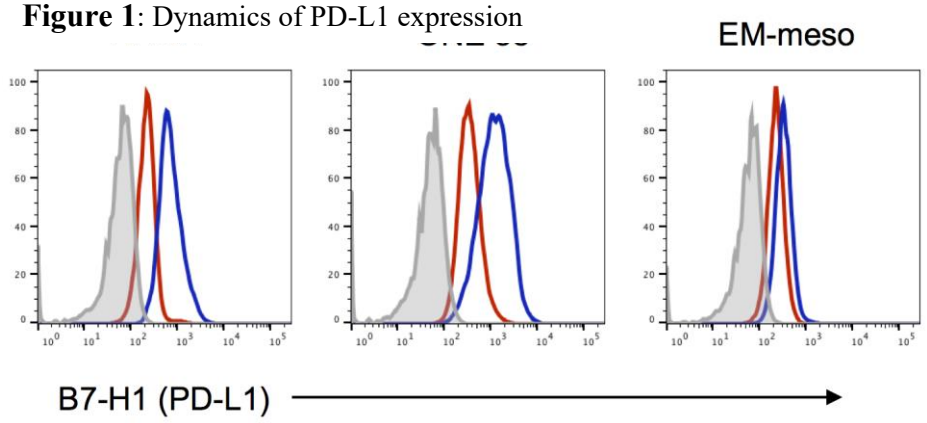
disease progression on or after platinum-containing chemotherapy. Patients with NSCLC and epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should also have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab. Pembrolizumab is approved in the US for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy.

Pembrolizumab has demonstrated initial clinical efficacy in single-arm monotherapy trials in patients with NSCLC, HNSCC, urothelial cancer, gastric cancer, triple negative breast cancer, and Hodgkin's Lymphoma as determined by response rate. Ongoing clinical trials are being conducted in these tumor types as well as a number of other advanced solid tumor indications and hematologic malignancies. For study details please refer to the Investigator's Brochure (2016).

2.3 Rationale

Anetumab ravtansine targets mesothelin and its activity is predicated on its internalization for DM4 release. Accordingly, patients who participate in this trial will be screened for high levels (2+/3+) of mesothelin expression. PD-L1 can be adaptively expressed in response to interferon-γ, or constitutively expressed due to signal pathway abnormalities that result from mutations such as loss of PTEN (31). Similarly, PD-L1 expression by tumor cells can be induced by chemotherapy (32) or radiotherapy (33) in many different cancers. We have demonstrated that microtubule inhibitors such as vinorelbine, which have a similar mechanism of action as the DM4 warhead of anetumab ravtansine, upregulate the expression of PD-L1 in MPM cell lines (72) (**Figure 1**). The dynamic expression of PD-L1 following chemotherapy suggests that there may be a benefit to combining chemotherapy with inhibitors of the PD-1/PD-L1 axis. In fact, combined cytotoxic therapy with PD-1 or PD-L1 inhibition has been shown to be synergistic in multiple syngeneic murine tumor models (32, 34).

Figure 1: Dynamics of PD-L1 expression



MPM cell lines were cultured with vinorelbine (5.5 µg/ml, blue lines) or vehicle control (saline, red lines) for 36-40 hours in vitro. After incubation, cells were washed and stained with anti-B7-H1 (PD-L1) antibody (clone MIH1, open lines) or isotype control (filled gray lines). Histograms are the representative data of three independent experiments.

MPM is a challenging disease to assess and standard RECIST criteria were not designed to measure pleural disease. Modified pleural RECIST (mRECIST) have been adopted by mesothelioma experts for the measurement of responses in MPM (27). The mRECIST are the most commonly used response criteria in clinical trials for MPM. Even though the gold standard for oncology outcomes is overall survival, cross-over to subsequent therapies and competing risks influence survival outcomes. In order to assess whether responses to treatment correlate with survival outcomes in MPM, we retrospectively reviewed the clinical trial that lead to FDA approval of the current standard of care first-line regimen of cisplatin and pemetrexed (5). We identified that patients with epithelioid MPM who responded to front-line therapy had a significantly longer overall survival (HR 0.341, 95% CI 0.239-0.486; median 20.6 months, 95% CI: 15.3-not reached) than those

who did not respond (median 9.4 months, 95% CI: 8.1-11.0). Similarly patients who responded to front-line therapy had a significantly longer progression-free survival (HR 0.496, 95% CI: 0.234-0.549; median 7.8 months, 95% CI: 6.5-8.5) than those who did not respond (median 3.7 months, 95% CI: 2.9-4.3). Although these findings may not cross-over to other types of therapy, they are suggestive that a decrease in tumor burden as assessed by mRECIST is associated with improved survival outcomes in MPM.

This clinical trial is a phase 2 randomized clinical trial of anetumab ravtansine and pembrolizumab compared to pembrolizumab for mesothelin-positive MPM that has been designed based on the preliminary data above. First, both anetumab ravtansine and pembrolizumab are active agents in MPM based on the early phase clinical trials that have been presented to date. Second, there is no FDA-approved second-line therapy for MPM. Third, anetumab ravtansine and pembrolizumab do not have significant overlapping toxicities; however, there is a steep dose-response with anetumab ravtansine which favors a dose de-escalation design. Fourth, pembrolizumab is an appropriate control arm. There is an ongoing phase 2 registration trial of anetumab ravtansine compared to vinorelbine for patients with mesothelin-positive MPM. The eligibility criteria are very similar for this proposed study and the registration study and the same companion diagnostic test for mesothelin expression will be used in both studies.

2.3.1 Rationale for Pembrolizumab Dose Selection

The dose of pembrolizumab planned to be studied in this trial is 200 mg administered every 3 weeks (q3w). The dose recently approved in the US and several other countries for treatment of melanoma patients is 2 mg/kg q3w. Information on the rationale for selecting 200 mg q3w is summarized below.

The initial phase 1 study of pembrolizumab (KN001) evaluated 5 dose levels (1 mg/kg every 2 weeks [q2w], 3 mg/kg q2w, 10 mg/kg q2w, 2 mg/kg q3w, and 10 mg/kg q3w) in patients with advanced solid tumors. All 5 dose levels were well tolerated and no dose-limiting toxicities (DLTs) were observed. Pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg, and 10 mg/kg q2w). No maximum tolerated dose (MTD) has been identified to date. In addition, 2 randomized cohort evaluations of melanoma patients receiving pembrolizumab 2 mg/kg or 10 mg/kg q3w have been completed and 1 randomized cohort evaluating 10 mg/kg q3w or 10 mg/kg q2w has also been completed. The clinical efficacy and safety data demonstrate a lack of any important differences in efficacy or safety profile across doses.

An integrated body of evidence suggests that 200 mg q3w is expected to provide similar response to 2 mg/kg q3w, 10 mg/kg q3w, and 10 mg/kg q2w. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in patients with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg q3w are expected to lie within this range and will be close to those obtained with 2 mg/kg q3w dose.

The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. The PK properties of pembrolizumab, specifically the weight-dependency in clearance and volume of distribution, are consistent with no meaningful advantage to weight-based dosing relative to fixed dosing.

In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in patients with melanoma can be expected. As the antitumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, it is rendered independent of the specific tumor type. In addition, available PK results in patients with melanoma, NSCLC and other tumor types support a lack of meaningful difference in PK exposures obtained at tested doses across tumor types. Thus, the 200 mg q3w fixed-dose regimen is considered an appropriate fixed dose for other tumor indications as well.

A fixed-dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed-dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. The existing data suggest 200 mg q3w as the appropriate dose for pembrolizumab.

2.3.2 Rationale for anetumab ravtansine dose selection

2.3.2.1 Phase 1

In the phase 1 clinical trial anetumab ravtansine appeared to have a very steep dose-response as very few patients with MPM responded at doses lower than the MTD. In the trial the following doses and frequencies of anetumab ravtansine were tested: 1.8 mg/kg q week; 2.2 mg/kg q week; 6.5 mg/kg q 3 weeks. Furthermore, there seem to be very few overlapping toxicities between anetumab ravtansine and Pembrolizumab. Accordingly, a dose de-escalation strategy was chosen with anetumab ravtansine based on the MTD identified in the phase 1 clinical trial.

2.3.2.2 Phase 2

The phase 1 safety run-in and expansion cohort for this trial accrued 13 participants to Dose Level 1 (6.5 mg/kg anetumab ravtansine IV with 200 mg pembrolizumab IV every 3 weeks), 12 of whom were evaluable for dose-limiting toxicity (DLT). No DLTs were observed therefore Dose Level 1 was selected as the Phase 2 dose for this trial.

2.4 Correlative Studies Background

2.4.1 Megakaryocyte Potentiating Factor (MPF)

MPF is cleaved from the amino terminus of a precursor protein that leaves mesothelin linked to the cell surface by glycophosphatidylinositol. Accordingly, serum MPF is correlated with mesothelin expression and provides a blood-based marker of mesothelin-positive tumor burden. In a recently published clinical trial that tested the anti-mesothelin immunotoxin SS1P in patients with MPM, serum MPF levels correlated with radiographic responses. Accordingly, serum MPF may also correlate with radiographic responses to treatment with anetumab ravtansine and pembrolizumab.

2.4.2 Mononuclear Phagocyte System (MPS)

Nanoparticles (NPs), monoclonal antibodies (mAb) and antibody-drug conjugates (ADC) are cleared via the mononuclear phagocyte system (MPS) (35, 36). Variability in MPS function has been shown to predict variability in the pharmacokinetics (PK) and pharmacodynamics (PD) of NPs such as pegylated liposomal doxorubicin in patients and preclinical tumor models (37). While NPs are cleared via phagocytosis by MPS cells, the MPS also serves as a natural mechanism of clearance for antibodies and immune complexes via their Fc-gamma-receptors (FcγR) on MPS cells (38-40). Myeloid cells express various forms of FcγRs (CD64, CD32 and CD16) that interact with extracellular monomeric or aggregated IgGs and therapeutic mAb and ADC (38). Due to the differences in types and affinity in FcγRs, a variation in receptor expression can lead to significant differences in the ability of MPS cells to clear immune complexes from the blood. This also translates to variation in MPS's ability to take up mAbs/ADCs which would affect their PK and PD.

The factors affecting the PK of NPs and mAb/ADCs are very similar and consistent with variability in MPS function (41). As with other NPs, there are very high and clinically relevant variability in the PK and PD of mAb and ADCs (42-44). Consistent with MPS mediated clearance, the PK of mAbs and ADCs are characterized by high distribution to the liver and spleen, saturable clearance at higher doses, PK differences based on MPS factors (gender, body composition, and tumor burden), and faster clearance of ADCs that have a greater number of linked drugs (45-48). In addition, studies suggest that the clearance of pertuzumab is greater in patients with gastric cancer compared with breast cancer and these results may be due to differences in the immune system and MPS (49-51). Moreover, preliminary data from Dr. Zamboni's lab at UNC show that the expression of CD64, CD32 and CD16 FcγRs on MPS cells is highly variable in healthy volunteers and patients with cancer (unpublished).

The high PK variability is important for mAbs, and especially for ADCs, as these agents have a narrow therapeutic index (52-55). Moreover, the combination of ADCs, such as anetumab ravtansine, with other mAbs and immune modulators may increase the likelihood of drug-drug interactions and altered PK and PD of the ADC as these agents are also cleared by and may alter the MPS. Thus, the MPS pharmacology studies are critically important to optimizing the treatment of anetumab ravtansine and other ADCs alone and in combination with other agents.

2.4.3 Soluble PD-L1 and Bim in Tumor-Reactive T cells

Recently, two PD-1 inhibitors and a PD-L1 inhibitor have collectively been approved for

the treatment of melanoma, NSCLC, renal cell carcinoma and bladder cancer by the FDA (56). Some of these agents require biomarker assessment of PD-L1 expression, whereas others do not. For example, 50% or greater expression of PD-L1 by tumor cells is required to administer the PD-1 inhibitor pembrolizumab for NSCLC, but the other PD-1 inhibitor nivolumab does not have this requirement for NSCLC. In contrast, no biomarker testing is required to administer these agents to patients with melanoma (56). The expression of PD-L1 in NSCLC varies over space and time, challenging the use of PD-L1 as a predictive biomarker for PD-1/PD-L1 axis inhibitors (57, 58). We have observed this same phenomenon more recently in MPM: in patients with paired lesions from resection of multiple sites of disease, or paired lesions from primary MPM and recurrent MPM, half of the cases had discrepant expression of PD-L1 (detectable compared to not detectable; abstract to be presented at USCAP 2017). Thus, it is challenging to assign treatment to a patient when the expression of the biomarker is dynamic and sampling error may affect its measurement.

Given the heterogeneity and dynamics of PD-L1 expression, tissue-based analysis of PD-L1 expression has demonstrated conflicting applicability for selecting patients to receive PD-1 or PD-L1 inhibitors (56). Other approaches to assess PD-L1 expression have been developed such as soluble PD-L1 (sPD-L1) (59). Using this assay, sPD-L1 can be detected in the supernatants of many PD-L1-positive cell lines and sPD-L1 retains pro-apoptotic signaling properties to T cells. Many patients with metastatic melanoma have significant elevations in sPD-L1 (60). With the difficulties detecting PD-L1 in tissue, sPD-L1 may represent a detectable circulating marker for PD-L1 expression and provide a means to non-invasively assess the dynamics of tissue PD-L1 expression. Additionally, the signaling cascade in T cells that follows PD-1 engagement with PD-L1 may be predictive of responses to immunotherapy. The identification of tumor-reactive T cells (T_{TR}) based on the expression of CD8, CD11a and PD-1 (61), and the use of knock-out models and blocking antibodies led to the identification of Bim as a downstream signaling molecule of the PD-1 pathway. High levels of Bim in circulating T_{TR} cells were prognostic of poor survival in patients with metastatic melanoma who did not receive anti–PD-1 therapy and were also predictive of clinical benefit (i.e., response) in patients with metastatic melanoma who were treated with the PD-1 inhibitor pembrolizumab. Moreover, this circulating T_{TR} cell population significantly decreased after successful anti–PD-1 therapy (62). Accordingly, sPD-L1 and Bim in T_{TR} may provide a non-invasive means of monitoring PD-L1 expression and the effects of PD-1 blockade on T_{TR} in mesothelioma.

2.4.4 Optional ePatient Outcomes Versions of the Common Terminology Criteria for Adverse Events (ePRO-CTCAE) Assessment

Participation in the ePRO-CTCAE assessment is optional for both sites and patients. Sites may elect to either participate or decline participation in this correlative. Sites who elect to participate may offer patients optional participation in the PRO-CTCAE assessment.

Missing data are a significant problem, particularly for PRO-CTCAE assessments. Unlike data for traditional endpoints, such as survival, PRO-CTCAE data cannot be accurately obtained retrospectively. This limits researchers' ability to accurately perform PRO-

CTCAE statistical analyses and negatively impacts the clinical relevance of this effort.

Typically, PRO-CTCAE forms are filled out in hardcopy (paper). To provide a more convenient method of completing PRO-CTCATE assessments, NCI, Theradex and the CTSU are working with Medidata Rave's ePRO Cloud product that offers patients on this study the option of completing their PROs forms electronically using an application (app) downloaded to their smart phone or from a tablet that has the ePRO-CTCAE app with Internet access.

Appendix D includes information on the Medidata Patient Cloud ePRO app including links to the training information for sites.

3. PATIENT SELECTION

For Phase 2, patients may be pre-registered and provide a tissue sample for testing of mesothelin expression prior to, during, or after receipt of frontline chemotherapy.

3.1 Pre-Registration Inclusion Criteria

3.1.1 Patients must have histologically or cytologically confirmed malignant pleural mesothelioma.

3.1.2 Patient is willing to submit a tissue sample to test for expression of mesothelin.

Note: Tissue sample for mesothelin assay may have been collected ***prior to***, ***during or after*** receipt of the frontline chemotherapy; patients will not be required to submit another tissue sample ***after*** receipt of the chemotherapy.

3.1.3 Patients must have received platinum based chemotherapy.

3.2 Registration Inclusion Criteria

3.2.1 For phase 2 only:

3.2.1.1 Patient has measurable disease per RECIST 1.1 for non-pleural disease or modified RECIST 1.1 (mRECIST) for pleural disease.

Note: For pleural disease, this is defined as at least one lesion that can be accurately measured perpendicular to the chest wall or mediastinum that is ≥ 10 mm (≥ 1 cm). For extra pleural disease, measurable disease is 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 ≥ 10 mm (≥ 1 cm) for non-nodal lesions and ≥ 15 mm (≥ 1.5 cm) for nodal lesions with spiral CT scan, MRI, or calipers by clinical exam as per RECIST 1.1.

3.2.1.2 Tissue submitted for testing at pre-registration shows moderate or stronger mesothelin expression in ≥ 30% of the tumor cells.

3.2.2 For phase 1 and phase 2:

3.2.2.1 Patients must have received platinum-based therapy with or without bevacizumab.

3.2.2.2 Age ≥18 years.

Note: Because MPM primarily affects older adults and no dosing or adverse event data are currently available on the use of anetumab ravtansine and pembrolizumab in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.2.2.3 ECOG performance status < 2 (Karnofsky ≥ 70%, see Appendix A).

3.2.2.4 Patients must have normal organ and marrow function as defined below:

• Leukocytes	≥ 3,000/mcL
• Absolute neutrophil count	≥ 1,500/mcL
• Platelets	≥ 100,000/mcL
• Total bilirubin	Within normal institutional limits
• AST (SGOT) AND ALT (SGPT)	≤ 2.5 × institutional upper limit of normal (ULN)
• Creatinine OR Creatinine clearance	Within normal institutional limits ≥ 60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

3.2.2.5 International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 x ULN AND partial thromboplastin time (PTT) or activated PTT (aPTT) ≤ 1.5 x ULN, unless patient is on stable dose of anti-coagulation therapy in which case patients will be allowed to participate if they have no signs of bleeding or clotting and the INR/PT and PTT/aPTT results are compatible with an acceptable risk-benefit ratio as per the Investigator's discretion.

3.2.2.6 Negative serum pregnancy test for females of child bearing potential.

Note: Females are considered to ***not*** be of child bearing potential if any of the following apply:

- Postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age, a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);
- Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;
- Has a congenital or acquired condition that prevents childbearing.

3.2.2.7 Patient agrees to use one of the following acceptable methods of contraception prior to study entry, during study participation, and for at least six months after receiving the last dose of study treatment:

Acceptable methods of contraception are:

Single method (1 of the following is acceptable):

- Abstinence, if consistently employed as the patient's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and Institutional Review Boards (IRBs)
- intrauterine device (IUD)
- vasectomy of a female patient's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of 2 of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

3.2.2.8 Ability to understand and the willingness to sign a written informed consent document, unless patient is of impaired decision making capacity in which case patient may be eligible if they have a Legal Authorized representative or caretaker available.

3.3 Exclusion Criteria

3.3.1 Patients who have received any monoclonal antibody therapy within 4 weeks prior to entering the study.

3.3.2 Patients who have not recovered from adverse events due to prior anti-cancer therapy (i.e., have residual toxicities > Grade 1).

Note: Patients with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion and may qualify for the study.

Note: If patients received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

3.3.3 Patients who are receiving any other investigational agents.

3.3.4 Patients with known brain metastases with progressive neurologic dysfunction, requirement of steroids and lack of improvement on head imaging obtained prior to consent to this clinical trial should be excluded because of their poor prognosis and because they would confound the evaluation of neurologic and other adverse events.

Note: Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging using the identical imaging modality for each assessment, either magnetic resonance imaging [MRI] or computed tomography [CT] scan, for at least 4 weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment.

Note: Patients with carcinomatosis meningitis should also be excluded.

3.3.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to anetumab ravtansine or pembrolizumab.

3.3.6 Patients receiving any medications or substances that are strong inhibitors or inducers of CYP3A4, including herbal preparation containing CYP3A4 inducers (e.g., St. John's Wort), grapefruit and grapefruit juice (CYP3A4 inhibitor), within 2 weeks before the start of study treatment.

3.3.7 Patients are prohibited from receiving the following therapies during the screening and treatment phases (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than anetumab ravtansine and pembrolizumab.
- Radiation therapy (Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case by case basis after consultation with CTEP. The patient must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.)
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies,

Bacillus Chalmette–Guérin (BCG), and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the study PI and CTEP.

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

3.3.9 Women who are pregnant or breastfeeding.

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

3.3.10 HIV-positive patients who do not meet all of the following and/or are on HIV medications considered to be strong inhibitors or inducers of CYP3A4:

- Undetectable HIV viral load by standard clinical assay within 6 months of registration
- Willing to adhere to antiretroviral therapy that has minimal overlapping toxicity or pharmacokinetic interactions with protocol therapy
- No AIDS-defining events other within the past 12 months
- Near normal life expectancy if not for the presence of the cancer

3.3.11 Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

3.3.12 Patients who are known to have a history of or a finding of corneal epitheliopathy at pre-study are excluded because anetumab ravtansine may worsen this condition and reduce vision.

3.3.13 Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, or *in situ* cervical cancer.

3.3.14 Receipt of transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including granulocyte colony-stimulating factor [G-CSF], granulocyte macrophage colony-stimulating factor [GM-CSF], or recombinant erythropoietin) within 4 weeks prior to study treatment.

3.3.15 Patient with active interstitial lung disease (ILD)/pneumonitis or a prior history of ILD/pneumonitis requiring treatment with steroids

3.3.16 Patient has received prior treatment with PD-1, PD-L1 or PD-L2 inhibitor.

3.4 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

This study will be available to all eligible patients regardless of race or ethnic group.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (*i.e.*, clinical site staff requiring write access to Oncology Patient Enrollment Network (OPEN), Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR: MD, DO, or international equivalent,
- NPIVR: advanced practice providers (*e.g.*, NP or PA) or graduate level researchers (*e.g.*, PhD),
- AP: clinical site staff (*e.g.*, RN or CRA) with data entry access to CTSU applications (*e.g.*, Roster Update Management System [RUMS], OPEN, Rave,),
- Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and
- Associate Basic (AB): individuals (*e.g.*, pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	**IVR**	**NPIVR**	**AP**	**A**	**AB**
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		

Documentation Required	IVR	NPIVR	AP	A	AB
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster,
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN,
- Act as the site-protocol Principal Investigator (PI) on the IRB approval, and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (*i.e.*, Alliance).

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

Sites participating with the NCI Central Institutional Review Board (NCI CIRB) must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol PI (*i.e.*, the investigator on the IRB/REB approval) must meet the following five criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status,
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster,

- If using NCI CIRB, rostered on the NCI CIRB Signatory record,
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile, and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federalwide Assurance (FWA) number,
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization, and
- Compliance with all protocol-specific requirements (PSRs).

4.2.1 Downloading Regulatory Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Participating Organization on the protocol.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password,
- Click on *Protocols* in the upper left of your screen
- Enter the protocol number in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select LAO-MA036, and protocol number *10107*,
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

4.2.2 Protocol Specific Requirements For 10107 Site Registration

Upon site registration approval in RSS, the enrolling site may access OPEN to complete enrollments. The enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen, and may need to answer additional questions related to treatment in the eligibility checklist.

- A site initiation teleconference (SIV TC) with the lead site

4.2.3 Requirements For Protocol # 10107 Site Registration for Sites Participating in the Medidata Patient Cloud ePRO to collect PRO-CTCAE Items

- After the patient is registered to the trial via OPEN, and if the patient reads or understands English, and is willing to participate in electronic data collection using their personal smart phone or tablet (or clinic owned tablets if available), the site staff will then need to complete a separate registration for the patient to

the Patient Cloud ePRO through iMedidata.

- For sites participating in the ePRO pilot, site CRAs must complete training prior to registering to ePRO. This training includes an eLearning module that will be made available in each CRA's iMedidata screen (Tasks panel) titled "Patient Cloud: Registering Your Subjects", as well as review of ePRO resource materials available on the CTSU website. Training information is in Appendix D.

- For patients who agree to participate, the pre-study visit questionnaires will not be available in paper form. Therefore, site CRAs must take the ePRO training when a patient is identified for the study, if they have not already taken the training so they can perform the ePRO registration.

- The registration to the Patient Cloud ePRO will create a unique patient registration code that the site staff will provide to the patient. The patient (with assistance from the site staff) should be instructed to download the Patient Cloud ePRO app onto his/her own device (IOS, Android, phone or tablet) and use the unique patient registration code to create an account. Once the patient's account is set up, the patient will be able to complete the submission of patient reported outcomes electronically for the trial.

- For sites providing a shared institutional device for use by multiple patients on site, the site staff should assist the patient with access and registration to the Patient Cloud ePRO app and the patient can then complete the electronic data submission independently. Site staff may need to assist patients with logging onto the device at each visit.

4.2.4 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal, log on to the CTSU members' website → Regulatory → Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

4.2.5 Checking **Site** Registration Status

You can verify your site's registration status on the members' side of the CTSU website.

- Log on to the CTSU members' website
- Click on *Regulatory* at the top of your screen

- Click on *Site Registration*
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account.
- To perform enrollments or request slot reservations: Be on an LPO roster, ETCTN Corresponding roster, or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- If a DTL is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes, and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at

https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with the registration system in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

4.3.1 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 609-619-7862 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 14 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Phase 2, Group 1: Pembrolizumab Alone
MK-3475 (Pembrolizumab) will be administered as a dose of 200 mg using a 30-minute IV infusion. Infusion timing should be as close to 30 minutes as possible; however, a window of minus 5 minutes and plus 10 minutes is permitted (i.e., infusion time is 30 minutes: minus 5 minutes to plus 10 minutes). Treatment with pembrolizumab may continue for up to 24 months total. Refer to Section 5.1.2.

Phase 1 and Phase 2, Group 2: Anetumab ravtansine and Pembrolizumab
Pembrolizumab will be administered as described for Group 1; anetumab ravtansine will be administered at 6.5 mg/kg as determined by the phase 1 safety lead-in portion of the study using

a 60-minute IV infusion. Infusion timing should be as close to 60 minutes as possible; however, a window of minus 5 minutes and plus 10 minutes is permitted (i.e., infusion time is 60 minutes: minus 5 minutes to plus 10 minutes). The study drugs are administered in the following order when give together: anetumab ravtansine first followed by pembrolizumab. Treatment with anetumab ravtansine may continue for up to 12 months total. Treatment with pembrolizumab may continue for up to 24 months total. For patients receiving both drugs, the intravenous catheter must be flushed with either D5W or 0.9% sodium chloride between the two infusions. Pre-medication is not needed unless a patient develops an infusion reaction. Refer to sections 5.1.1 and 5.1.2.

Phase 1 Dose Safety Run-In Schedule

Dose De-Escalation Schedule for Phase 1 Study [1, 2]		
Dose Level	**Dose**	
	Anetumab ravtansine (mg/kg)	**Pembrolizumab (mg)**
1*	6.5	200
-1	5.5	200
-2	4.5	200

1. Both agents will be given every 21 days. Anetumab ravtansine will be administered prior to pembrolizumab.
2. In obese patients, anetumab ravtansine dose should be calculated considering a maximum weight of 100 kg

* Starting dose level

Randomized Phase 2 Dose Schedule

Dose Schedule for Randomized Phase 2 Study					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Anetumab ravtansine	None	6.5 mg/kg[1, 2]	IV over 1 hour	Days 1	21 days (3 weeks)
Pembrolizumab[3]	None	200 mg[1]	IV over 30 minutes ***after*** anetumab ravtansine in patients assigned to the combination	Day 1	

1. Doses may be modified or held as per Section 6 Dosing Delays/Dose Modifications
2. In obese patients, anetumab ravtansine dose should be calculated considering a maximum weight of 100 kg
3. In subjects randomized to receive the combination, anetumab ravtansine will be administered prior to pembrolizumab when given together.

5.1.1 Anetumab Ravtansine

Administer anetumab ravtansine as an IV infusion over 1 hour. Please refer to section 8.1.1 for compatible infusion set materials including the in-line filter.

No specific prophylactic medications are recommended for anetumab ravtansine. Full supportive care is recommended as per community standards of medical care as determined by the treating physician; however, patients should not take any medications or substances that are strong inhibitors or inducers of CYP3A4 including herbal preparation containing CYP3A4 inducers (e.g. St. John's Wort), grapefruit and grapefruit juice (CYP3A4 inhibitor) within 2 weeks before the start of study treatment or while on treatment because DM4 is a substrate of CYP3A4. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference for a list of drugs to avoid or minimize use of.

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 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.

5.1.2 Pembrolizumab (MK-3475)

Pembrolizumab will be administered on Day 1 of each 3-week treatment cycle after all procedures/assessments have been completed. Pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons (up to 5 days after randomization is permitted).

Note: Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons (i.e., elective surgery, unrelated medical events, patient vacation and holidays) not related to study therapy. Patients should be placed back on study therapy within 3 weeks of the scheduled interruption. The reason for interruption should be documented in the patient's study record.

Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. Infusion timing should be as close to 30 minutes as possible; however, a window of minus 5 minutes and plus 10 minutes is permitted (i.e., infusion time is 25 to 40 minutes. Please refer to section 8.1.2 for compatible infusion set materials including the in-line filter.

Anetumab ravtansine will be given prior to pembrolizumab for the combination therapy

when given together.

No specific prophylactic medications are recommended for pembrolizumab. Full supportive care is recommended as per community standards of medical care as determined by the treating physician.

Infusion-related reactions have been reported with pembrolizumab. Infusion-related reactions may present as allergic reaction (hypersensitivity), serum sickness, infusion and infusion-like reactions, cytokine release syndrome, or anaphylaxis. Mild infusion reactions can generally be treated with interruption of the infusion and medical intervention including IV fluids, antihistamines, nonsteroidal anti-inflammatory drugs, acetaminophen, and narcotics as needed. More severe or life-threatening reactions may require vasopressors, corticosteroids, and epinephrine. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. In the case of severe or life-threatening reactions, subsequent doses of pembrolizumab should not be administered.

5.2 Phase 1 Study

Since this combination has not been studied to date, the first 6 patients treated at dose level 1 will be used as an early safety lead-in per Section 13.2. If 2 or more patients experience a dose-limiting toxicity (DLT) as defined below, then the starting dose level will be adjusted and additional cohorts may be evaluated at dose levels -1 and -2 in the safety lead-in stage as described in section 13.1.2. The acceptable DLT rate is 0.20.

5.2.1 Definition of Dose Limiting Toxicity (DLT)

The NCI-CTCAE version 5.0 will be used to assess toxicities. Dose limiting toxicities (DLT) will be defined as any of the following events possibly related to the study drugs that occur during the first 2 cycles of therapy (6 weeks):

- Non-resolving (within 6 weeks) grade $\geq$ 2 corneal ulcer
- Any grade $\geq$ 3 uveitis or non-resolving (within 6 weeks) grade 2 uveitis
- Any grade $\geq$ 3 pneumonitis or non-resolving (within 6 weeks) grade 2 pneumonitis
- Any treatment-related grade 4 adverse event or non-resolving (within 6 weeks) treatment-related grade 3 adverse event
- Infusion reaction or hypersensitivity to anetumab ravtansine not controlled by infusion rate reduction and anti-allergic prophylaxis.
- Grade 5 toxicity

The DLT period is during the first two cycles. Patients who (a) have been on treatment for at least 28 days and received at least 85% of the total prescribed dose of each drug (combined over the 2 cycles) or (b) have experienced a DLT, will be “DLT evaluable” and included in the dose de-escalation decisions. Non-evaluable patients will be replaced for DLT assessment.

Management and dose modifications associated with the above adverse events are outlined in Section 6.

Note: PRO-CTCAE data should not be used for determining attribution, dose modifications or reporting of serious adverse events.

5.3 Phase 2 Study

Patients will be randomized 1:1 to receive the safe dosing combination of anetumab ravtansine with pembrolizumab identified during phase 1 or pembrolizumab alone.

5.4 General Concomitant Medication and Supportive Care Guidelines

Supportive care is otherwise recommended per community standards and may include oral and parenteral anti-coagulation if deemed necessary by the treating physician's discretion; prophylactic anti-emetics such as 5-HT3 blocks (granisetron, ondansetron); bisphosphonates or denosumab; analgesics; beta-blockers or digoxin.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with CTEP. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary physician; however, the decision to continue the patient on trial therapy or vaccination schedule requires the mutual agreement of the Investigator, CTEP, and the patient.

Acceptable Concomitant Medications: All treatments that the investigator considers necessary for a patient's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 30 days before the first dose of study treatment and 30 days after the last dose of study treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for serious adverse events (SAEs).

Prohibited concomitant medications are listed in the exclusion criteria, sections 3.31, 3.36 and 3.37. Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Patients may receive other medications that the investigator deems to be medically necessary. The study team should check a frequently- updated medical reference for a list of drugs to avoid or minimize use of. Appendix B Patient Drug Information Handout and Wallet Card should be provided to patients.

There are no prohibited therapies during the post-treatment follow-up portion of the study.

5.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment with anetumab ravtansine may continue for up to a maximum of 12 months and treatment with pembrolizumab (all groups) may continue for up to 24 months or until one of the following criteria applies:

- Disease progression; see sections 5.7 and 5.9.
- Intercurrent illness that prevents further administration of treatment
- Adverse event(s) which require(s) treatment discontinuation:
    - Any dosing interruption lasting >12 weeks with the following exceptions: Dosing interruptions >12 weeks that occur for non-drug-related reasons may be allowed if approved by the Principal Investigator. Prior to re-initiating treatment in a patient with a dosing interruption lasting >12 weeks, the Principal Investigator must be consulted.
    - Tumor assessments should continue as per protocol even if dosing is interrupted.
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression is defined as occurring when a patient's condition has deteriorated and the patient cannot continue with study treatment per the investigator's judgment regardless of imaging findings
- Patient non-compliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent
- If a patient has had a confirmed complete response (CR) that have been treated for at least 24 weeks with pembrolizumab and has continued at least two cycles beyond complete response, discussion between the treating physician and investigator regarding discontinuation of study treatment may be considered.

The reason(s) for protocol therapy discontinuation must be documented in the Case Report Form (CRF).

5.6 Duration of Follow Up

Patients will be followed for 12 months after removal from study treatment or until death, whichever occurs first. Patients will be followed every three months by a telephone call or letter to assess vital status. Patients removed from study for unacceptable adverse event(s) will be followed longer if needed until resolution or stabilization of the adverse event.

5.7 Criteria for Removal from Study

Patients will be removed from study treatment when any of the applicable criteria, including confirmed progressive disease as the overall objective status (Section 11.1.5.3), adverse events, patient withdrawal or inability to follow study protocol as listed in Section 5.5. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

If radiologic imaging shows progressive disease (PD), tumor assessment should be repeated by the site ≥ 4 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression as per section 5.9.

As per section 5.6 patients will be followed for 12 months after removal from study treatment or until death, whichever occurs first. Patients will be followed every three months by a telephone call or letter to assess vital status. Patients removed from study for unacceptable adverse event(s) will be followed longer if needed until resolution or stabilization of the adverse event.

5.8 Criteria to Resume Treatment Following a Drug-Related Adverse Event

For non-autoimmune or inflammatory events, patients may resume treatment with study drug when the drug-related AE(s) resolve to ≤ Grade 1 or baseline value, with the following exceptions:

- Patients may resume treatment in the presence of Grade 2 fatigue.
- Patients with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin.
- Patients with combined Grade 2 AST/ALT AND total bilirubin values meeting study parameters outlined in Section 6.1 should have treatment permanently discontinued.
- Non-drug-related toxicity including hepatic, pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed.
- Drug-related endocrinopathies (not including drug-related adrenal insufficiency or hypophysitis) adequately controlled with only physiologic hormone replacement may resume treatment after replacement correction and clinically stable regimen.

If the criteria to resume treatment are met, the patient should restart treatment no sooner than the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol, the treatment should resume at the earliest convenient point that is within the 12 week delay period.

If treatment is delayed >12 weeks, the patient must be permanently discontinued from study therapy, except as specified in Section 5.5 (Duration of Therapy).

Note: PRO-CTCAE data should not be used for determining treatment resumption following a drug-related symptomatic adverse event.

5.9 Treatment Beyond Progression

Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions. The date of initial progression will be used for the determination of the primary endpoint of overall response rate.

If radiologic imaging shows progressive disease (PD) and the patient is clinically stable, tumor assessment may be repeated by the site ≥ 4 weeks later in order to confirm PD with the option of continuing treatment per below while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating PD (i.e., PD is not confirmed), treatment may be continued as per treatment calendar. If repeat imaging confirms PD, patients will be discontinued from study therapy. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions as defined in Section 11.1.5.1 and Section 11.1.5.2. The decision to continue study treatment after the first evidence of disease progression determined by radiologic imaging is based on the clinical status of the patient as described in the table below.

Patients may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD	Repeat imaging at ≥ 4 weeks to confirm PD	Continue study treatment while awaiting confirmatory scan	Repeat imaging at ≥ 4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment	No additional imaging required	Discontinue treatment
Repeat scan shows SD, PR, or CR	Continue regularly scheduled imaging assessments	Continue study treatment	No additional imaging required	Discontinue treatment

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 PRO-CTCAE Data

PRO-CTCAE data should not be used for determining dose delays or dose modifications or any other protocol directed action.

6.2 Dose Modifications for Anetumab Ravtansine

Dose Level	Anetumab Ravtansine Dose
1	6.5 mg/kg
-1	5.5 mg/kg
-2	4.5 mg/kg

Neutrophil count decreased[1, 2]	Management/Next Dose
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3	Hold[2] until < Grade 2. Resume at one dose level lower.
Grade 4	Hold[2] until < Grade 2. Resume at one dose level lower.

1. Patients with febrile neutropenia should hold[**] until < grade 2 and resume at one dose level lower.
2. 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 (63) or at the discretion of the investigator; however they may not be substituted for a required dose reduction.
3. Patients requiring a delay of > 12 weeks should go off protocol therapy.

Platelet count decreased[1]	Management/Next Dose
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3	Hold[2] until < Grade 2. Resume at one dose level lower.
Grade 4	Hold[2] until < Grade 2. Resume at one dose level lower.
1. Patients with active bleeding related to drug-induced thrombocytopenia should reduce by one dose level. 2. Patients requiring a delay of > 12 weeks should go off protocol therapy.	

Non-hematologic toxicities	Management/Next Dose
≤ Grade 1	No change in dose.
Grade 2	No change in dose.
Grade 3	Hold[1] until ≤ Grade 2. Resume at same level or at one dose level lower, per investigator's discretion.[2]
Grade 4	Off protocol therapy
1. Patients requiring a delay of > 12 weeks should go off protocol therapy. 2. Patients requiring > two dose reductions should go off protocol therapy.	

Corneal Epitheliopathy	Definition	Management/Next Dose[1, 2]
Grade 0	No pathologic changes	No change in anetumab ravtansine; ocular lubricants at discretion of investigator or ophthalmologist
Grade 1	Any stage of superficial punctate keratitis (SPK; as per the Oxford Schema for grading SPK from stage 0 to IV)	No change in anetumab ravtansine; ocular lubricants; add topical steroids if SPK shows treatment emergent progression by ≥ 2 SPK grades
Grade 2	Epithelial opacities; micro-cysts, micro-deposits; corneal erosion; non-central stromal opacity	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 and ophthalmologist; intensive treatment with ocular lubricants enhanced with ointments; topical steroids; therapeutic contact lens may be considered at the discretion of investigator and ophthalmologist

Corneal Epitheliopathy	Definition	Management/Next Dose[1, 2]
Grade 3	Corneal ulcer without risk of acute rupture; Central stromal opacity	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); Intensive therapy with ointments; topical steroids; therapeutic contact lens or occlusion recommended at the discretion of investigator and ophthalmologist
Grade 4	Corneal ulcer more severe than grade 3	Discontinue anetumab ravtansine; 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 and ophthalmologist

1. Other remedial therapies for corneal epitheliopathy may be added or substituted at investigator's discretion or according to the institutional standards.
2. Treatment decisions are based on corneal morphology changes only, not on visual acuity changes.

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

Corneal Epitheliopathy	Definition	Management/Next Dose[1, 2]
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 to provide adequate protection to the corneal epithelium. The remedial therapy for the treatment-emergent changes in the Schirmer's test (dry eye) should be chosen at investigator's discretion or according to the institutional standards. These measures may include topical lubricants such as eye drops and ointments, punctual occlusion, use of therapeutic contact lenses and any other treatment approaches according to the local standard of care.		

Note: PRO-CTCAE data should not be used for determining dose delays or dose modifications.

6.3 Dose Modifications for Pembrolizumab (MK-3475)

Both serious and non-serious adverse events associated with pembrolizumab may represent an immunologic etiology and may occur shortly after the first dose or several months after the last dose. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs.

Dose interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation and/or holidays). Patients should be placed back on study therapy within 3 weeks of the scheduled interruption. The reason for interruption should be documented in the patient's study record.

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology guidelines include the use of oral or IV treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance as outlined below.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of the evaluation of the event.

General instructions:
1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.

2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 - 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or	

			equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3, 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 – 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

[a] AST/ALT: >3.0 - 5.0 x ULN if baseline normal; >3.0 - 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 - 3.0 x ULN if baseline normal; >1.5 - 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 - 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 - 10.0 x ULN if baseline normal; >3.0 - 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis.

Note: PRO-CTCAE data should not be used for determining dose delays or dose modifications

6.4 Continuation of Therapy When One Agent is Held or Discontinued

Patients who participate in the Phase 1 portion of this trial or are assigned to Treatment Group 2 (the combination of anetumab ravtansine and pembrolizumab) may continue to receive one agent if the other is held or discontinued for toxicity, and the toxicity is clearly attributable to the held or discontinued agent. If the toxicity in question is possibly related to either agent, then both agents should be held. These decisions may be discussed with the Principal Investigator.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Sections 7.2 and 7.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) in addition to routine reporting.

Clinician graded CTCAE is the AE (adverse event) safety standard. PRO-CTCAE items are to complement CTCAE reporting. Patients will respond to PRO-CTCAE items but no protocol directed action will be taken. The specific PRO-CTCAE items for this protocol can be found in Appendices C and D.

7.1 Comprehensive Adverse Events and Potential Risks List (CAEPRs)

7.1.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Anetumab ravtansine (BAY 94-9343, NSC 791065)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited

reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 652 patients.* Below is the CAEPR for Anetumab ravtansine (BAY 94-9343).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, November 14, 2019[1]

Adverse Events with Possible Relationship to Anetumab ravtansine (BAY 94-9343) (CTCAE 5.0 Term) [n= 652]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
EYE DISORDERS			
	Blurred vision		***Blurred vision (Gr 2)***
	Dry eye		***Dry eye (Gr 2)***
Eye disorders - Other (corneal disorder)[2]			***Eye disorders - Other (corneal disorder)[2] (Gr 2)***
	Keratitis		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		
Diarrhea			***Diarrhea (Gr 2)***
	Gastroesophageal reflux disease		
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Blood bilirubin increased		
	Lipase increased		
	Lymphocyte count decreased		
		Neutrophil count decreased	
	Platelet count decreased		***Platelet count decreased (Gr 2)***
	Weight loss		
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Muscle cramp		
	Myalgia		

Adverse Events with Possible Relationship to Anetumab ravtansine (BAY 94-9343) (CTCAE 5.0 Term) [n= 652]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		
	Nervous system disorders - Other (neuropathy peripheral)		***Nervous system disorders - Other (neuropathy peripheral) (Gr 2)***
	Paresthesia		
	Peripheral sensory neuropathy		***Peripheral sensory neuropathy (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Dyspnea		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Corneal disorder includes corneal cyst, corneal deposits, corneal epithelial microcycsts, corneal epitheliopathy, corneal epithelium defect, corneal erosion, corneal intraepithelial microcycsts, corneal neovascularization, corneal opacity, and corneal verticillata.

Adverse events reported on anetumab ravtansine (BAY 94-9343) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that anetumab ravtansine (BAY 94-9343) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Disseminated intravascular coagulation; Febrile neutropenia
CARDIAC DISORDERS - Atrial fibrillation; Chest pain - cardiac; Palpitations; Pericardial effusion; Pericarditis; Sinus tachycardia; Supraventricular tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus; Vertigo
ENDOCRINE DISORDERS - Hypothyroidism
EYE DISORDERS - Cataract; Eye disorders - Other (blepharitis); Eye disorders - Other (eye irritation); Eye disorders - Other (eye pruritus); Eye disorders - Other (keratopathy); Eye disorders - Other (macular degeneration); Eye disorders - Other (ocular hyperemia); Eye disorders - Other (Schirmer's test abnormal); Eye pain; Floaters; Photophobia; Retinal vascular disorder; Vision decreased
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Dry mouth; Dyspepsia; Esophagitis; Flatulence; Gastritis; Mucositis oral; Periodontal disease
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); Infusion site extravasation; Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders - Other (hepatocellular injury)
IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis
INFECTIONS AND INFESTATIONS - Bronchial infection; Conjunctivitis; Sepsis; Skin infection; Thrush; Urinary tract infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Fall
INVESTIGATIONS - Cholesterol high; Creatinine increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; Electrocardiogram T wave abnormal; GGT increased; Serum amylase increased

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Flank pain; Generalized muscle weakness; Joint range of motion decreased; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Dizziness; Dysesthesia; Headache; Lethargy; Movements involuntary; Nervous system disorders - Other (neurotoxicity); Nervous system disorders - Other (polyneuropathy); Neuralgia; Peripheral motor neuropathy; Tremor
PSYCHIATRIC DISORDERS - Anxiety; Insomnia
RENAL AND URINARY DISORDERS - Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Epistaxis; Hiccups; Hypoxia; Nasal congestion; Oropharyngeal pain; Pleural effusion; Pleuritic pain; Sinus disorder; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Nail changes; Pruritus; Rash acneiform; Urticaria
VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Thromboembolic event

Note: Anetumab ravtansine (BAY 94-9343) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.2 Comprehensive Adverse Events and Potential Risks list (CAEPR) for MK-3475 (pembrolizumab, NSC 776864)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3793 patients.* Below is the CAEPR for MK-3475 (pembrolizumab).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.6, July 15, 2021[1]

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia[2]		
		Blood and lymphatic system disorders - Other (immune thrombocytopenic purpura)[2]	
	Lymph node pain[2]		
CARDIAC DISORDERS			
		Myocarditis[2]	
		Pericarditis[2]	

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Endocrine disorders - Other (thyroiditis)[2]		
	Hyperthyroidism[2]		
	Hypophysitis[2]		
	Hypopituitarism[2]		
	Hypothyroidism[2]		
EYE DISORDERS			
		Uveitis[2]	
		Eye disorders - Other (Vogt-Koyanagi-Harada syndrome)	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		
	Diarrhea[2]		***Diarrhea[2] (Gr 2)***
	Mucositis oral[2]		
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[2]		
	Small intestinal mucositis[2]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills[2]		
Fatigue			***Fatigue (Gr 2)***
	Fever[2]		
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (autoimmune hepatitis)[2]		
		Hepatobiliary disorders - Other (sclerosing cholangitis)	
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis[2]	
		Cytokine release syndrome[2]	
		Immune system disorders - Other (acute graft-versus-host-disease)[2,3]	
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis)[2]	
	Immune system disorders - Other (pseudoprogression/tumor inflammation)[2]		
	Immune system disorders - Other (sarcoidosis)[2]		
		Serum sickness[2]	
INFECTIONS AND INFESTATIONS			
	Infection[4]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Infusion related reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased		

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased		
	CPK increased		
		GGT increased	
		Serum amylase increased	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Hyponatremia		
		Metabolism and nutrition disorders - Other (diabetic ketoacidosis)[2]	
		Metabolism and nutrition disorders - Other (type 1 diabetes mellitus)[2]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia[2]		***Arthralgia[2] (Gr 2)***
	Arthritis[2]		
	Avascular necrosis[2]		
	Back pain		
	Joint effusion[2]		
	Joint range of motion decreased		
	Musculoskeletal and connective tissue disorder - Other (tenosynovitis)[2]		
	Myalgia[2]		
	Myositis[2]		
NERVOUS SYSTEM DISORDERS			
		Guillain-Barre syndrome[2]	
		Nervous system disorders - Other (myasthenic syndrome)[2]	
		Nervous system disorders - Other (neuromyopathy)[2]	
		Nervous system disorders - Other (non-infectious encephalitis)[2]	
		Nervous system disorders - Other (non-infectious meningitis)[2]	
		Nervous system disorders - Other (non-infectious myelitis)	
		Nervous system disorders - Other (polyneuropathy)[2]	
		Paresthesia	
		Peripheral motor neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (autoimmune nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Pleuritic pain[2]		
	Pneumonitis[2]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Bullous dermatitis[2]		

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Erythema multiforme[2]	
	Erythroderma		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus[2]		***Pruritus[2] (Gr 2)***
	Rash acneiform[2]		
	Rash maculo-papular[2]		***Rash maculo-papular[2] (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (dermatitis)[2]		
	Skin hypopigmentation[2]		
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis	
	Urticaria[2]		
VASCULAR DISORDERS			
		Vasculitis[2]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Immune-mediated adverse reactions have been reported in patients receiving MK-3475 (pembrolizumab). Adverse events potentially related to MK-3475 (pembrolizumab) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of MK-3475 (pembrolizumab), administration of corticosteroids and supportive care.

[3]Acute graft-versus-host disease has been observed in patients treated with MK-3475 (pembrolizumab) who received hematopoeitic stem cell transplants.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on MK-3475 (pembrolizumab) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MK-3475 (pembrolizumab) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Hemolysis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Myocardial infarction; Pericardial effusion; Pericardial tamponade; Ventricular arrhythmia
EYE DISORDERS - Eye pain
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Constipation; Duodenal hemorrhage; Dysphagia; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intussusception); Oral pain; Rectal hemorrhage; Small intestinal perforation; Upper gastrointestinal hemorrhage; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Edema limbs; Facial pain; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); Generalized edema; Malaise; Non-cardiac chest pain; Pain
INVESTIGATIONS - Cholesterol high; Creatinine increased; Fibrinogen decreased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia;

Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity
NERVOUS SYSTEM DISORDERS - Aphonia; Depressed level of consciousness; Dysarthria; Edema cerebral; Encephalopathy; Headache; Hydrocephalus; Lethargy; Meningismus; Nervous system disorders - Other (brainstem herniation); Seizure; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury; Nephrotic syndrome; Proteinuria; Renal and urinary disorders - Other (hydronephrosis); Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Hypoxia; Laryngeal inflammation; Pleural effusion; Pneumothorax; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Skin and subcutaneous tissue disorders - Other (drug eruption)
VASCULAR DISORDERS - Hypertension; Peripheral ischemia; Thromboembolic event

Note: MK-3475 (pembrolizumab) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

- PRO-CTCAE is not intended for expedited reporting, real time review or safety reporting.

7.3 Expedited Adverse Event Reporting

7.3.1 Rave-CTEP-AERS Integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of post-baseline AEs entered in Rave to determine whether they require expedited reporting, and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period, and used to collect AEs that start during the period or persist from the previous reporting period. CRA will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Event form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct, and
- AEs are recorded and complete (no missing fields) and the form is query-free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence that Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents > Education and Promotion, and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information > User Guides & Help Topics.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

7.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires <u>both</u> routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

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

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **<u>MUST</u>** immediately report to the sponsor (NCI) **<u>ANY</u>** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **<u>ANY</u>** of the following outcomes:

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

<u>ALL</u> <u>SERIOUS</u> adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

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

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below ***do not*** require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism (Section 7.4):

CTCAE SOC	Adverse Event	CTCAE Grade at which the event will not require expedited reporting[1]
Investigations	Neutrophil count decreased	≤ Grade 4
	Platelet count decreased	≤ Grade 4
	White blood count	≤ Grade 4
	Lymphocyte count decreased	≤ Grade 4
Blood and lymphatic system disorders	Anemia	≤ Grade 4
Endocrine disorders	Hyperthyroidism	≤ Grade 2
	Hypothyroidism	≤ Grade 2
Musculoskeletal and connective tissue disorders	Chest wall pain	≤ Grade 3
Respiratory, thoracic and mediastinal disorders	Dyspnea	≤ Grade 3

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

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

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

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

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must <u>also</u> be reported in routine study data submissions.**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

Symptomatic Adverse Events reported by patients through PRO-CTCAE are not safety reporting and may be presented with other routine AE data.

7.5 Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia (AML)

- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol. The pathology report documenting the diagnosis of the secondary malignancy is required to be submitted for review.

7.6 Second Malignancy

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

7.7 Pregnancy

If a patient inadvertently becomes pregnant while on treatment with pembrolizumab, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn. If a male patient impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy reported and followed.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in Section 7.1.

8.1 CTEP IND Agent(s)

8.1.1 Anetumab ravtansine (NSC 791065)

Chemical Name or Amino Acid Sequence: Immunoglobulin G1, anti-(human mesothelin) human monoclonal MF-T-IgG1 heavy chain, disulfide with human monoclonal MF-T-IgG1 gamma--chain, dimer, triamide with N2′-[4-[(3-carboxypropyl) dithio]-4-methyl-1-oxopentyl]-N2′-deacetylmaytasine

Other Names: BAY 94-9343

Classification: antibody-drug conjugate (ADC) targeting mesothelin

Molecular Weight: ~150 kDa

CAS Registry Number: 1375258-01-7

Approximate Solubility: At least 5 g/L in 10 mM histidine/130 mM glycine buffer at pH 5.5

Mode of Action: Anetumab ravtansine is an ADC consisting of a fully human IgG1 antibody directed at the mesothelin antigen and conjugated to a maytansine derivative, which acts as a tubulin polymerization inhibitor. Mesothelin is a tumor differentiation antigen frequently overexpressed in certain tumors while showing limited expression in nonmalignant tissues.

Description: White to off-white lyophilized cake or powder. Clear to slightly opalescent solution pH 5.5 following reconstitution.

How Supplied: Bayer HealthCare AG supplies and CTEP, DCTC, NCI distributes anetumab ravtansine as 60 mg lyophilized powder for injection. It is packaged in 30 mL single use, clear glass vials with coated bromobutyl rubber stoppers and flip-off caps. The excipients used to manufacture anetumab ravtansine include histidine, glycine, sucrose, polysorbate 80, hydrochloric acid, and water for injection.

Preparation: Using appropriate aseptic technique, reconstitute each 60 mg vial of anetumab ravtansine with 11.9 mL sterile water for injection (SWFI) to yield a 5 mg/mL solution. The SWFI should be directed to the glass wall of the vial and not directly to the lyophilized cake. Do not let the syringe needle come into contact with the lyophilized cake. Avoid shaking. The reconstituted solution should be clear to slightly opalescent and free from visible particles. Do not use if the reconstituted solution contains visible particles. Anetumab ravtansine must be further diluted with 0.9% sodium chloride or dextrose 5% to a final concentration between 0.1 and 3 mg/mL prior to administration in IV infusion bags composed of PVC, polyethylene or polypropylene. A slight turbidity may occur during dilution but does not affect the quality of the drug product. Mix gently. Do not shake.

Storage: Store intact vials refrigerated between 2° to 8°C in the original box until use. Protect from sunlight.

If a storage temperature excursion is identified, promptly return anetumab ravtansine to 2°to 8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Stability studies of the intact vials are ongoing. Avoid exposure to bright light. Standard room illumination does not necessitate any precautions. Administer prepared infusions immediately following preparation within 2 hours if stored at room temperature. If the diluted solution is not used immediately, store it between 2° to 8°C and use within 6 hours.

CAUTION: The single-use lyophilized dosage form contains no antibacterial preservatives. Reconstituted vials are to be used immediately. If not used immediately,

store between 2º to 8º C and discard 6 hours after reconstitution.

Route of Administration: IV infusion.

Method of Administration: Administer anetumab ravtansine as an IV infusion over 1 hour using PVC, polyurethane, polybutadiene, or polyethylene infusion sets with 0.2 to 1.2 micron polyethersulfone in-line filter. If the diluted solution is refrigerated, it takes approximately one hour for 100 mL of solution to reach room temperature.

Potential Drug Interactions: The maytansinoid-derivative toxophore or DM4 (BAY 100-6640) and its active S-methyl metabolite DM4-Me (BAY 100-6641) are mainly metabolized by CYP3A4 in vitro with minor contribution from CYP3A5 and 2D6. Therefore, concomitant administration of strong inhibitors and inducers of CYP3A4 are prohibited within 2 weeks before the start of and during treatment with anetumab ravtansine. DM4 and DM4-Me are substrates of P-gp but not substrates for BCRP, OATP1B1, or OATP1B3 in vitro. Use caution when given with potent inhibitors or inducers of P-gp.

In vitro DM4 and DM4-Me do not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, and 2E1. Both showed little inhibitory effect on CYP3A4 and no clinically relevant inhibition toward P-gp, BCRP.

Both DM4 and DM4-Me are not inducers of CYP1A2 and 3A4.

Both DM4 and DM4-Me are highly protein bound in vitro.

Patient Care Implications: Anetumab ravtansine is expected to adversely affect male and female reproduction in vitro. Women of childbearing potential and men must use adequate contraception during the study and for at least 6 months after the last dose of anetumab ravtansine. Breast-feeding should be discontinued before start of treatment, during treatment, and for 8 weeks after end of treatment.

8.1.2 Pembrolizumab (MK-3475) (NSC 776864)

Other Names: SCH 900475, pembrolizumab (MK-3475)

Classification: Anti-PD-1 MAb

Molecular Weight: 148.9-149.5 KDa

CAS Number: 1374853-91-4

Mode of Action: The programmed cell death 1 (PD-1) receptor is an inhibitory receptor expressed by T cells. When bound to either of its ligands, PD-L1 or PD-L2, activated PD-1 negatively regulates T-cell activation and effector function. The pathway may be engaged by tumor cells to suppress immune control. Pembrolizumab blocks the negative immune regulatory signaling by binding to the PD-1 receptor, inhibiting the interaction

between PD-1 and its ligands.

Description: Pembrolizumab is a humanized MAb of the IgG4/kappa isotype.

How Supplied: Pembrolizumab (MK-3475) is supplied by Merck & Co., Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. Pembrolizumab (MK-3475) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution for intravenous use. Each vial contains 100 mg of pembrolizumab (MK-3475) in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab (MK-3475) and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

Preparation: Pembrolizumab solution for infusion must be diluted prior to administration. Do not shake the vials. Do not use if opaque or extraneous particulate matter other than translucent to white proteinaceous particles is observed. Do not use if discolored. To prepare the infusion solution add the dose volume of pembrolizumab to an infusion bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Gently invert the bag 10-15 times to mix the solution. The final concentration must be between **1 mg/mL to 10 mg/mL**.

Compatible IV bag materials: PVC plasticized with DEHP, non-PVC (polyolefin), EVA, or PE lined polyolefin

Storage: Store intact vials between 2°C - 8°C (36°F - 46°F). Do not freeze. Protect from light by storing in the original box. If a storage temperature excursion is identified, promptly return pembrolizumab to between 2-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Refer to the package label for expiration.
Administer prepared solutions immediately after preparation. If not administered immediately, prepared solutions may be stored refrigerated for up to 24 hours. Pembrolizumab (MK-3475) solutions may be stored at room temperature for a cumulative time of up to 6 hours. This includes room temperature storage of liquid drug product solution in vials, room temperature storage of infusion solution in the IV bag, and the duration of infusion.

Route of Administration: IV infusion only. Do not administer as an IV push or bolus injection.

Method of Administration: Infuse over approximately 30 minutes (range: 25 - 40 minutes) using an infusion set containing a low-protein binding 0.2 to 5 µm in-line filter made of polyethersulfone or polysulfone. Infusion rate should not exceed 6.7 mL/min. A central line is not required; however if a patient has a central venous catheter in place, it is recommended that it be used for the infusion. Do not co-administer other drugs through the same infusion line. Following the infusion, flush the IV line with normal saline.

Compatible infusion set materials: PVC plasticized with DEHP or DEHT, PVC and tri-(2-ethylhexyl) trimellitate, polyethylene lined PVC, polyurethane, or polybutadiene

Patient Care Implications: Refer to the protocol for information on evaluation and management of potential immune-related adverse events.

Availability: Pembrolizumab is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Pembrolizumab is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.3 Agent Ordering and Agent Accountability

8.1.3.1 NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Subjects must be enrolled and randomized prior to submitting the clinical drug request to PMB. Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

8.1.3.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.1.3.3 Investigator Brochures - The current versions of the IBs for PMB-supplied agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. Questions about IB access may be directed to the PMB IB coordinator via email.

8.1.3.4 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)
- IB Coordinator: ibcoordinator@mail.nih.gov

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Specimen Requirements for Correlative Studies

In this study, we propose several correlative studies, as detailed below. These assays are specifically chosen to provide information on immunologic markers that may be predictive of treatment responses as well as specific information related to the mechanism of action of the study drugs. Six integrated biomarker studies have been included; all other correlative studies will be exploratory in nature. They are intended to be hypothesis-generating and will help us advance our understanding of the systemic immunologic environment.

Submission of archived tumor tissue is mandatory ***if archived tissue is available from a prior biopsy or surgery***; do ***not*** perform a biopsy solely to provide tissue for this correlative study. All tumor biopsy tissue will be submitted in either slides or formalin-fixed paraffin-embedded (FFPE) tissue blocks and will be used to produce specimens for an exploratory biomarker study of tissue expression of PD-L1.

Serial collection of peripheral blood is also mandatory for patients participating in this study. Peripheral blood will be collected at pre-study, day 1 of each cycle, cycle 1 day 8 and cycle 3 day 8. Peripheral blood will be used to assay the 1) pharmacokinetics of anetumab ravtansine; 2) presence of anti-anetumab ravtansine antibodies; 3) megakaryocyte potentiating factor; 4) mononuclear Phagocyte System (MPS) - Fc-gamma-receptors (FcγR); 5) chemokine mediators of mononuclear phagocyte system; 6) Bim in tumor reactive T cells T_{TR} and 7) soluble PD-L1.

Any surplus of blood, plasma, serum, DNA, cells and tissue will be banked at Mayo Clinic for additional studies for the patients who provide additional consent for specimen banking. If consent for specimen banking was not provided by the patient, the remaining blocks or slides will be returned to the original institution and the remaining blood, plasma, serum, DNA and cells will be discarded if the patient did not provide consent for

banking of specimens.

Summary Table for Specimen Collection

All correlative specimens in the table below are required unless noted otherwise.

Study and Time Point(s)	Specimen and Quantity	Send Specimens to:
Baseline		
Mesothelin expression Ph 1: Pre-study (only if available); Ph 2: Pre-registration	FFPE block **OR** 5-10 X 4-5µ unstained, positively charged slides from archival tissue **OR** Fresh tissue (Ph 2 only)	Hematogenix Laboratory Services (HLS)
Tissue expression of PD-L1[1] (only if available)	FFPE block **OR** 3-5 X 4-5µ unstained, positively charged slides from archival tissue	Mayo Clinic
MPF	4 mL whole blood in red tube top	Liang Cao, NCI
Bim in T_{TR}	10 mL whole blood in EDTA (purple top) tube	Mayo Clinic
sPD-L1		
Cycle 1 Day 1		
PKs[3]: • Pre-treatment; • end of anetumab ravtansine infusion[2]; • 7 hrs post-anetumab ravtansine infusion[2].	Whole blood in 1 X 3 mL lavender top EDTA tube per time point **AND** Whole blood in 1 X 2.7 mL lavender top EDTA monovette per time point	Covance
ADA[3]	Whole blood in 1 X 4 mL gold top SST	Covance
MPS-chemokine mediators	Whole blood in 1 X 5 mL gold top SST processed to serum	Bill Zamboni, UNC
MPS-FcɣRs	20 mL whole blood in K2 EDTA (purple top) tubes processed to PBMCs	Bill Zamboni, UNC
Cycle 1 Day 8		
PKs[3]: • Any time	Whole blood in 1 X 3 mL lavender top EDTA tube per time point **AND** Whole blood in 1 X 2.7 mL lavender top EDTA monovette per	Covance

Study and Time Point(s)	Specimen and Quantity	Send Specimens to:
	time point	
MPS-chemokine mediators	Whole blood in 1 X 5 mL gold top SST processed to serum	Bill Zamboni, UNC
MPS- FcɣRs	20 mL whole blood in K2 EDTA (purple top) tubes processed to PBMCs	Bill Zamboni, UNC
Cycle 2 Day 1		
MPF	4 mL whole blood in red top tube	Liang Cao, NCI
Bim in T_{TR}	10 mL whole blood in EDTA (purple top) tube	Mayo Clinic
sPD-L1		
Cycle 3 Day 1		
MPS-chemokine mediators	Whole blood in 1 X 5 mL gold top SST processed to serum	Bill Zamboni, UNC
MPS-FcɣRs	20 mL whole blood in K2 EDTA (purple top) tubes processed to PBMCs	Bill Zamboni, UNC
ADA[3]	Whole blood in 1 X 4 mL gold top SST	Covance
Cycle 3 Day 8		
MPS-chemokine mediators	Whole blood in 1 X 5 mL gold top SST processed to serum	Bill Zamboni, UNC
MPS-FcɣRs	20 mL whole blood in K2 EDTA (purple top) tubes processed to PBMCs	Bill Zamboni, UNC
Cycle 4 Day 1		
MPF	4 mL blood in red top tube	Liang Cao, NCI
Bim in T_{TR}	10 mL whole blood in EDTA (purple top) tube	Mayo Clinic
sPD-L1		
Cycle 6 Day 1		
ADA[3]	Whole blood in 1 X 4 mL gold top SST	Covance
Cycle 9 Day 1 then every 3 months through 1 year from registration then every 6 months through 2 years from registration		
ADA[3]	Whole blood in 1 X 4 mL gold top SST	Covance

[1]*Testing for mesothelin expression should take priority over testing for PD-L1 expression.*

[2] *Samples should be drawn within +/- 15 minutes of the stated time point.*
[3] *These may be discontinued for patients who discontinue treatment with anetumab ravtansine.*

9.2 Integral Laboratory Studies

9.2.1 Mesothelin Expression

Anetumab ravtansine is an IgG1 antibody-drug conjugate that recognizes mesothelin and is bound to a potent microtubule inhibitor, DM4. Patients in Phase 2 of the study will be selected for participation in this clinical trial based on mesothelin expression by immunohistochemistry (clone SP74).

Please refer to Hematogenix lab manual for additional instructions.

9.2.1.1 Collection of Specimen(s)

Archival formalin fixed tumor tissue can be submitted in blocks or in freshly cut sections, depending on availability. Fresh core biopsies may also be submitted if archival tissue is not available or sufficient for testing.

If tissue is provided in sections, unstained slides should be provided: minimum of 5 slides of 4-5 microns thickness. Sections must be mounted on positively charged glass slides of the correct type – Super frost® Plus Micro Slides (positively charged microscope slides).

Fine needle aspiration (FNA) material is not acceptable.

9.2.1.2 Handling of Specimens(s)

For the archival specimens, storage temperatures ranges between 15°C and 25°C are preferred. Mesothelin stability on cut slides is not expected to exceed 7 months.

For fresh core biopsies, if the size of the material is larger than 3 mm, please cut the tumor into 2 pieces to allow for formalin penetration and fixation. Transfer the tumor biopsy to the container of 10% neutral-buffered formalin (NBF) as soon as possible (within 15 minutes) of tumor removal. The formalin solution should be at least 10 times the volume of the tumor specimen. Allow the tumor biopsy to stay in formalin for 24 hours +/- 1 hour at 4°C. Transfer the tumor biopsy to the vial containing 70% histology alcohol. Dispose of the 10% NBF in an appropriate hazardous waste container at your facility. Store the biopsy in the vial with 70% histology alcohol at 4°C until shipping. Please ship immediately to the analytical laboratory below for further processing into FFPE tumor blocks. Do not ship specimens in formalin. Tumor tissue needs to be embedded within 1 week of biopsy.

9.2.1.3 Shipping of Specimen(s)

Supplies for preparing and shipping of tissue samples should be provided by the sites. The central lab will provide labels for specimens, a requisition form to submit along with the tissue sample for mesothelin testing, and airway bills for shipping. Samples should be shipped as soon as they are available.

9.2.1.4 Site Performing Correlative Study

Mesothelin testing will be performed by Hematogenix. Results will be available on the central lab's HematoPass portal. Results should be available within 3-5 days of sample receipt.

9.3 Integrated Correlative Studies

9.3.1 Anetumab Ravtansine Pharmacokinetics (PKs)

Anetumab Ravtansine PK studies consist of three analyses:

1. BAY 94-9343 ADC
2. BAY 94-9343 TAB (Total Antibody)
3. DM4 (BAY 1006640) and DM4-Me (BYA1006441)

Refer to Covance lab manual for additional instructions.

9.3.1.1 Collection of Specimen(s)

a. BAY 94-9343 ADC and BAY 94-9343 TAB

Collect minimum 2.7 mL whole blood in 3 mL lavender top EDTA tubes at the collection time points listed in Section 9.1.

b. DM4 (BAY 1006640) and DM4-Me (BYA1006441)

Collect minimum 2.7 mL whole blood in 2.7 mL lavender top EDTA monovette at the collection time points listed in Section 9.1.

9.3.1.2 Handling of Specimens

a. BAY 94-9343 ADC and BAY 94-9343 TAB

Store collected blood in refrigerator until centrifugation. Centrifuge at 2000g at ~4ºC for 10 min. Transfer plasma equally into labeled polypropylene tubes; each tube must contain at least 0.2 mL of plasma. *Total duration time between sample collection at room temperature and final storage MUST NOT exceed 60 min.* Store frozen at < -15ºC until shipping.

b. DM4 (BAY 1006640) and DM4-Me (BYA1006441)

Immediately centrifuge at 2000g at ~4ºC for 10 min. Transfer exactly 0.8 mL of plasma into labeled plasma collection tube prefilled with 0.08 mL 10% aqueous formic acid); thoroughly vortex. *Total duration time between sample collection at room temperature and final storage MUST NOT exceed 30 min.* Store frozen at < -15ºC until shipping.

9.3.1.3 Shipping of Specimen(s)

All samples to be stored in freezer as outlined in handling instruction and then batched and shipped to Covance using air bills and requisitions provided every 3 months on dry ice according to instructions.

9.3.1.4 Site(s) Performing Correlative Study

a. BAY 94-9343 ADC: Syrinx Bioanalytics
b. BAY 94-9343 TAB (Total Antibody): Syrinx Bioanalytics
c. DM4 (BAY 1006640) and DM4-Me (BYA1006441): Swiss BioQuant (SBQ), Switzerland

9.3.2 Anti-Anetumab Ravtansine Antibodies (ADA)

Anetumab ADA consists of 2 studies:

a. BAY 94-9343 ADA
b. BAY 94-9343 nAB (neutralizing antibodies)

Refer to Covance lab manual for additional instructions.

9.3.2.1 Collection of Specimen(s)

a. BAY 94-9343 ADA

Collect minimum 2 mL whole blood in 4 mL gold top serum separation tube at the collection time points listed in Section 9.1. Collection may be combined with nAB collection.

b. BAY 94-9343 nAB (neutralizing antibodies)

Collect minimum 2 mL whole blood in 4 mL gold top serum separation tube at the collection time points listed in Section 9.1. Collection may be combined with BAY 94-9343 ADA collection.

9.3.2.2 Handling of Specimens(s)

a. BAY 94-9343 ADA and BAY 94-9343 nAB (neutralizing antibodies)

Total duration between blood sample collection and final storage of the serum sample must not exceed 120 min. Store blood samples at ambient temperature (<25°C) for 30 minutes. Centrifuge blood samples at approx. 2000g for approx. 10 minutes at approx. 4°C. After centrifugation, transfer serum equally into the labeled polypropylene tubes. Each tube must contain at least 0.5 mL of serum. Store samples in an upright position until shipment at <–15°C in a temperature controlled freezer.

9.3.2.3 Shipping of Specimen(s)

All samples to be stored in freezer as outlined in handling instruction and then batched and shipped to Covance using air bills and requisitions provided every 3 months on dry ice according to instructions.

9.3.2.4 Site(s) Performing Correlative Study

Bayer, Germany

9.3.3 Megakaryocyte Potentiating Factor (MPF)

MPF is cleaved from the amino terminus of a precursor protein that leaves mesothelin linked to the cell surface by glycophosphatidylinositol (65, 66). Thus, serum MPF is correlated with mesothelin expression and provides a blood-based marker of mesothelin-positive tumor burden. In a recently published clinical trial that tested the anti-mesothelin immunotoxin SS1P in patients with MPM (67), serum MPF levels correlated with radiographic responses. Accordingly, it is hypothesized that serum MPF may correlate with radiographic responses to treatment with anetumab ravtansine in this clinical trial.

In the current trial, MPF is not intended to provide clinical guidance. Results will be provided at an interim point and at the end of the study when all of the samples have been collected to explore the associations of MPF with treatment response.

Testing for MPF has demonstrated a sensitivity of < 10 pg/mL with an analytic range of 0.02-100 ng/mL. With adjustments for 5-fold sample dilution, the test has a quantification range of 0.10-500 ng/mL. The current upper reference value is 1.2 mg/mL, with values above the reference level considered to be elevated.

The test of MPF test was effective in mesothelioma patients with elevated MPF. In mesothelioma patients, MPF was elevated in a high percentage of these patients (70%). Thus, statistically significant data can be obtained with as few as 20 treatment naïve mesothelioma patients in our study.

Blood will be collected from patients concurrently with clinical blood draws, when possible, in order to minimize any discomfort.

9.3.3.1 Collection of Specimens

A venous blood collection tube will be used to collect 4 mL of blood at pre-study, C2D1 and C4D1.

9.3.3.2 Handling of Specimens

Gently invert the tube 5 times and allow a clotting time of a minimum of 30 minutes at room temperature. The blood samples should be processed the same day of blood draw. If the samples must be stored overnight before processing, after 30 minutes of coagulation at room temperature, the blood collection tube can then be stored at 4°C for up to 24 hrs.

Centrifuge the tubes at 1200 RCF for 10 min in a swing-head centrifuge, or 15 min in a fixed angle centrifuge (balance the tube in the centrifuge). Carefully aspirate the supernatant (serum) into a new centrifuge tube. Inspect serum for turbidity. Turbid samples should be centrifuged and aspirated again to remove insoluble matter. Aliquot each sample into two cryovials with printed labels with a sample identifier

and store them at -80ºC.

9.3.3.3 Shipping of Specimens

The samples should be shipped to Dr. Liang Cao at the National Cancer Institute in batches on dry ice. A separate sample sheet with at least a patient identifier and a sample identifier for each sample should be provided via secured electronic mail. A separate email with tracking information should be sent to the recipient at the time of shipping to ensure the receiving of the samples package on time.

Shipping information is as follows:

Liang Cao, Ph.D.
Center for Cancer Research
National Cancer Institute
37 Convent Dr. MSC 4265
Bldg 37, Rm 6040
Bethesda, MD 20892-1906
Phone: (301) 435-9039
E-mail: caoli@mail.nih.gov

9.3.3.4 Site Performing Correlative Study

Testing for MPF will be performed in Professor Cao's laboratory at the National Cancer Institute. Professor Cao has developed the MPF assay and his laboratory has extensive expertise with it.

9.3.4 Mononuclear Phagocyte System (MPS) - Fc-gamma-receptors (FcγR)

MPS-FcγRs is an integrated biomarker assay comparing the three primary FcγRs (CD64, CD32, CD16) on the surface of monocytes ($CD14^+$) from a peripheral blood mononuclear cell (PBMC) fraction obtained from blood. Compared to small molecule drugs, nanoparticles (NPs), monoclonal antibodies (mAb) and antibody-drug conjugates (ADC) are cleared via the cells of MPS, also called antigen presenting cells. Variability in MPS function and chemokines mediators (CCL2 and CCL5) have been shown to predict variability in the pharmacokinetics (PK) and pharmacodynamics (PD) of NPs such as PEGylated liposomal doxorubicin (Doxil; PLD) in patients and preclinical tumor models (36). While NPs are cleared via phagocytosis by MPS cells, the MPS also serves as a natural mechanism of clearance for antibodies and immune complexes via their FcγR on MPS cells. Myeloid cells express various forms of FcγRs (CD64, cD32, CD16) that will interact with monomeric or aggregated IgGs and therapeutic mAbs and ADCs. Due to the differences in types and affinity in FcγRs, variations in receptor expression can lead to significant differences in the ability of MPS cells to clear immune complexes from the blood. Preliminary data from our group shows that the expression of CD64, CD32 and CD16 FcγRs on MPS cells is highly variable in healthy volunteers and patients with cancer. Thus, variability in MPS FcγRs and mediators in blood may be responsible for the high and clinically relevant variability in the PK and PD of mAb and ADC.

The high PK variability is clinically important for mAbs, and especially for ADCs, as these agents have a narrow therapeutic index. Moreover, the combination of ADCs, such as anetumab ravtansine, with other mAbs and immune modulators has the high likelihood of causing drug-drug interactions which results in altered PK and PD of the ADC and mAb as both undergo clearance by the MPS. Thus, the evaluation of biomarkers of the MPS, such as FcγRs, is critically important to optimizing the treatment of anetumab ravtansine and other ADCs alone and in combination with other agents.

The MPS-FcγRs assay has been validated as a relative quantitative flow cytometry-based assay using standard methods. Data will be obtained on the flow cytometry instrument as mean fluorescence intensity (MFI). Data will be converted to mean equivalent soluble fluorophore (MESF) and antibody bound to cell (ABC) units using appropriate bead-based standards. Appropriate background and controls will be collected for analytical determination/compensation. This assay has demonstrated a coefficient of variation of sensitivity of 0.3-1.1% using frozen PBMCs.

It is hypothesized that mAbs and ADCs (anetumab ravtansine) are cleared via the FcγRs on MPS cells and that biomarkers of MPS-FcγRs can be used to evaluate patient-specific differences in PK and PD of these agents and drug-drug interactions, especially for regimens combining these agents with other mAbs and immune modulators. We anticipate that patients with lower expression of FcγRs will have slower clearance of anetumab ravtansine and increased risk of significant drug-drug interactions when combined with other mAbs and immune modulators.

The MPS-FcγRs biomarker will be used retrospectively to evaluate the mechanisms associated with the variability in the pharmacokinetics and pharmacodynamics of anetumab ravtansine and mechanisms of drug-drug interactions of anetumab. Blood should be collected from patients concurrently with clinical blood draws, when possible, in order to minimize any discomfort.

9.3.4.1 Collection of Specimen(s)

EDTA vacutainers will be used to collect 20 mL of whole blood at C1D1, C1D8, C3D1 and C3D8.

9.3.4.2 Handling of Specimens(s)

Whole blood will be processed into PBMCs and cryo-preserved at each clinical study site per institutional SOP. Clinical study sites may choose to follow the SOP detailed in Appendix E. Whole blood should be processed to PBMCs by staff/technicians within 3 hours of venipuncture. Frozen PBMCs will be stored in liquid nitrogen (preferred) or at -80ºC.

At the time of analysis, frozen PBMCs will be brought to 37ºC rapidly via water bath and culture rested overnight (~18 hours) using standard methods before undergoing additional sample processing for analysis by flow cytometry. Cultured PBMCs will be stained with fluorescent antibodies before fixation and analysis using a flow cytometer.

Note: On a case-by-case basis, it may be possible for sites unable to perform PBMC

isolation to make advanced arrangements to ship whole blood samples to the Zamboni Lab at UNC for processing. Ahead of collection, sites should contact Drs. Zamboni and Lucas using the information listed below for confirmation this would be acceptable and to ensure the lab is able to receive and process the samples.

9.3.4.3 Shipping of Specimen(s)

Cryo-preserved PBMC samples for FcγRs analyses should be shipped over night on enough dry ice to guarantee temperature for at least 36 hours to Dr. Zamboni's laboratory at the University of North Carolina. ***Samples should only be batch shipped approximately every 3 months on Monday, Tuesday or Wednesday.*** Samples should ***NOT*** be shipped on Thursday, Friday, Saturday or Sunday.

If prior arrangement has been made to ship samples to UNC for processing, whole blood samples (EDTA/purple-top tubes) should be shipped ambient overnight the day of collection to the address noted below. Samples should be shipped ***Monday, Tuesday, or Wednesday***. If shipment outside of that time frame is deemed necessary, contact the lab ahead of time to determine if alternate arrangements can be made.

Shipping information is as follows:

Attn: Andrew Lucas
Zamboni Lab at UNC
120 Mason Farm Road
1022A Genetic Medicine Building, CB#7361
Chapel Hill, NC 27599
Lab Phone: (919) 966-1622

Please email Drs. Lucas (andrew_lucas@unc.edu) and Zamboni (zamboni@unc.edu) at UNC prior to shipping samples.

9.3.4.4 Site(s) Performing Correlative Study

The MPS- FcγRs assay will only be performed at UNC in the facility listed above. We plan to perform all analyses on the same cytometer. In addition, day-to-day operation and potential instrument-to-instrument variability will be monitored and normalized using MESF calibration beads.

9.3.5 Chemokine Mediators of the MPS

Differences in exposures of CCL2 and CCL5 chemokines can lead to significant variability in MPS function and the ability of MPS cells to take up mAbs and ADCs. The change in MPS function could then affect the PK and PD of anetumab ravtansine. Accordingly, the evaluation of chemokine biomarkers such as CCL2 and CCL5 is critically important to optimizing the treatment of anetumab ravtansine and other ADCs alone and in combination with other agents.

The assay for chemokine biomarkers CCL2 and CCL5 has been validated as an absolute quantitative bead-based Luminex assay against a known standard curve. Data will be obtained on instrumentation as mean fluorescence intensity (MFI).

Known standard concentrations will be plotted against their determined MFI on a log-log plot to generate the standard curve. Patient samples will be analyzed and their corresponding MFI compared to the standard curve to determine unknown concentrations of chemokines.

It is hypothesized that mAbs and ADCs (anetumab ravtansine) are cleared via MPS cells and that chemokine mediators can be used as biomarkers of the MPS and to evaluate patient-specific differences in PK and PD of these agents and drug-drug interactions, especially for regimens combining anetumab ravtansine with other mAbs and immune modulators. Specifically, it is anticipated that patients with lower exposures of CCL2 and CCL5 chemokines will have lower MPS function, slower clearance of anetumab ravtansine and increased risk of significant drug-drug interactions when combined with other mAbs and immune modulators.

The chemokine biomarkers will be used retrospectively to evaluate the mechanisms associated with the variability in the pharmacokinetics and pharmacodynamics of anetumab ravtansine and mechanisms of drug-drug interactions of anetumab ravtansine.

9.3.5.1 Collection of Specimen(s)

Blood will be obtained by venipuncture in a 5 mL serum-separator tube (SST; gold-top). Collected blood samples should be stored at ambient room temperature and upright when possible until processed.

9.3.5.2 Handling of Specimens(s)

Whole blood will be allowed to clot, with the tube standing up-right, for at least 30 minutes at room temperature. It will then be processed into serum via centrifugation at 1,500 x g for 15 minutes at 4ºC. Whole blood should be processed to serum by each clinical site within 3 hours after obtaining the sample from the patient. Based on published literature, chemokines will have begun to significantly degrade if left at ambient temperatures for longer than 3 hours. Sera will be aliquoted into separate tubes (2 mL cryo-vials) and stored at -80ºC.

At the time of analysis, frozen plasma samples will be brought to the UNC Cytokine and Biomarker Core Facility in dry ice for processing. Samples will be stored and processed per Core Facility methods. Plasma samples will be diluted and analyzed per the manufacturer's protocol provided with the analytical kits. Assay results will be returned to Dr. Zamboni's laboratory for analysis.

9.3.5.3 Shipping of Specimen(s)

Frozen serum samples will batched and shipped in enough dry ice to guarantee temperature for at least 36 hours overnight to Dr. Zamboni's laboratory at the University of North Carolina. ***Samples should only be batch shipped every 3 months on Monday, Tuesday or Wednesday.*** Samples should ***NOT*** be shipped on Thursday, Friday, Saturday or Sunday.

Shipping information is as follows:

Attn: Andrew Lucas

Zamboni Lab at UNC
120 Mason Farm Road
1022A Genetic Medicine Building, CB#7361
Chapel Hill, NC 27599
Lab Phone: (919) 966-1622

Please email Drs. Lucas (andrew_lucas@unc.edu) and Zamboni (zamboni@unc.edu) at UNC prior to shipping samples.

9.3.5.4 Site(s) Performing Correlative Study

The CCL2 and CCL5 chemokine assay will only be performed at UNC Cytokine and Biomarker Core Facility. Plasma samples will be analyzed in batches in order to reduce variability due to sample processing issues. Appropriate controls and instrument quality control sample will also be used to address for day-to-day variability.

9.4 Exploratory Correlative Studies

9.4.1 Bim in tumor-reactive T cells (T_{TR})

In order to improve upon the use of tumor cell PD-L1 expression as a predictive biomarker, work has been done to identify the signaling cascade in T cells that follows PD-1 engagement with PD-L1 and to determine if these events are predictive of responses to immunotherapy. The identification of tumor-reactive T cells (T_{TR}) based on the expression of CD8, CD11a and PD-1 (61), and the use of knock-out models and blocking antibodies, led to the identification of Bim as a downstream signaling molecule of the PD-1 pathway (62). High levels of Bim in circulating T_{TR} cells were prognostic of poor survival in patients with metastatic melanoma who did not receive anti–PD-1 therapy, and were also predictive of clinical benefit (i.e. response) in patients with metastatic melanoma who were treated with the PD-1 inhibitor pembrolizumab. Moreover, this circulating T_{TR} cell population significantly decreased after successful anti–PD-1 therapy (62). Accordingly, we hypothesize that Bim expression in T_{TR} will provide a non-invasive means of predicting responses to PD-1 inhibition in mesothelioma.

9.4.1.1 Collection of Specimen(s)

Please draw 10 mL of peripheral blood into an EDTA tube at pre-study, C2D1 and C4D1. Gently invert the tube 8-10 times to mix immediately after collection.

9.4.1.2 Shipping of Specimen(s)

Blood may be shipped overnight at ambient temperature.

Please ship specimens to the address listed below as close to collection date as possible. Please ship samples only ***Monday through Thursday,*** please do not ship samples Friday, Saturday or Sunday. Please call or email Xin (Cindy) Liu to notify her of an impending shipment:

Xin Liu

Mayo Clinic
Guggenheim 406
200 First Street SW
Rochester, MN 55905
Telephone: (507) 266-5004
Email: Liu.Xin2@mayo.edu

9.4.1.3 Site(s) Performing Correlative Study

The assay for Bim in T_{TR} will be completed in Dr. Haidong Dong's laboratory, at the address above, where the assay was developed.

9.4.2 Soluble PD-L1 (sPD-L1)

Given the heterogeneity and dynamics of PD-L1 expression by tumor cells, sPD-L1 is a potential blood-based biomarker that can detect PD-L1 expression when a biopsy does not. sPD-L1 can be detected in the supernatants of many PD-L1-positive cell lines, and that sPD-L1 retains pro-apoptotic signaling properties to T cells (59). sPD-L1 has been detected in patients with renal cell carcinoma, is associated with a more aggressive phenotype (59). A preliminary study also suggests that sPD-L1 is predictive of worse survival in patients with metastatic melanoma. In this clinical trial, we hypothesize that detection of sPD-L1 will correlate with responses to treatment.

The first assay for sPD-L1 was developed in Dr. Dong's laboratory. This assay detects sPD-L1 with a dynamic range of 0.1-10 ng/mL, is specific for PD-L1, and is reproducible with interplate correlation of r^2=0.99.

9.4.2.1 Collection, Handling and Shipment of Specimen(s)

The blood drawn for Bim in T_{TR} will suffice for measurement of sPD-L1. No extra blood needs to be drawn.

9.4.2.2 Site(s) Performing Correlative Study

The assay for sPD-L1 will be completed in Dr. Dong's laboratory, at the address above, where the assay was developed.

9.4.3 Tissue expression of PD-L1

PD-L1 is commonly expressed in MPM and is associated with poor survival (23). Although PD-L1 is thought to provide some degree of prediction for response to inhibition of the PD-1/PD-L1 axis, one of the early phase clinical trials for MPM has identified responders despite lack of detectable PD-L1 (29). This may be due to the heterogeneity and dynamics of PD-L1 expression seen in other malignancies (57, 58), and in preliminary data also occurs in MPM. Due to the uncertainty of the predictive significance of PD-L1 expression in MPM, we would like to measure PD-L1 expression in available archival tissue. Our null hypothesis is that 5% or greater PD-L1 expression is not predictive of response to treatment. Mayo Clinic developed the first immunohistochemical assay for PD-L1 (21, 24), and has since validated the use of the newer PD-L1 clones on archival tissue, including the companion diagnostic for pembrolizumab 22C3.

9.4.3.1 Collection of Specimen(s)

Submission of tissue is mandatory ***if archived tissue is available from a prior biopsy or surgery***; do ***not*** perform a biopsy solely to provide tissue for this correlative. Archival formalin fixed material can be submitted in tumor blocks or in freshly cut sections, depending on availability. Fine needle aspiration (FNA) material is not acceptable. If tissue is provided in sections, unstained slides should be provided: minimum of 3 slides of 4-5 microns thickness. Sections must be mounted on positively charged glass slides (positively charged microscope slides).

Fresh core biopsies may also be provided if a biopsy was performed because archival tissue is not available or sufficient. Do not perform a biopsy solely for this correlative study.

9.4.3.2 Handling of Specimens(s)

For the archival specimens, storage temperatures ranges between 15°C and 25°C are preferred. Samples are expected to be shipped as soon as they are available.

9.4.3.3 Shipping of Specimen(s)

Please ship specimens to the address listed below as close to collection date as possible. Please ship samples only ***Monday through Thursday,*** please do not ship samples Friday, Saturday or Sunday. Please call or email Xin (Cindy) Liu to notify her of an impending shipment.

Xin Liu
Mayo Clinic
Guggenheim 406
200 First Street SW
Rochester, MN 55905
Telephone: (507) 266-5004
Email: Liu.Xin2@mayo.edu

9.4.3.4 Site(s) Performing Correlative Study

PD-L1 expression by tumor cells will be assessed at Mayo Clinic's Pathology Research Core with the 22C3 companion diagnostic.

9.5 Patient-Reported Outcomes Versions of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Assessment

9.5.1 Site Study Team Medidata Patient Cloud ePRO Training

For sites participating in the ePRO pilot, at least one member of the site study team must successfully complete the training to use the Medidata Patient Cloud ePRO, see Appendix D for information about this training.

10. STUDY CALENDAR

Tumor tissue for the mesothelin expression assay is mandatory at pre-registration to establish eligibility for Phase 2 subjects. Pre-study evaluations are to be conducted within 14 days of registration unless stated otherwise. An ophthalmological exam is to be conducted within 28 days prior to the start of protocol therapy. Scans and x-rays must be done < 4 weeks prior to the start of therapy. Windows of ± 1 to 2 days are permissible for cycles 1, 2 and 3; windows of ± 3 days are permissible for cycles 4 and beyond. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-registration (Phase 2 only)	Pre-study	Cycle 1			Cycle 2			Cycle 3			Cycle 4 and higher			Off Study [k]
			Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	
Anetumab ravtansine			A			A			A			A			
Pembrolizumab			B			B			B			B			
Informed consent		X													
Concurrent meds		X	X----------X												
Physical exam [a]		X	X			X			X			X			X
Ophthalmologic exam [b]		X				X			X			X			
Performance status		X	X			X			X			X			X
CBC w/diff, plts		X	X	X	X	X	X	X	X	X	X	X			X
Serum chemistry [c]		X	X	X	X	X	X	X	X	X	X	X			X
TSH, T3, T4 [d]		X	X			X			X			X			X
PT/INR, aPTT		X													
Serum pregnancy [e]		X													
ECG		X				X			X			X			

	Pre-registration (Phase 2 only)	Pre-study	Cycle 1			Cycle 2			Cycle 3			Cycle 4 and higher			Off Study [k]
			Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	
Echo or MUGA [f]		X													
Adverse event evaluation			X----------X												X
Radiologic evaluation/ Tumor measurements		X	Radiologic evaluation and tumor measurements are performed at the end of cycle 3/before cycle 4 begins and every 3 cycles thereafter. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X
Tissue for mesothelin assay [g]	X	X													
Tissue for PD-L1 assay [h]		X													
Blood for PKs and correlative studies [i]		X	X	X		X			X	X		X			
PRO-CTCAE [j]			X	X	X	X	X	X	X	X	X				X

A: Anetumab Ravtansine: ***For all phase 1 and phase 2 group 2 patients***: Dose as determined by the phase 1 study by IV infusion over 60 minutes on day 1 of each cycle for up to 12 months total. Anetumab ravtansine is to be administered prior to pembrolizumab.

B: Pembrolizumab: 200 mg by IV infusion over 30 minutes on day 1 of each cycle for up to 24 months total for all groups.

a: Physical exam at pre-study includes height/weight, vital signs, demographics and medical history. Physical exam at all other visits includes weight and vital signs. Vital signs include pulse, blood pressure and temperature.

b: For all patients at screening then only those randomized to receive anetumab ravtansine: Perform ophthalmologic exam within 28 days prior to Cycle 1 Day 1. The exam will include visual acuity [BCVA according to ETDRS, or Snellen, or Landolt C or other charts], intra-ocular pressure, dry eye test [Schirmer test] and slit lamp. For all subsequent cycles after Cycle 1, visual acuity and a slit lamp examination will be repeated before infusion in every cycle and at safety follow-up visit, or more frequently at investigator's and ophthalmologist's discretion. The IOP measurement is to be repeated during anetumab ravtansine therapy if the

patient receives steroid eye drops for more than 10 days as treatment for corneal epitheliopathy. This measurement is performed at 2 weeks and 6 weeks after the initiation of steroid treatment. If IOP increases by < 7 mmHg, the frequency of IOP evaluation can be reduced to every 4 months. If IOP increases by ≥ 7 mmHg, a medical management plan with follow-up IOP evaluations will be initiated after consultation with an ophthalmologist and investigator. The Schirmer test is performed at baseline and then at C3D1 and C5D1. All these tests may be repeated during treatment at the investigator's discretion.

Note: Ophthalmologic exams do not need to be continued for patients assigned to combination therapy who later discontinue anetumab ravtansine due to non-ocular toxicities.

c: Labs include albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

d: Patients receiving pembrolizumab should be monitored for changes in thyroid function at the timepoints listed in the calendar and as clinically indicated for clinical signs and symptoms of thyroid disorders.

e: Serum pregnancy test for females of childbearing potential.

f. Echocardiogram or Multigated Acquisition Scan (MUGA; radionucleotide angiography) is performed at pre-study and then only as clinically indicated.

g: For Phase 2, submission of a tissue sample at pre-registration is required to perform the mesothelin expression assay to establish eligibility. Archived tumor tissue may be submitted; if archived tumor tissue is not available to establish eligibility, a fresh tumor tissue sample must be obtained by biopsy. If a biopsy is required, it may be performed ≤ 28 days prior to start of therapy. For Phase 1 subjects, submission of archived tumor tissue, if available, is required for mesothelin expression testing. Please refer to Section 9.

h: For subjects in both Phases 1 and 2, submission of a stored tissue sample is mandatory, ***if available***, for the tissue expression of PD-L1: do ***not*** perform a biopsy solely to provide tissue for this correlative. Tumor tissue may be submitted as blocks or slides; please refer to section 9.

i: Blood samples for correlatives are collected as follows (see also Section 9):

1) Phase 1 and Phase 2 Group 2 patients only: Pharmacokinetics of anetumab ravtansine (including anetumab ravtansine ADC, anetumab ravtansine total antibody, and DM4/DM4-Me) on C1D1: pre-treatment, end of anetumab ravtansine infusion (+/- 15 minutes), and 7 hours after the end of anetumab ravtansine infusion (+/- 15 minutes); C1D8: any time. Note: These may be discontinued for patients who discontinue anetumab ravtansine.
2) Phase 1 and Phase 2 Group 2 patients only: Anti-anetumab ravtansine antibodies (including anetumab ravtansine ADA and neutralizing antibodies) pre-dose on Day 1 of Cycles 1, 3, 6 and 9 and pre-dose every 3 months after cycle 9 in the first year and every 6 months in the second year of treatment. Note: These may be discontinued for patients who discontinue anetumab ravtansine.
3) Megakaryocyte Potentiating Factor: pre-study, C2D1, and C4D1.
4) Mononuclear Phagocyte System-FcγR: C1D1, C1D8, C3D1 and C3D8.
5) Chemokine Mediators of Mononuclear Phagocyte System: C1D1, C1D8, C3D1 and C3D8.
6) Bim in Tumor Reactive T cells and soluble PD-L1: pre-study, C2D1, and C4D1.

j: For sites and patients that agree to participate, PRO-CTCAE is completed by ePRO application on patients' personal devices or on a tablet kept at the study site weekly during the first 3 cycles and at off-study. Questionnaires should be administered prior to treatment on days study treatment is administered. See Appendices C and D.

k: Off-study evaluation to be performed at 30 ± 3 days after the last dose of study drug.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using modified pleural RECIST for pleural disease (27) and the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) for non-pleural disease (68). 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.

11.1.1 Schedule of Evaluations

For the purposes of this study, patients should be re-evaluated for response every 9 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4-6 weeks following initial documentation of objective response.

11.1.2 Definitions

11.1.2.1 Evaluable for Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with anetumab ravtansine and pembrolizumab or pembrolizumab.

11.1.2.2 Evaluable for Objective Response

All patients meeting the eligibility criteria who have signed a consent form, have been randomized and have begun treatment will be evaluable for response. These patients will have their response classified according to the definitions stated below

11.1.3 Disease Parameters

11.1.3.1 Pleural Measurable Disease

At baseline, the pleural disease to be measured should have a short-axis diameter of at least 1 cm for at minimum one of the 6 measurements, as lesions < 1 cm are considered non-measurable. Unidimensional measurements of tumor thickness perpendicular to the chest wall or mediastinum should be performed, measured in 2 sites (or positions) at 3 separate levels on transverse cuts of contrast-enhanced CT scan (or MRI). The sum of the measurements which meet the definition of measurable disease defines a pleural unidimensional measure: sum of up to 6 pleural thickness measurements = 1 univariate diameter. Transverse cuts used for measurements must be at least 1 cm apart and related to anatomical landmarks in the thorax as determined by the reviewer during baseline assessment by means of appropriate markers these cuts are chosen to allow reproducible assessment at later time points. If measureable tumor is present, transverse cuts in the upper thorax, above the level of division of the main bronchi are

preferred. At reassessment, pleural thickness must be measured at the same position at the same level and by the same observer, whenever possible. This is not necessarily the greatest tumor thickness at that level.

Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If there is demonstrable progression following radiation, then a previously irradiated lesion may be included as measurable.

11.1.3.2 Extra-Pleural Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

11.1.3.3 Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm (≥ 1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

11.1.3.4 Non-Measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm [< 1 cm] or pathological lymph nodes with ≥ 10 to < 15 mm [≥ 1 to < 1.5 cm] 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.

11.1.3.5 Target Lesions

All measurable lesions including the sum of the pleural thickness measurements and 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.

11.1.3.6 Non-Target Lesions

Any other lesions (or sites of disease) beyond the 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.

11.1.4 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.

11.1.4.1 Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) 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.

11.1.4.2 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.

11.1.4.3 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 (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), 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.

11.1.4.4 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.

11.1.4.5 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.

11.1.4.6 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.

11.1.4.7 Tumor Markers

Tumor markers alone cannot be used to assess response.

11.1.4.8 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.

11.1.4.9 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.

11.1.4.10 Measurement at Follow-up Evaluation

A subsequent scan must be obtained at least 4 weeks (within 8 weeks but not less than 4 weeks apart) following initial documentation of an objective status of either complete response (CR), partial response (PR), or preliminary progression (PD) for confirmation.

11.1.5 Response Criteria

11.1.5.1 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 (<1 cm).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum 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 (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

Due to the natural evolution of MPM, an isolated new pleural or pericardial effusion should be only considered as a new lesion and thus calling for PD in case it is substantial, cytological malignancy is confirmed and the patient had not had any pleural or pericardial effusion history before treatment. However, any isolated new or significant increases in existing pleural or pericardial effusions in a stable or responding patient, without any other evidence of progression, is insufficient evidence to call progression.

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

11.1.5.2 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 [<1 cm] 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).

11.1.5.3 Evaluation of Overall Objective Status

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

For Patients with Measurable Disease

Target Lesions	Non-Target Lesions	New Lesions	Previous Overall Objective Status –Preliminary PD	Overall Objective Status
CR	CR	No	N/A	CR
CR	Non-CR/ Non-PD Not Evaluated	No	N/A	PR
PR	Non-CR/ Non-PD/ Not evaluated	No	N/A	PR
SD	Non-CR/ Non-PD/ Not evaluated	No	N/A	SD
PD	Any	Yes or No	No	Preliminary PD
PD	Any	Yes or No	Yes	PD (Confirmed)
Any	Unequivocal PD	Yes or No	No	Preliminary PD
Any	Unequivocal PD	Yes or No	Yes	PD (Confirmed)
Any	Any	Yes	No	Preliminary PD
Any	Any	Yes	Yes	PD (Confirmed)
Not All Evaluated	CR Non-CR/ Non-PD Not evaluated	No	N/A	Not Evaluated (NE)

For Patients with Non-Measurable Disease

Non-Target Lesions	New Lesions	Previous Overall Objective Status –	Overall Objective Status

		Preliminary PD	
CR	No	N/A	CR
Non-CR/Non-PD	No	N/A	Non-CR/ Non-PD
Not all evaluated	No	N/A	Not evaluated
Unequivocal PD	Yes or No	No	Preliminary PD
Unequivocal PD	Yes or No	Yes	PD (Confirmed)
Any	Yes	No	Preliminary PD
Any	Yes	Yes	PD (Confirmed)

Preliminary Progressive Disease (PD)

All of the following must be true:

a. Progressive Disease defined in Section 11.5.1 and 11.5.2 in the target lesions and non-target lesions, or appearance of new lesions.
b. No substantial clinical decline.

Confirmed Progressive Disease (PD)

Patients without substantial clinical decline who meet all the following would have confirmed PD as their overall object status:

a. Previously considered Preliminary PD.
b. Repeating imaging at least 4 weeks apart after initial imaging shows progressive disease.

Confirmed complete response (CR) or partial response (PR)

A subsequent scan must be obtained at least 4 weeks (within 8 weeks but not less than 4 weeks apart) following initial documentation of an objective status of either complete response (CR), partial response (PR), or preliminary progression (PD) for confirmation.

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

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

11.1.6 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 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 first date that progressive disease is objectively documented taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.7 Progression-Free Survival

PFS is defined as the duration of time from start of treatment until the first date that progressive disease is objectively documented or death from any cause, whichever occurs first.

11.1.8 Response Review

For trials where the response rate is the primary endpoint, it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach. For this trial, review by the local investigator will be sufficient.

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

For the phase 1 portion of this study, the Protocol Principal Investigator will have at least monthly, or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and adverse events and unanticipated problems.

During the randomized phase 2 portion of the study, the Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

12.2 Data Reporting

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account, and
- Assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.
    - To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type,
    - To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR, and
    - To hold Rave Read Only role, site staff must hold an Associates (A) registration type.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Rave section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/clinicalTechnologies/National-Cancer-Institute-NCI-11. On-site audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

For ePRO-CTCAE data, once a patient electronically submits the responses, the data is transmitted from the device into the Rave database. There are no documents to audit. The electronic responses are the source documentation.

PRO-CTCAE is not intended for expedited reporting, real time review or safety reporting. PRO-CTCAE data are exploratory and not currently intended for use in data safety monitoring or adverse event stopping rules.

12.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will

be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the recommended phase 2 dose (RP2D), and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

12.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave

Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

12.4 CTEP Multicenter Guidelines

Not applicable

12.5 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said

other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). -Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

12.6 Genomic Data Sharing Plan

Not applicable

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

13.1.1 Overview

This is a phase 1 safety run-in and randomized phase 2 study designed to evaluate the safety and efficacy of the addition of anetumab ravtansine to pembrolizumab for patients with mesothelin positive malignant pleural mesothelioma. The study will utilize a randomized phase 2 study design to determine the anti-tumor activity of combination therapy with anetumab ravtansine and pembrolizumab (Group 2; experimental group) as compared to pembrolizumab alone (Group 1; control group), where response will be evaluated based on the modified pleural RECIST for pleural disease.

13.1.2 Primary Endpoint

The primary endpoint of the phase 1 safety run-in is the randomized phase 2 dose of anetumab ravtansine with combination of pembrolizumab.

The primary endpoint of the randomized phase 2 is the confirmed tumor response rate, which will be compared between the two groups. A confirmed tumor response rate defined as 100% times the number of eligible patients who have started the treatment and whose objective tumor status was a CR or PR on 2 consecutive evaluations at least 4 weeks apart (using RECIST v1.1 criteria) divided by the number of eligible patients who have started the treatment. All patients meeting the eligibility criteria who have signed a consent form, have been randomized and have begun treatment will be evaluable for overall response.

13.1.3 Statistical Design

13.1.3.1 Phase 1 Safety Run-In

A phase 1 safety run-in will be performed after the first 6 patients have been accrued to the safety lead-in portion of the study at dose level 1 and observed for one cycle. If 2 or more of the first 6 patients experience a DLT as defined in Section 5.2.1, then the starting dose level will be adjusted and additional cohorts may be evaluated at dose levels -1 and -2 as described below. Accrual will be halted while evaluating each cohort in the safety lead-in analysis.

- Dose level 1: Six evaluable patients will be accrued onto dose level 1 and observed until they complete two cycles of treatment. If 0 or 1 out of 6 patients experience a DLT, accrual will continue in the phase 2 portion at dose level 1 after the expansion cohort per Section 13.2.2. If 2 or more patients experience a DLT on dose level 1, the toxicity level for dose level 1 will be considered unacceptable and six additional patients will be treated on dose level -1.

- Dose de-escalation to dose level -1: If dose level 1 has an unacceptable level of toxicity, six evaluable patients will be accrued onto dose level -1. If 0 or 1 out of 6 patients experience a DLT on dose level -1, accrual will continue in the phase 2 portion at dose level -1 after the expansion cohort per Section 13.2.2. If 2 or more patients experience a DLT, the toxicity level for dose level -1 will be considered unacceptable and six additional patients will be treated on dose level -2.

- Dose escalation to dose level -2: If dose level -1 has an unacceptable level of toxicity, six evaluable patients will be accrued onto dose level -2. If 0 or 1 out of 6 patients experience a DLT on dose level -2, accrual will continue in the phase 2 portion at dose level -2 after the expansion cohort per Section 13.2.2. If 2 or more patients experience a DLT, the toxicity level for dose level -2 will be considered unacceptable and accrual to the study will be temporarily closed, evaluated and potentially amended.

The simulations below demonstrate the chance of the design to select a dose with an acceptable probability of DLT of 0.2.

	Dose Level				
	1 (6.5 mg/kg)	-1 (5.5 mg/kg)	-2 (4.5 mg/kg)	No selection %	Ave # of pts
True DLT rate	0.2	0.1	0.05		
Select %	68	30	2	0	8.04
# pts treated	6	1.92	0.12		
True DLT rate	0.4	0.2	0.1		
Select %	31	49	18	2	11.34
# pts treated	6	4.14	1.20		
True DLT rate	0.5	0.4	0.2		
Select %	14	19	43	24	15.18
# pts treated	6	5.16	4.02		

13.1.3.2 Expansion Cohort

Once the final dose level is determined, an additional 6 patients will be enrolled to the final dose level to ensure safety. If 2 or less out of the 12 patients experience a DLT, this dose level will be determined as the safe dose for the randomized phase 2 study. If 3 or more than 3 patients experience a DLT, this dose level will considered unacceptable and accrual to the study will be temporarily closed, evaluated and potentially amended. With a maximum of 12 patients at the randomized phase 2 dose, the probability of observing at least one grade 3 or higher AE is 86% when the true

rate of such AE is 15% for the combination arm.

13.1.3.3 Randomized Phase 2 Study

Decision Rule: A randomized phase 2 trial comparing combination therapy with anetumab ravtansine and pembrolizumab as compared to pembrolizumab alone will be conducted, once a safe combination of doses is identified. We will enter 49 evaluable patients on each arm (98 total) of the study using a 1:1 randomization scheme utilizing the permutated block procedure, where patients are stratified based on ECOG performance score (0 vs. 1). A sample size of 49 patients per arm provides 80% power to detect an improvement in response rate from 20% to 40%, using a one-sided test at a significance level of 0.10. The baseline response rate of 20% is based on a prior study[73]. In addition, this trial implements a group sequential design with a single interim analysis, adopting the Rho family (Rho=2) beta spending function for controlling the overall type II error rates. The interim and final analysis boundaries and characteristics were generated using the East 6 clinical trial software program (version 6.4, Cytel Inc.).

The Z-score will be calculated for testing the null hypothesis that the difference of response rates between two arms is equal to zero, based on the normal approximation with pooled variance of standardized test statistics. The study design will be implemented as follows:

Interim Analysis Decision Rule: An interim analysis will be performed for futility. After the first 25 patients randomized into each arm (the first 50 patients in both arm) become evaluable for the primary endpoint, if the z-score is less than -0.072, we will terminate accrual and consider this early evidence that the experimental arm does not have a higher overall response rate and accrual will be terminated. Otherwise, we will continue accrual.

Final Decision Rule: If the interim analysis criteria are met for full accrual, a total of 49 evaluable patients per arm will be enrolled into this study. At the final analysis, it will be concluded that the experimental arm (combination therapy) is superior to the control arm (pembrolizumab alone), if the z-score is greater than 1.282. This will be considered sufficient evidence that the experimental arm may be recommended for further testing in subsequent studies. Otherwise, we will conclude that there is no statistical evidence of superiority of the experimental regimen (combination therapy).

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

NOTE: The trial will not be halted while the first 25 patients in each group are evaluated for the interim analysis. However, if the accrual is especially rapid, we may temporarily suspend accrual to prevent missing important acute toxicity patterns.

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

Power and Significance Level: Assuming that the response rate is binomially distributed in each group, the operating characteristics of the current design can be tabulated according to various true difference of the proportions, including the probabilities of the experimental arm (combination therapy) is superior to control arm (pembrolizumab alone), i.e. power which warrants further studies on experimental regimen, and probabilities of stopping the trial early due to futility of the experimental regimen.

If the true difference of proportion is	**-0.1**	**0**	**0.1**	**0.2**	**0.3**
Then the probability of declaring that the experimental regimen warrants further studies is…	0.004	0.009	0.424	0.805	0.970
*Probability of stopping at the interim analysis due to futility is…	0.805	0.458	0.183	0.051	0.009

*Probabilities are based on simulation study with 50,000 replicates

13.2 Analysis Plan

The analysis for this trial will commence at planned time points and at the time the patients have become evaluable for the primary endpoint. Such a decision will be made by the Statistician and Study Chair, in accord with ETCTN Standard Operating Procedures, availability of data for secondary endpoints (e.g. laboratory correlates), and the level of data maturity.

13.2.1 Phase1 Safety Run-in Primary Analysis

All patients that have received any amount of the combination anetumab ravtansine and pembrolizumab will be evaluable for toxicity. Please note this is different from the definition of evaluable for dose-limiting toxicity (DLT) where patients who cannot complete the planned dose due to reasons other than toxicity will be replaced.

13.2.2 Randomized Phase 2 Primary Endpoint Estimation

The proportion of successes will be estimated in each group by the number of successes

divided by the total number of evaluable patients. Confidence intervals for the true success proportion will be calculated in each arm. Comparison of confirmed response rates between the two treatment groups will be performed using a one-sided z-test with pooled variance at significance level 0.10.

13.3 Sample Size/Accrual Rate

13.3.1 Sample Size

The phase 1 safety lead-in is expected to require a minimum of 12 patients and a maximum of 24 patients. The randomized phase 2 portion of this study is expected to require a minimum of 50 and a maximum of 98 evaluable patients. We anticipate accruing an additional 12 patients during the phase II portion of the trial to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, the phase II portion is expected to accrue a maximum of 110 patients and overall sample size will be a maximum of 134 patients.

13.3.2 Accrual Rate and Study Duration

The anticipated accrual rate is approximately 4-5 patients per month. Therefore, the accrual period for phase 2 portion is expected to be about 34 months. The final analysis can begin approximately 39.5 months after the phase 2 portion begins, i.e. as soon as the final patient randomized to this trial has been followed for at least 18 weeks.

13.3.3 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender or ethnic origin.

There is no information currently available regarding differential effects of this regimen in subsets defined by race or gender, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

Based on prior studies involving similar disease sites, we expect about 20-25% of patients will be classified as minorities by race and about 40% of patients will be women. The expected sizes of racial by gender subsets are shown in the following table:

PLANNED ENROLLMENT REPORT

Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	1	2	0	0	**3**

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
Asian	1	1	0	0	**2**
Native Hawaiian or Other Pacific Islander	0	1	0	0	**1**
Black or African American	1	3	0	0	**4**
White	36	51	7	10	**104**
More Than One Race	3	6	4	7	**20**
Total	**42**	**64**	**11**	**17**	**134**

13.4 Stratification Factors

13.4.1 For the randomized phase 2: ECOG performance score: 0 vs. 1

13.5 Analysis of Secondary Endpoints

13.5.1 Duration of Response

Duration of response is defined for all evaluable patients who have achieved a response as the date at which the patient's objective status is first noted to be a PR or CR to the earliest date progression is objectively documented. If a patient has not had disease progression, they will be censored on the date of their last disease assessment. The distribution of duration of response will be estimated using the method of Kaplan-Meier. The comparison of duration of response between two treatment arms will be based on the log-rank test. This calculation will start with the date of start of treatment.

13.5.2 Overall Survival

Overall survival is defined as the time from the start of treatment to death due to any cause. The distribution of survival time will be estimated using the method of Kaplan-Meier. The comparison of overall survival between two treatment arms will be based on the log-rank test.

13.5.3 Progression Free Survival

Progression free survival is defined as the start of treatment to the earliest date that

disease progression is objectively documented or death due to any cause. The distribution of progression-free survival will be estimated using the method of Kaplan-Meier. The comparison of progression-free survival between two treatment arms will be based on the log-rank test.

13.5.4 Adverse Events

All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed for each arm to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration. The overall adverse event rates for Grade 3 or higher hematologic and non-hematologic adverse events at least possibly related to treatment will be compared between the two treatment groups using the Chi-square test (or Fisher's exact test if the data in the contingency table is sparse).

13.5.5 The Pharmacokinetics of Anetumab ravtansine

The analysis of the pharmacokinetics of anetumab ravtansine (including anti-drug conjugate (ADC) anetumab ravtansine, total antibody, DM4 (BAY 1006640) and DM4-Me (BAY 1006641)) will be largely descriptive. Changes over time will be plotted and assessed for each patient.

13.5.6 Megakaryocyte Potentiating Factor (MPF)

The test for MPF is quantitative and continuously distributed. A reference value will be provided and samples with tumor antigen MPF levels above the reference value will be considered positive. The relative changes in biomarker levels will be compared by best overall response groups using the non-parametric Wilcoxon rank-sum test. Also, the associations between changes in MPF levels and ordered response categories (i.e. CR-PR-SD-PD) will be assessed with the Jonckheere-Terpstra test for trend.

13.5.7 MPS-FcγRs and chemokine mediators of MPS

The mean equivalent soluble fluorophore (MESF) and antibody bound to cell (ABC) will be determined for each specimen. Linear regression will be used to explore the linear relationship between the continuous values of these MPS-FcγRs probes and anetumab ravtansine levels.

The concentrations of CCL2 and CCL5 will be determined for each specimen. Linear regression will be used to explore the linear relationship between the continuous values of these chemokines and anetumab ravtansine levels.

13.6 Analysis of Exploratory Endpoints

13.6.1 Measurements of Bim in T_{TR} as a predictor of responses to treatment.

Based on previous experiences with the distribution of Bim in T_{TR}, it is anticipated that a non-parametric test such as the Mann-Whitney test should be used to compare Bim in T_{TR} between subjects that do and do not respond to therapy.

13.6.2 Measurements of soluble PD-L1 as a predictor of responses to treatment.

Based on previous experiences with the distribution of sPD-L1, it is anticipated that a non-parametric test such as the Mann-Whitney test should be used to compare sPD-L1 between subjects that do and do not respond to therapy.

13.6.3 PD-L1 expression in archival tissue as a predictive marker of response to pembrolizumab-based therapy.

We will compare whether there is a difference in the number of responders with 50% or greater PD-L1 tumor cell expression and those without with the Chi-square test (or Fisher's exact test if the data in the contingency table is sparse).

13.6.4 PRO-CTCAE
Protocol investigators should provide appropriate analysis of the data and account for missing data.

13.7 Data and Safety Monitoring

13.7.1 DSMB Review

The principal investigator and the study statistician will review the study at least every quarter to identify accrual, adverse event, and any endpoint problems that might be developing. The accrual and safety data provided by Theradex for this trial will be reviewed and monitored by the Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) at least twice a year, or more frequently as warranted.

13.7.2 PRO-CTCAE
PRO-CTCAE data should not be used in adverse event stopping rules.

13.7.3 Phase 2 Adverse Event Stopping Rule

The stopping rule applies to each group independently.

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

Accrual will be temporarily suspended to both groups if at any time we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as "possible," "probable," or "definite") that satisfy either of the following:

- if 4 or more patients in the first 20 treated patients in either group experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.

- if after the first 20 patients have been treated, 25% of all patients in either group experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.

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

After consideration by the Principal Investigator and the statisticians and consultation with CTEP and CIRB, a decision will be made as to whether and how the study will proceed.

13.8 Reporting and Exclusions

13.8.1 PRO-CTCAE

Refer to Appendices C and D for PRO-CTCAE references.

13.8.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those

who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Sub analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active 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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers, and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, anetumab ravtansine and pembrolizumab. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Anetumab ravtansine interacts with specific enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

- The enzymes in question are **CYP3A4/5 and 2D6**. Anetumab ravtansine is broken down by these enzymes and may be affected by other drugs that inhibit or induce these enzymes. Strong inhibitors and inducers of CYP3A4 are prohibited within 2 weeks of the start of and during treatment with anetumab ravtansine.
- The protein in question is P-gp. Anetumab ravtansine is moved in and out of cells/organs by this transport protein.
- Anetumab ravtansine is highly protein bound. Patients receiving other medications that are also highly protein bound may need to be monitored more frequently.

<u>To the patient:</u> Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Anetumab ravtansine and pembrolizumab may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Anetumab ravtansine must be used very carefully with other medicines that use certain ***liver enzymes or transport proteins to be effective or to be cleared from your system.*** Before you

enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered ***strong inducers/inhibitors of CYP3A4/5, 2D6 or P-gp***.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- You may need to be monitored more frequently if you are receiving other medications that are also highly protein bound.
- Do not eat or drink grapefruit juice, grapefruit, or Seville oranges while taking anetumab ravtansine.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is

_____ and he or she can be contacted at

_____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **anetumab ravtansine.** This clinical trial is sponsored by the NCI. Anetumab ravtansine may interact with drugs that are ***processed by your liver or use certain transport proteins in your body***. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- You may need to be monitored more frequently if you are receiving other medications that are also highly protein bound.
- Do not eat or drink grapefruit juice, grapefruit, or Seville oranges while taking anetumab ravtansine.

Anetumab ravtansine interacts with ***specific liver enzyme called CYP3A4/5,2D6 and transport protein P-gp*** and must be used very carefully with other medicines that interact with ***these enzymes or transporter.***

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered ***strong inducers/inhibitors of CYP3A4/5, 2D6 or transporter P-gp.***
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____.

APPENDIX C: PRO-CTCAE QUESTIONNAIRE

PRO-CTCAE is intended to enhance the quality of adverse event data reporting in clinical trials, provide data that complements and extends the information provided by clinician reporting using CTCAE, represent the patient perspective of the experience of symptomatic adverse events, and improve detection of potentially serious adverse events.

The selection of PRO-CTCAE should be complementary to the clinician identified AEs for ongoing monitoring.

Adverse Events Specific to Protocol 10107 / MC1721:

System/ Organ/ Class	Anetumab ravtansine Adverse Event term from IB	Pembrolizumab (MK-3475) Adverse Event term from CAEPR	Possible Related PRO-CTCAE Items	Attributes
Eye Disorders	Corneal toxicity syndrome		**Blurred vision**	Severity, Interference
Gastrointestinal Disorders	Diarrhea	Diarrhea	**Diarrhea**	Frequency
	Nausea	Nausea	**Nausea**	Frequency, Severity
	Vomiting		**Vomiting**	Frequency, Severity
General Disorders	Fatigue	Fatigue	**Fatigue**	Severity, Interference
Metabolism and Nutrition Disorders	Decreased appetite		**Decreased appetite**	Severity, Interference
Musculoskeletal Disorders		Arthralgia	**Joint pain**	Frequency, Severity, Interference
Nervous System Disorders	Neuropathy peripheral		**Numbness and tingling**	Severity, Interference
Skin and Subcutaneous Tissue Disorders		Pruritus	**Itching**	Severity
		Rash maculopapular	**Rash**	Present/Absent

Please refer to the PRO-CTCAE Terms of Use website at https://healthcaredelivery.cancer.gov/pro-ctcae/terms_of_use.html for more information.

References

• PRO-CTCAE Website: https://healthcaredelivery.cancer.gov/pro-ctcae/
• PRO-CTCAE Items Library

- PRO-CTCAE NCI Scientific Leadership Team
- PRO-CTCAE Development Team
- Publications

Study Specific PRO-CTCAE Questionnaire: All subjects on the study will receive the same PRO-CTCAE questions as listed below. **For this study, questions will be administered via ePRO and thus will be formatted for electronic delivery.**

NCI PRO-CTCAE ™ ITEMS

Item Library Version 1.0
English
Form Created on 15 December 2020

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days…

1a. In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
1b. In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
O Not at all	OA little bit	O Somewhat	O Quite a bit	O Very much

2a. In the last 7 days, how OFTEN did you have NAUSEA?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
2b. In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

3a. In the last 7 days, how OFTEN did you have VOMITING?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
3b. In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

4a. In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly

5a. In the last 7 days, did you have any RASH?	
O Yes	O No

6a. In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

The PRO-CTCAE™ items and information herein were developed by the Division of Cancer Control and Population Sciences in the NATIONAL CANCER INSTITUTE at the NATIONAL INSTITUTES OF HEALTH, in Bethesda, Maryland, U.S.A. Use of the PRO- CTCAE™ is subject to NCI's Terms of Use.

7a. In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
7b. In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

8a. In the last 7 days, what was the SEVERITY of your BLURRY VISION at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
8b. In the last 7 days, how much did BLURRY VISION INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

9a. In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
9b. In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
9c. In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

10a. In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
10b. In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

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Population Sciences in the NATIONAL CANCER INSTITUTE at the NATIONAL INSTITUTES OF HEALTH, in Bethesda, Maryland, U.S.A. Use of the PRO- CTCAE™ is subject to NCI's Terms of Use.

OTHER SYMPTOMS	
Do you have any other symptoms that you wish to report?	
O Yes	O No
Please list any other symptoms:	
1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe

The PRO-CTCAE™ items and information herein were developed by the Division of Cancer Control and Population Sciences in the NATIONAL CANCER INSTITUTE at the NATIONAL INSTITUTES OF HEALTH, in Bethesda, Maryland, U.S.A. Use of the PRO- CTCAE™ is subject to NCI's Terms of Use.

APPENDIX D: MEDIDATA RAVE ePRO INFORMATION

Optional Electronic Completion of PRO-CTCAE Assessments

Missing data are a significant problem, particularly for PRO-CTCAE assessments. Unlike data for traditional endpoints, such as survival, PRO-CTCAE data cannot be accurately obtained retrospectively if it is not provided by the patient at the appropriate time point. This limits researchers' ability to accurately perform PRO-CTCAE statistical analyses and negatively impacts the clinical relevance of this effort.

Typically, PRO-CTCAE forms are filled out in hardcopy (paper). To provide a more convenient method of completing PRO-CTCAE assessments, NCI, Theradex and the CTSU are working with Medidata Rave's ePRO Cloud product that offers patients on this study the option of completing their PRO-CTCAEs questionnaires electronically using an application (app) downloaded to their smart phone or from a tablet that has the ePRO app with Internet access.

ePRO Operational Information for Protocol Appendices (06/27/2017)

1. Introduction

Electronic collection of patient-reported outcomes (ePRO) through Medidata Patient Cloud ePRO is preferred but not mandatory. Patients who will be submitting PRO data via Patient Cloud ePRO must be registered to Patient Cloud ePRO by an authorized site user after the patient has been registered to the study. Patients may use their own device or a tablet maintained at the site.

A site-specific tablet may be used for multiple study participants. If a site-specific tablet is used, CRAs need to setup the tablet for multiple users. Multi-user mode lets multiple study participants log in to Patient Cloud ePRO with their passwords or their PIN codes on the same device. Section 4 provides instruction on setting the Patient Cloud ePRO App to Multi-User Mode.

2. CRA Site Users

Site users of Patient Cloud ePRO require the same access as Rave. Access to the trial in the Patient Cloud ePRO is granted through the iMedidata. Site users will receive an invitation to Patient Cloud ePRO and the site user must accept the invitation to begin patient registration. Users who have not previously activated their iMedidata/Rave account at the time of initial approval of site registration will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Please note, site users will not be able to access the study in the Patient Cloud ePRO until all required Rave and study specific trainings are completed.

Additional information on iMedidata/Rave is available on the CTSU members' website under the

Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

3. CRA Patient Registration Instructions for ePRO

Please visit the Medidata Learning Tool for reference information on Patient Cloud ePRO for CRAs. https://learn.mdsol.com/patient-cloud/en/video-library-for-providers-102101952.html

i. The subject registration process starts in iMedidata. Begin by selecting the Patient Cloud ePRO Registration link for your study
ii. The patient management app will display, select your STUDY and SITE from the drop downs and click Launch.
iii. Now you can register your first patient. Create a subject ID and select a Country / Language from the drop down, (these are the only required data fields). The subject initials are optional, but are helpful in identifying which subject ID maps with which activation code. When finished, click Add.
iv. The subject added and will include the date the patient was added, the subject ID, subject initials, (if included) and a unique auto-generated activation code. The activation code is unique for each patient and linked to the subject ID, it is not interchangeable. In addition, there is a status section, which indicates if the patient has registered. When the patient has registered the status will change from "invited" to "registered".

4. CRA Instructions for Setting the Patient Cloud ePRO App to Multi-User Mode

Sites conducting studies entirely on premise, where participants travel to the sites to fill out questionnaires, can use multi-user mode. Multi-user mode lets multiple study participants log in to Patient Cloud with their passwords or their PIN codes on the same device. If patients will be using devices supplied by the institution, site staff will need to help the patient to access the device if the device is locked.

The study provider will download the Patient Cloud ePRO app to the device and set the Patient Cloud ePRO App to multi-user mode if applicable.

To switch from personal mode (default setting) to multi-user mode:

1. Tap **About** at the bottom of the log in screen.
2. Scroll to the bottom and tap **Advanced User**.
3. Tap **Mode** and then select **Multi-User**.
4. Tap **Yes** to confirm.
5. Tap the back arrows to return to the log in screen.

Note: If enabling multi-user mode on a device, it is highly recommended that completion reminders are turned off on that device. For a video demonstration, see Show Me How to Switch to Multi-User Mode.

5. Patient Users

To use the Patient Cloud ePRO, patients will need to use their own device (IOS, Android phone or tablet). Short term data will only appear on the patient's device until responses are completed and submitted. The patient data will import directly into the database once the patient selects the "Submit" button and will no longer be visible on the patient's device.

6. Patient Instructions for Accessing the Patient Cloud Using Your Personal Device

Downloading the Patient Cloud ePRO App

If you are using your personal device, and you do not have the Patient Cloud ePRO app, use the following instructions. When downloading the app, you must use the Apple ID or Google account associated with the device. If the Patient Cloud ePRO app is already on the device, or if you are using a provider's device, you can skip this section.

You will need an email address that you agree to use for this purpose. The e-mail address is needed to identify you on the Patient Cloud Application and for you to receive notifications to let you know when forms are due. Your e-mail address will only be used for this survey study, and will not be used for mail or marketing purposes.

If you decide to use the electronic method to complete the questionnaires, and do not have an e-mail address, you may sign up for one at no charge at many different websites. A few sites that are commonly used and will allow you to create an email address very easily are Yahoo, Gmail, and Outlook.

For iOS:
1. An Apple ID is required for downloading the Patient Cloud ePRO app.
2. Tap the App Store icon.
3. Search for Medidata Patient Cloud and follow the installation instructions.

Note: Patient Cloud ePRO is listed as an iPhone App in the App store. When using an iPad, please view the search results under iPhone apps.

For Android:
1. A Google account is required for downloading the Patient Cloud ePRO app
2. Tap the Play Store icon.
3. Search for Medidata Patient Cloud and follow the installation instructions.

Registering

You must register in order to complete and submit your study forms. When you register, you will create a username, which is your email address, and a password that allows you to log in to the Patient Cloud ePRO app.

Note**:** You must have an activation code to begin this process. If you do not have an activation code, please contact your provider.

There are two possible ways to register. Your provider may have sent you a link to a web address where you may register from any web browser, including the one on your device. The other way to register is on the Patient Cloud ePRO app.

1. If registering from the Patient Cloud app, tap Register on the bottom of the log in page. If registering on the web, open the URL shield.imedidata.com on a web browser.
2. Enter your activation code and tap Activate.
3. On the next page, read the instructions and tap Next.
4. Read the privacy notice and tap I agree. Then tap OK to confirm.
5. Enter and confirm your email address. Tap Next.
6. Enter and confirm your password. Tap Next.
7. Choose a security question by scrolling through the dropdown menu to display the question of your choice.
8. Enter your security question response.
9. Tap Create my account to complete your registration.

If you registered on the Patient Cloud ePRO app, it automatically logs you out. If you registered on the web, you are presented with the option to download the Patient Cloud ePRO app. You can then proceed to log in with the credentials you created.

Logging in to the App

1. Enter your Email and Password that you created during the registration process. (If you previously set a PIN code, just enter your four-digit PIN.)
2. Tap Log in.

   Note: If you do not remember your password, tap **Forgot Password**, and follow the instructions provided

Setting a PIN Code

The first time you log in to the Patient Cloud ePRO app, you are given the option to create a PIN code. A PIN code allows you to bypass the step of entering your email and password every time you need to log in to the Patient Cloud ePRO app. Instead, you can enter a four-digit PIN.

1. If you wish to set a PIN code the first time you log in, tap Yes when prompted.
2. Note: You can also set your PIN at a later time by tapping the options menu on the top left of most pages and selecting Set PIN.
3. Enter a four-digit PIN.
4. Re-enter the four-digit PIN to confirm.

If you forget your PIN code, tap **Forgot PIN** and you can access the app using your email and password. You may reset your PIN by tapping the options menu on the top left of most pages and selecting Set PIN.

Resetting Your Password

You can reset your password by using the options menu at the top left of most pages.

1. Tap the options menu icon.
2. Tap Reset Password.
3. Follow the instructions to reset your password.

Completing and Submitting Forms

Once logged in, forms related to your study display on the Tasks page. If you are enrolled in multiple studies, select the appropriate study first, and then select a form. New forms can appear on the Tasks page at any time, depending on how the study is designed.

There are two types of forms displayed on the Task List page:

- *Scheduled Forms* (with a icon): These forms have a "Due Date" indicator in them so you are aware of the last day by which you will need to complete the form. If the form is due in less than one day, you will see the due time in hours.
- *Anytime Forms* (with a + icon): These forms have "Last Completed Time" indicator on them which tells the most recent date or time when you completed the form. If you start a form, but do not complete it, you will see an 'Incomplete" status beneath the form name, along with a half-moon icon.

1. Select the appropriate form.
2. Follow the on-screen instructions until you reach the end of the form where you are given the opportunity to review and change your responses prior to submitting.
3. Review your responses by scrolling down the list.
4. If you need to change an answer, tap the question to go back and change the answer.
5. When you are ready to submit, tap Submit Your Data.

Note: Once a form is submitted, you will be unable to edit any of your responses. In some cases, you may be asked to acknowledge your submission by entering your password.

7. Patient Compliance

The patient data imports directly from a device into the Rave database. There are no documents to audit. The patient-submitted electronic responses are the source documentation.

8. Security

All data is encrypted on the device (256 bit encryption and Hyper Text Transfer Protocol Secure [https]) and the app requires each user to have a unique username and password for access. If the user is idle for too long (5 minutes inactivity time), the app will time out and the user will need to log in again.

The data will only reside on the device for a short period of time. Once the user clicks "Submit," the data is securely transferred over HTTPS between the device and internal relay to the Rave database. Except for the patient's email address, no identifying information is stored in iMedidata. The email address is stored for what purpose? The patient's email links the device (used) and (ePRO) account to where the data is stored. The patient's email is not visible to anyone in the system.

The Patient information (email/password) does not reside in Medidata Rave EDC and the patient accounts are hidden in iMedidata from sites and LPOs.

The Patient Cloud ePRO application is 21 CFR Part 11 compliant and acts as a gateway between the device and Medidata Clinical Cloud (MCC).

Messages and information communicated to and from the Patient Cloud ePRO are encrypted and therefore this information cannot be read if intercepted while in transit.

9. Checklist for Activities Prior to Consenting a Patient

Contact the LPO to request appropriate Rave access to register patients in Patient Cloud ePRO
Accept study invitation at iMedidata.com
- Note: you must be rostered in RSS and have received an invitation to Patient Cloud ePRO

Complete required eLearning
Verify the IOS or Android operating system is using the most current version
Verify Patient Cloud ePRO app is using the most current version
If using institutional shared devices, first patient only: Verify Patient Cloud ePRO app is in Multi-User mode
Refer to Review Quick Reference Guides for videos and other procedural information

https://learn.mdsol.com/patient-cloud/en/video-library-for-providers-102101952.html

APPENDIX E: SOP for Cryo-preservation of PBMCs for Quantification of FcγRs & PBMC PK Studies

Collection of Specimen(s): Blood samples (20 mL) will be obtained using K2 EDTA (purple-top) tubes. These whole blood samples will be processed to PBMCs to measure the number of FcγRs on the surface of MPS cells (CD14+ monocytes and DCs) and pharmacokinetic exposure of anetumab ravtansine in PBMC. In brief, whole blood will be processed to PBMCs using density- gradient centrifugation, then aliquoted into 4 separate cryo-vials (~5 million cells in each cryo-vial) and stored under cryo-preservation. If fewer cells are collected that cannot meet the ~5 million cells per tube, tubes should be aliquoted as to create as many 5 million cell vials as possible (e.g., three vials with 5 million cells and one with 2 million cells; or two vials with 5 million cells and one with 3 million cells, etc.) A more thorough description of the PBMC processing is detailed below:

1. Prepare LeucoSep tube
    a. Warm-up Ficoll medium to room temperature (RT) protected from light.
    b. Fill the Leucosep tube with Ficoll medium using the syringe and needle: 15 ml when using tubes 227 290.
    c. Close the LeucoSep tubes containing the separation medium with the screw-cap and centrifuge for 30 seconds at 1000 x g at RT.
2. Prepare Wash Media (all under aseptic technique)
    a. Warm/thaw 100 mL FBS-HI, and 5 mL of antibiotic concentrate (e.g. Gibco Pen/Strep/Glutamine 100x) in a 37ºC water bath.
    b. Transfer all thawed reagents and 500 mL RPMI media (no phenol red) container into the hood using ethanol. RPMI media can be cold for the purposes of cryo-preservation.
    c. Remove and discard 105 mL of RPMI media from the bottle.
    d. Add 100 mL of FBS-HI and 5mL of antibiotic concentrate to the media bottle. Mix thoroughly.
    e. Bring final RPMI/20%FBS/(+)Abx media bottle to 4°C. This can also be aliquoted frozen at -20°C for longer term storage, then thawed as needed.
3. Prepare Freezing Media (all under aseptic technique)
    a. In a 15 mL conical tube, add 9 mL of the cold Wash media (RPMI/FBS/Abx media) prepared earlier under aseptic technique.
    b. Slowly add 1 mL of DMSO to the tube and mix thoroughly.
    c. Store RPMI/FBS/Abx/DMSO media on ice or at 4°C until used.
4. PBMC Specimen Processing
    a. Pour 20 mL of DPBS into the previously prepared LeucoSep tubes.
    b. Pour the anticoagulated blood sample (~20mL K2 EDTA; thus a 2:1 dilution) directly from the vacutainer into the LeucoSep tube. The sample volume should be
    c. ~40 mL in this example.
    d. Place the screw cap on the LeucoSep tube and invert gently 3-4x to mix the blood sample.
    e. Centrifuge for 15 minutes at 800 x g at RT in a swinging bucket rotor. Switch-off

brakes of the centrifuge.

f. Aspirate and discard roughly half of the plasma above the interphase/PBMC layer.
g. Harvest the enriched cell fraction (lymphocytes / PBMCs) by means of a Pasteur pipette or by pouring the supernatant above the porous barrier from the Leucosep tube into another 50 mL centrifugation tube.
h. Wash the enriched cell fraction with 10 ml of cold Wash Media, subsequently centrifugate for 10 minutes at 250 x g at 4°C.
i. Aspirate and discard the supernatant.
j. Repeat the washing step twice with 5 mL of cold Wash Media, subsequently centrifugate for 5 minutes at 250 x g at 4°C.
k. Aspirate and discard the supernatant.
l. Re-suspend cell pellet using 4 mL of Freezing Media (RPMI/FBS/Abx/DMSO) previously prepared and stored on ice. Avoid making bubbles.
m. Distribute 1 mL (roughly 5 million cells/mL) of cell suspension into each of four cryo-vials.
n. Each cryovial tube [e.g. Corning 2 mL externally-threaded cryo-vial (Corning catalog #430659). Alternatively, any brand of cryovial can be used as long as the cryovial is externally threaded) should be marked on a temperature-resistant label with the following mandatory information:
    i. Study Number
    ii. Subject Sequence Number
    iii. Time point
    iv. Date sample drawn and processed
    v. Sample Type (PBMC)
    vi. Cell number
    vii. Freezing Volume

Handling of Specimen(s): Each vial should be put in a pre-chilled slow freezing container (e.g. Mr. Frosty) to guarantee that the temperature drops 1 degree/minute, and put it in -80°C freezer for 18-72 hours prior to storing them in a cryogenic storage unit (liquid nitrogen in the vapor phase; roughly -140°C) using a properly labelled cryogenic storage box. All vials should be transferred to cryogenic storage if possible. Otherwise, cells should be removed from the slow freezing container (e.g. Mr. Frosty) and stored at -80°C using a properly labelled cryogenic storage box.

Shipping of Specimen(s): Ship according to instructions in Section 9.3.4.3.