A Phase 2b, Randomized, Double-blind Study Comparing Tremelimumab to Placebo in Second- or Third-line Treatment of Subjects with Unresectable Pleural or Peritoneal Malignant Mesothelioma

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List of Abbreviations

Abbreviation or Specialized Term	Definition
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immune deficiency syndrome
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine transaminase
APC	antigen-presenting cell
AST	aspartate transaminase
AUC	area under the concentration-time curve
AZ DES	AstraZeneca Data Entry Site
β-hCG	beta-human chorionic gonadotropin
B7.1	CD80
B7.2	CD86
BPI-sf	brief pain inventory-short form
BUN	blood urea nitrogen
CD	cluster of differentiation
CD45RO	protein tyrosine phosphatase, receptor type C
CIS	carcinoma in situ
CL	Clearance
Cmax	peak concentration
Cmax,ss	steady-state peak concentration
Cmin	trough concentration
Cmin,ss	steady-state trough concentration
CNS	central nervous system
CR	complete response
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CSR	clinical study report
CT	computed tomography
CTLA-4	cytotoxic T lymphocyte-associated antigen 4
CXCL10	C-X-C motif chemokine 10
DCR	disease-control rate
DEHP	bis (2-ethylhexyl) phthalate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECG	Electrocardiogram

Abbreviation or Specialized Term	Definition
ECL	electrochemiluminescence assay
ECOG	Eastern Cooperative Oncology Group
EDTA	edetate dehydrate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EPS	EORTC prognostic factors
ePRO	electronic patient-reported outcome
EQ-5D-3L	EQ-5D 3 level version
EQ-VAS	EQ visual analog scale
EU	European Union
FCGR2B	Fc gamma receptor 2 B
FGF	fibroblast growth factor
FOXP3	forkhead box P 3
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GMP	Good Manufacturing Practice
hCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HPF	high power field
HR	heart rate
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN	Interferon
IGF	insulin-like growth factor
IgG2	immunoglobulin G2
IL	Interleukin
IRB	Institutional Review Board
irAE	immune-related adverse event
IRE	immediately reportable event
irRC	immune-related response criteria
ITT	Intent-to-treat
IV	intravenous(ly)
IXRS	interactive voice or web response system
LCSS-Meso	Lung Cancer Symptom Scale-mesothelioma
LDH	lactate dehydrogenase
LIF	leukemia inhibitory factor

Abbreviation or Specialized Term	Definition
mAb	monoclonal antibody
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
miRNA	micro ribonucleic acid
MRI	magnetic resonance imaging
MSD	Meso Scale Discovery
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PD1	programmed cell death 1
PD-L1	programmed cell death 1 ligand 1
PES	Polyethersulfone
PFS	progression-free survival
PK	pharmacokinetic(s)
PP	Per-protocol
PR	partial response
PRO	patient-reported outcome
PSA	prostate specific antigen
PVC	polyvinylchloride
PVDF	polyvinylidene fluoride DRF
q3 months	every 3 months
Q4W	every 4 weeks
Q12W	every 12 weeks
QoL	quality of life
QTc	the time between the start of the Q wave and the end of the T wave corrected for heart rate
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
SID	subject identification
SMC	Safety Monitoring Committee
SMRP	soluble mesothelin-related protein
SOCS3	suppressor of cytokine signaling 3

Abbreviation or Specialized Term	Definition
SUSAR	suspected unexpected serious adverse reactions
t½	half-life
TIMP1	tissue inhibitor of metalloproteinase 1
Tmax	time to peak concentration
Tmax,ss	time to steady-state peak concentration
TNF	tumor necrosis factor
TOTM	tri octyl trimelitate
T-reg	regulatory T lymphocytes
TSH	thyroid stimulating hormone
ULN	upper limit of normal
USA	United States of America
US FDA	United States Food and Drug Administration
VEGF	vascular endothelial growth factor
Vss	volume of distribution at steady-state
WBC	white blood cell

Study Abstract

TITLE

A Phase 2b, Randomized, Double-blind Study Comparing Tremelimumab to Placebo in Second- or Third-line Treatment of Subjects with Unresectable Pleural or Peritoneal Malignant Mesothelioma

OBJECTIVES

The primary objective is to compare the overall survival (OS) between the 2 treatment arms (tremelimumab and placebo) in subjects with unresectable malignant mesothelioma.

Secondary objectives are:

- To estimate and compare OS rate at 18 months between the 2 treatment arms;
- To estimate and compare the durable disease-control rate (DCR) between the 2 treatment arms;
- To estimate and compare the progression-free survival (PFS) between the 2 treatment arms;
- To evaluate the effect of tremelimumab on patient-reported outcomes (PROs) including disease-related symptoms, pain symptoms, and time to deterioration of disease-related symptoms;
- To estimate and compare the overall response rate (ORR) and duration of response between the 2 treatment arms;
- To describe the safety and tolerability of tremelimumab in treated subjects;
- To evaluate the immunogenicity of tremelimumab in treated subjects;
- To describe the pharmacokinetics (PK) of tremelimumab in treated subjects.

Exploratory objectives are:

- To estimate and compare durable DCR, PFS, ORR, and duration of response based on immune-related response criteria (irRC) between the 2 treatment arms;
- To examine health-related QoL, disease-related symptoms, pain, and health status in subjects with durable clinical activity;
- To examine biomarkers and their association with tremelimumab treatment and clinical outcome.

STUDY DESIGN

This is a Phase 2b, randomized, double-blind, placebo-controlled study in adults with unresectable pleural or peritoneal malignant mesothelioma who have progressed after previous receipt of 1 or 2 prior systemic treatment regimens that included pemetrexed (or other anti-folate) in combination with a platinum agent. For subjects in whom pemetrexed was contraindicated or not tolerated or not an approved therapy (eg, peritoneal mesothelioma), prior therapy with a first-line platinum-based regimen is required. Though the number of subjects not receiving prior pemetrexed is expected to be small, the proportion of such subjects enrolled in the study will be capped at 20%. Subjects will be randomized in a 2:1 ratio to receive either tremelimumab or placebo. Randomization will be stratified by the European Organization for Research and Treatment of Cancer (EORTC) status (low-risk vs high-risk), line of therapy (second vs third), and anatomical site (pleural vs peritoneal). Approximately 564 subjects will be enrolled at approximately 180 study centers in multiple countries.

Following review of the primary analysis data from Study D4880C00003 which demonstrated no statistically significant improvement in overall survial of tremelimumab compared with placebo in subjects with unresectable malignant mesothelioma, the sponsor recommended that all patients remaining on study treatment were unblinded. After unblinding, all patients will have the option to discontinue study treatment and withdraw from the study, or continue on the study as detailed below, depending on the study arm that they were originally on.

Patients currently receiving tremelimumab who, in the opinion of the investigator, are receiving clinical benefit will be given the option to continue to receive tremelimumab. These patients can continue to receive study treatment until a study discontinuation criterion (eg, withdrawal of consent) has been met as assessed by the investigator. Investigators will report all SAEs to the sponsor until 90 days after receipt of their last dose of study treatment. Drug accountability data will also be collected.

Patients who have discontinued tremelimumab and have completed the 90-day safety follow-up are to be withdrawn from study at the earliest opportunity and no further data will be collected from these patients after withdrawal.

Patients currently receiving placebo or those who have discontinued placebo are expected to withdraw from the study. Investigators will report all serious adverse events to Medimmune until date of withdrawal from study.

SUBJECT POPULATION

The subjects in this study will be male or female adults with unresectable pleural or peritoneal malignant mesothelioma who have progressed after no more than 2 prior systemic treatment regimens for advanced malignant mesothelioma.

TREATMENT REGIMEN

Tremelimumab is to be administered as an intravenous (IV) solution of 10 mg/kg at a rate of 250 mL/hr. Subjects will receive one dose of investigational product every 4 weeks (Q4W) for 6 doses, followed by doses every 12 weeks (Q12W) unless permanent discontinuation criteria are met.

ASSESSMENT OF ENDPOINTS

The primary endpoint is OS which is defined as the time from randomization until death due to any cause. For subjects who are alive at the time of data cutoff for the primary analysis or lost to follow-up, OS will be censored on the last date when subjects are known to be alive. The distribution of OS times will be estimated using the Kaplan-Meier method (Kaplan and Meier, 1958). The primary comparison of the 2 treatment arms will be performed after 456 OS events (deaths) have been observed by a stratified log-rank test with 3 stratification factors, at an overall 2-sided significance level of 0.05. In addition, the hazard ratio (HR) of tremelimumab vs placebo and its 95% confidence interval (based on profile-likelihood method) will be estimated by stratified Cox regression model with ties handled by the Efron method (Efron, 1977). The primary analysis will be based on the Intent-to-treat (ITT) Population.

The secondary efficacy endpoints include OS rate at 18 months, durable DCR, PFS, PROs, ORR, and duration of response, based on modified Response Evaluation Criteria in Solid Tumors (RECIST) for pleural mesothelioma and RECIST criteria v1.1 for peritoneal mesothelioma.

Patient-reported outcomes will be assessed using the Lung Cancer Symptom Scale-mesothelioma (LCSS-Meso) for disease-related symptoms and health-related QoL, the brief pain inventory-short form (BPI-sf) for pain, and the EQ-5D 3 level version (EQ-5D-3L) for health status.

The safety endpoints include adverse events (AEs) and SAEs, changes from baseline in clinical laboratory evaluations, electrocardiograms (ECGs), and vital signs. Adverse events and SAEs will be assessed for severity and relationship to investigational product.

The immunogenic potential of tremelimumab will be analyzed descriptively by summarizing the number and percentage of subjects who develop detectable anti-tremelimumab antibodies. The immunogenicity titer will be reported for samples confirmed positive for the presence of anti-tremelimumab antibodies. The effect of immunogenicity on PK, pharmacodynamics, and safety will be evaluated.

Pharmacokinetics of tremelimumab will be assessed by estimating PK parameters after the first and steady-state doses using a non-compartmental analysis approach. A population PK model will be developed using a non-linear mixed-effects modeling approach in subjects with malignant mesothelioma. The impact of physiologically-relevant subject characteristics (covariates) and disease on PK will be evaluated. The relationship between tremelimumab blood exposure and OS or safety will be evaluated.

INTERIM ANALYSIS

Two interim analyses are planned to assess futility and superiority of OS. The first interim analysis will be performed after 128 OS events (deaths) are observed from the first 180 subjects randomized, with the futility analysis based on these 180 subjects and efficacy analysis based on all subjects randomized up to this time. The second interim analysis will be performed after 342 OS events (75% of the total 456 OS events) have been observed. The futility boundary at the first interim is based on predictive power being less than 10% (corresponding approximately to HR = 1). The interim and final efficacy boundaries are based on O'Brien-Fleming type flexible alpha spending methods (Jennison and Turnbull, 1999) and are presented in the following table if the two interim analyses occur at exactly 50% and 75% information time, respectively ( ).

Table 1-1 Futility and Efficacy Boundaries at Interim and Final Analyses

Analysis	# of OS events (% of information)	Futility and Efficacy Boundary
Interim 1	Futility: 128 OS events from first 180 subjects	Futility boundary: predictive power < 10% (HR ≈1)
	Efficacy: all OS events (≈ 228 [50]) from all randomized subjects at this time	Efficacy boundary: 2-sided p < 0.0030 (HR ≈ 0.66)
Interim 2	342 (75)	2-sided p < 0.0184 (HR ≈ 0.76)
Final	456 (100)	2-sided p < 0.0440 (HR ≈ 0.82)

The actual efficacy boundaries at 2 interim and final analyses will be adjusted according to the actual number of observed events at each analysis time so that the overall type I error is controlled at 2-sided 0.05 level.

SAMPLE SIZE AND POWER CALCULATIONS

The planned sample size for this study is approximately 564 subjects, which is based on the group sequential design with 2 planned interim analyses. Subjects will be randomly assigned to the tremelimumab and placebo arms in a 2:1 ratio. If the interim boundaries specified for the interim analysis are not crossed, then the final analysis will take place after observing a total of 456 OS events (deaths). The 2-sided significance level for the final analysis will be determined by O'Brien-Fleming type flexible alpha spending function. For example it is 0.0440 (corresponding approximately to HR = 0.82) under scenario presented in Table 1-1.

The sample size and power calculations are based on a simulation method under a non-proportional hazard model that accounts for the potential delayed treatment effect for immunotherapy. Assuming exponential distribution of OS with a median time of 7 months for placebo (Krug et al, 2011) and 4-month delayed effect (ie, HR = 1 for the first 4 months and HR = 0.56 thereafter) for tremelimumab (Roberts et al, 2011), a total of 456 OS events (deaths) are required to provide approximately 90% power at the overall 2-sided alpha level of 0.05 with two planned interim analyses. The detailed simulation description will be provided in the SAP.

With a planned accrual period of 32 months (approximately 15 subjects/month for the first 12 months and 19 subjects/month thereafter) , it is expected that a total of 564 subjects are needed in order to observe 456 OS events at an approximate follow-up period of approximately 10 months. The 128 OS events from the first 180 subjects needed for the first interim analysis are expected to be reached after approximately 12 months of accrual and 11 months of follow-up. The 342 OS events for the second interim analysis are expected to be reached after approximately 32 months of accrual.

1 INTRODUCTION

1.1 Disease Background

Mesothelioma is a rare malignant tumor originating from the cells lining the surface of the coelomic cavities of the body, specifically the pleura, peritoneum, pericardium, and tunica vaginalis testis. Pleural mesothelioma is the most common anatomical site (67% to 75%) of presentation, followed by peritoneal (25% to 33%) (van Meerbeeck et al, 2011). Therapies for both types employ similar first-line treatment regimens with peritoneal mesothelioma having a slightly better prognosis than pleural mesothelioma. Mesothelioma is classified into 3 broad histological subtypes: epithelioid, sarcomatoid, and biphasic, comprising approximately 50% to 70%, 10% to 20%, and 20% to 40% percent of malignant mesothelioma, respectively. Patients with the sarcomatoid or biphasic subtype have a poor outcome compared to the epithelioid subtype (Musk et al, 2011).

Mesothelioma is mainly caused by occupational exposure to asbestos (eg, mining, industry) and as a result is most prevalent in men. Due to the long latency of the onset of disease after exposure to asbestos (mean 40 years after exposure, range 15 to 67; van Meerbeeck et al, 2011), mesothelioma typically develops in the sixth or seventh decade of life. There are prominent differences in the incidence of mesothelioma reported from different countries worldwide, with annual incidence rates varying from 7 cases per million inhabitants in Japan to 40 per million in Australia. The incidence in the United States of America (USA) is estimated to be approximately 15 cases per million (Robinson and Lake, 2005). In Europe the incidence is approximately 20 cases per million with large inter-country variation. These differences are assumed to be due to differences in historical asbestos exposure. Due to a lack of accurate tools and of a curative treatment, screening for mesothelioma - even in populations at risk - is currently not recommended (Pass and Carbone, 2009).

The clinical presentation of malignant mesothelioma varies according to the anatomical site of onset of the tumor. For pleural mesothelioma, the most common clinical symptoms at the time of diagnosis are shortness of breath and chest-wall pain (60% of patients) (Robinson and Lake, 2005). The natural history of pleural mesothelioma is further characterized by progressive local expansion and invasion of contiguous organs. Invasion of the thoracic wall with its intercostal nervous structures causes chest pain (costo-pleural syndrome) and the development of chest wall lumps. Loco-regional progression of the tumor results in loco-regional symptoms, such as pneumonia, superior vena cava syndrome, Pancoast or Horner's syndrome, dysphagia, heart tamponade, and arrhythmias. Peritoneal mesothelioma is characterized by multiple variably sized nodules throughout the abdominal cavity. As the disease progresses, the nodules become confluent to form plaques or masses, or to uniformly cover peritoneal surfaces

(van Meerbeeck et al, 2011), thus causing ascites, constipation, or even bowel obstruction. In most patients, death eventually occurs as a result of loco-regional progression within the thoracic or abdominal cavity. Clinical lymphatic and hematogenous dissemination occurs only late in the natural history of mesothelioma but is fairly common in autopsy series. Constitutional symptoms (eg, fatigue, hyperhidrosis, and weight loss) are usually late symptoms.

The average interval between onset of mesothelioma symptoms and diagnosis is 2 to 3 months (Robinson and Lake, 2005). Nearly 75% to 80% of the patients will be diagnosed with unresectable disease. Mesothelioma has a dismal prognosis: median survival of untreated cases is 6 to 9 months with less than 5% of patients surviving 5 years. Prognostic factors associated with better outcome are earlier stage and epithelioid histological type, as well as asymptomatic disease, better performance status, younger age, and absence of weight loss. The European Organization for Research and Treatment of Cancer (EORTC) published guidelines for a prognostic scoring system (Curran et al, 1998). Edwards et al validated the EORTC and Cancer and Leukaemia Group B scoring systems and compared them (Edwards et al, 2000).

In the last few years a number of articles have examined the role of asbestos in causing immunosuppression and immune dysfunction. This immunosuppression appears to be mainly driven by a hyper-activation of regulatory T cells (T-reg) and an over-production of interleukin (IL)-10 and tumor necrosis factor (TNF)-β, leading to an inhibition of T cells (cluster of differentiation [CD]8+ and CD4+) and natural killer (NK) cells (Maeda et al, 2010; Kumagai-Takei, 2011; Robinson et al, 2011). Multiple studies involving preclinical models and subjects with mesothelioma have demonstrated an overall immunosuppressive environment in this cancer and have shown that T-reg cells in the tumor microenvironment are important for tumor initiation, promotion, and progression.

Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4, CD152) is a cell-surface receptor expressed primarily on activated T cells. Upon T-cell activation, CTLA-4 expression is upregulated and acts to dampen immune responses, modulating and eventually switching off T-cell activation. The natural ligands for CTLA-4 are B7.1 (CD80) and B7.2 (CD86), which are present on antigen-presenting cells (APCs). Binding of B7 ligands to CTLA-4 delivers a negative regulatory signal to T cells. In animal models of cancer, blockade of this negative signal results in enhanced T cell immune function and antitumor activity. Additionally, nonclinical and clinical studies conducted to date involving immunostimulatory agents show benefits in subjects treated with immunopotentiating cytokines, including interferons (IFNs) and IL-2, and provide the basis for using anti-CTLA-4 therapy in other types of cancer (Bograd et al, 2011).

In the advanced disease setting, cisplatin and pemetrexed combination therapy has become the established first-line treatment for pleural mesothelioma based on an approximate 3-month increase in median overall survival (OS) in patients treated with pemetrexed and cisplatin versus cisplatin alone (12.1 months vs 9.3 months, respectively) (Vogelzang et al, 2003). There is no approved treatment for peritoneal mesothelioma; however, pemetrexed and cisplatin are commonly used in first-line treatment regimens. In second-line treatment, no therapies have shown survival benefits (Ceresoli et al, 2010) and no agents are currently approved for pleural or peritoneal mesothelioma after progression from first-line treatment. As a result, a significant unmet medical need exists in this disease setting.

1.2 Tremelimumab Background

Tremelimumab is briefly described below. Refer to the current Investigator's Brochure for details.

1.2.1 Product Derivation

Tremelimumab is a human immunoglobulin G2 (IgG2) kappa monoclonal antibody (mAb) that is directed against the CTLA-4 and blocks its interaction with B7.1 and B7.2. Tremelimumab is produced in cell culture by a NS0 (murine myeloma) cell line and has an overall molecular weight of approximately 149 kDa including oligosaccharides. Tremelimumab blocks the inhibitory effect of CTLA-4, and therefore enhances T cell activation.

1.2.2 Summary of Nonclinical Experience

In vitro, specific mAbs directed against CTLA-4 enhance T-cell function, measured by increased production of IL-2, IFN-γ, and other cytokines. In CTLA-4 knock-out mice, extensive, polyclonal lymphoproliferation develops that is consistent with dysregulated activation of lymphocytes. Treatment of tumor-bearing mice with anti-mouse CTLA-4 mAb (9H10) can induce antitumor immunity and markedly enhance T-cell-mediated killing of various mouse solid tumors. At a concentration of approximately 30 μg/mL 9H10, anti-tumor activity of 9H10 was observed in vivo. Thus, a concentration of ~ 30 μg/mL was identified as the target plasma concentration for anti-CTLA-4 antibodies.

1.2.2.1 Pharmacokinetics

The pharmacokinetics (PK) of tremelimumab were evaluated in cynomolgus monkeys following single (0.75, 10, 30, and 100 mg/kg) and multiple (5 to 50 mg/kg weekly) intravenous (IV) administrations. The PK of tremelimumab is characterized by a low plasma clearance (CL 4.32 mL/day/kg), small volume of distribution at steady-state (V_{ss} 53.8 mL/kg), and

long half-life (t½ 9.1 days). In toxicologic studies in cynomolgus monkeys, systemic exposures of tremelimumab, assessed by the mean peak observed concentration (C_{max}) and mean area under the concentration-time curve (AUC), increased dose-proportionally within the dose ranges examined following single or multiple IV administrations. No evidence of nonlinear PK or gender-related differences in exposures were observed. Anti-drug antibody (ADA) responses were detected in some animals from all dose groups following single or multiple IV administrations of tremelimumab. Finally, PK and ADA responses of clonally- and nonclonally-derived tremelimumab were comparable.

1.2.2.2 Toxicology

The toxicology program conducted for tremelimumab consisted of in vivo general toxicology studies in cynomolgus monkeys for up to 6 months duration, an embryo-fetal development study in monkeys, tissue cross-reactivity studies in both monkey and human tissues, and blood compatibility studies. Overall, tremelimumab toxicities were consistent with inhibition of CTLA-4 and with clinical safety findings, and indicated that chronic clinical use of tremelimumab may lead to adverse effects on the gastrointestinal tract, skin, lymphoid organs, thyroid tissues, and hematological systems. Dose-limiting toxicities (DLTs) were identified in chronic toxicity studies in monkeys and include persistent diarrhea microscopically correlated with mononuclear cell inflammation in the cecum, colon, and/or duodenum, weight loss, and development of adverse skin conditions (scabbed areas; open sores; swollen eyelids; dry, scaly, or crusted skin; rash or reddened skin; yellowish skin) accompanied histologically with mononuclear cell inflammation. Most toxicities were reversible or showed a trend towards reversibility.

An embryo-fetal development study was conducted in pregnant cynomolgus monkeys during the period of organogenesis. Tremelimumab was administered IV once weekly from Day 20 to 50 of gestation at doses of 0 (control), 5, 15, or 30 mg/kg. Tremelimumab did not elicit maternal toxicity, developmental toxicity, or teratogenicity.

1.2.3 Summary of Clinical Experience

As of the data cutoff date of 30Aug2013, 15 sponsored clinical studies have been conducted as part of the tremelimumab clinical development program. Of these studies, 13 have been completed and 2 are ongoing. Tremelimumab has been administered as monotherapy to subjects participating in 10 of the 15 clinical studies, 2 of which are ongoing. In total, 973 subjects with a variety of tumor types have been treated with tremelimumab monotherapy in the completed studies.

Across the clinical development program for tremelimumab, a pattern of efficacy has emerged, also observed for the related anti-CTLA-4 antibody, ipilimumab (YERVOY®), which appears to be consistent across tumor types for this class of agents. Response rates to anti-CTLA-4 antibodies are generally low, approximately 10%. However, in subjects who respond, the responses are generally durable, lasting several months even in subjects with aggressive tumors such as refractory metastatic melanoma. In a single-arm, second-line Phase 2 study (Study A3671008) of tremelimumab administered at 15 mg/kg q3months to patients with refractory melanoma, a response rate of 7% and median OS of 10 months in the second-line setting (as compared to approximately 6 months with best supportive care) was observed (Kirkwood et al, 2010). In a randomized, open-label, first-line Phase 3 study of tremelimumab (administered at 15 mg/kg q3 months) versus chemotherapy (dacarbazine or temozolomide) in metastatic melanoma (Study A3671009), results of the final analysis showed a response rate of 11% and median OS of 12.58 months in this first-line setting (as compared to 10.71 months with standard chemotherapy) (Ribas et al, 2008). Additionally, in a Phase 2 study in non-small cell lung cancer, the tremelimumab arm showed a 22.7% progression-free survival (PFS) at 3 months, while the best supportive care arm showed an 11.9% PFS at 3 months (Study A3671015).

In some patients treated with tremelimumab or other anti-CTLA-4 agents, responses can be preceded by an apparent progression of their disease that may be caused by increase in tumor size due to infiltration of immune cells or related immune processes. This makes the utilization of conventional response criteria limited. Overall, the impact on conventionally-defined PFS can be small; however, the durable response or stable disease (SD) seen in a proportion of patients can lead to significant prolongation of OS. The adverse event (AE) profile across the tremelimumab clinical program is explained by the mechanism of action of anti-CTLA-4 activating of the immune system and thereby AEs are mostly inflammatory in nature. In subjects treated with tremelimumab monotherapy, the events reported at a frequency of ≥ 5% and assessed by the investigator as related to treatment (listed in descending order of frequency) included diarrhea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite, headache, abdominal pain, and colitis. Of these, the events of diarrhea, rash, and pruritus are considered as identified risks. Infusion-related AEs are rare. Acute renal failure was seen in subjects who received the combination of tremelimumab and sunitinib in a Phase 1 study in patients with metastatic renal cell carcinoma; however, acute renal failure has not been an expected AE for single-agent tremelimumab.

In an Italian investigator-sponsored Phase 2 study (Calabro et al, 2012) in subjects with advanced malignant mesothelioma, 29 subjects with previously treated advanced mesothelioma received tremelimumab at a dose of 15 mg/kg every 12 weeks (Q12W). Clinical activity has

been reported with 2 subjects experiencing durable partial response (PR) (including one that occurred after initial progressive disease [PD]). Disease control was noted in 9 (31%) subjects. For the 29 subjects, median PFS was 6.2 months and median OS was 10.7 months. The 1 year survival was 48.3% and survival was 36.7% at 2 years. Twenty-seven subjects (93%) reported at least one Grade 1 2 treatment-emergent AE (mainly cutaneous rash, pruritus, colitis, or diarrhea), and 4 subjects (14%) reported at least one Grade 3 4 treatment-emergent treatment-related AEs (2 colitis or diarrhea events, 1 peripheral neuropathy event, 1 increased ALT event, 1 increased AST event and 1 increased amylase or lipase event). An increase in CD4+, ICOS+ T cells was detected on Days 14, 30, and 60 (p 0.03 at Day 60) of the first cycle of treatment in patients who achieved disease control as compared with non-responders. Given the encouraging results of tremelimumab in mesothelioma, an extension study where tremelimumab is given at 10 mg/kg every 4 weeks (Q4W) for 6 doses followed by doses of 10 mg/kg Q12W, a dosing regimen that has been shown to produce higher tremelimumab exposure and potentially improved survival and long-term outcomes in melanoma subjects, was initiated. This extension study has completed enrollment.

1.3 Research Hypothesis

The primary objective of this study is to compare the OS of subjects with unresectable malignant pleural or peritoneal mesothelioma treated with tremelimumab compared to placebo. Secondary objectives include comparisons of durable disease-control rate (DCR), PFS, patient-reported outcomes (PROs), overall response rate (ORR), duration of response, and safety in subjects treated with tremelimumab versus placebo.

The research hypothesis is that in subjects with unresectable pleural or peritoneal malignant mesothelioma receiving best supportive care, tremelimumab will reduce the risk of death by approximately 29% (hazard ratio 0.71) over placebo while maintaining an acceptable safety profile. A reduction in the risk of death by 29% will be both statistically significant and clinically meaningful, as there are no available therapies that offer an OS benefit in second- or third-line pleural or peritoneal malignant mesothelioma.

1.4 Rationale for Study Conduct

Patients with pleural or peritoneal malignant mesothelioma who fail first-line treatment have a significant unmet medical need given their poor prognosis, lack of any approved agent in this disease setting, and absence of a clinically meaningful OS benefit with existing salvage regimens. Mesothelioma resulting from asbestos exposure may have an immune-mediated component and so an agent such as tremelimumab that blocks CTLA-4 may lead to enhanced T cell immune function and antitumor activity. Preclinical and clinical studies conducted to date

involving immunomodulators such as interferons and IL-2 demonstrated clinical activity and provide the basis for using anti-CTLA-4 therapy in cancer (Bograd et al, 2011). The pooled analysis of the Phase 2-3 melanoma studies showed a positive correlation between OS and exposure, with higher exposure showing better survival. This effect was consistent even in the multivariate analyses controlling for confounding factors (eg, LDH, CRP level, M1c status, etc). The PK modeling suggests that a higher exposure can be reached with 10 mg/kg Q4W dosing. Data suggesting tremelimumab could augment activation of the human immune system in malignant mesothelioma, the high unmet medical need in this disease setting (second/third line), and the activity seen to date in the recently published Italian investigator-sponsored Phase 2 study of tremelimumab in malignant mesothelioma collectively support the expansion of the current MedImmune-sponsored study in malignant mesothelioma utilizing the 10 mg/kg Q4W dose and schedule, which may provide for better OS and long-term outcomes in this patient population.

1.5 Benefit-risk and Ethical Assessment

In the nonclinical setting, treatment of tumor-bearing mice with anti-mouse CTLA-4 mAb (9H10) induced antitumor immunity and markedly enhanced T cell-mediated killing of various mouse solid tumors. Clinical trials of tremelimumab, and of the related anti-CTLA-4 antibody ipilimumab, in melanoma suggest activity (improved survival) of these agents in melanoma. Tremelimumab has also shown activity (objective responses and prolonged disease stabilization) in the recurrent malignant mesothelioma setting at doses of 15 m/kg Q12W, with results suggesting that tremelimumab may lead to improved survival with 48.3% of subjects alive at 1 year and 36.7% of subjects alive at 2 years. Outcomes may be improved with the revised dose of 10 mg/kg due to anticipated increased exposure.

Overall, tremelimumab nonclinical toxicities were consistent with inhibition of CTLA-4, with adverse effects noted for the gastrointestinal tract, skin, lymphoid organs, thyroid tissues, and hematological systems. Dose-limiting toxicities identified in chronic toxicity studies in monkeys included skin rash and gastrointestinal effects. Most toxicities were reversible or showed a trend towards reversibility.

The profile of AEs from > 1000 treated subjects and the spectrum of event severity are consistent with the pharmacologic class and with the signal observed in nonclinical toxicology studies. Adverse events have been observed in every organ system and are mainly due to the inflammation caused by tremelimumab's mechanism of action. The most frequent AEs involve skin, the gastrointestinal tract, and endocrine system, and are usually mild in nature. Events reported at a frequency of ≥ 5% and assessed by the investigator as related to treatment (listed in descending order of frequency) were diarrhea, rash, pruritus, fatigue, nausea, vomiting,

decreased appetite, headache, pyrexia, abdominal pain, and colitis. Infusion-related AEs were rare. Diarrhea, rash, and pruritus have been classified as identified risks for tremelimumab.

Overall, the observed benefit-risk profile supports the further investigation of tremelimumab in the patient population chosen for this study.

2 STUDY OBJECTIVES

2.1 Primary Objective

To compare the OS between the 2 treatment arms (tremelimumab and placebo) in subjects with unresectable malignant mesothelioma.

2.2 Secondary Objectives

1. To estimate and compare OS rate at 18 months between the 2 treatment arms;
2. To estimate and compare the durable DCR between the 2 treatment arms;
3. To estimate and compare the PFS between the 2 treatment arms;
4. To evaluate the effect of tremelimumab on PROs including disease-related symptoms, pain symptoms, and time to deterioration of disease-related symptoms;
5. To estimate and compare the ORR and duration of response between the 2 treatment arms;
6. To describe the safety and tolerability of tremelimumab in treated subjects;
7. To evaluate the immunogenicity of tremelimumab in treated subjects;
8. To describe the PK of tremelimumab in treated subjects.

2.3 Exploratory Objectives

1. To estimate and compare durable DCR, PFS, ORR, and duration of response based on immune-related response criteria (irRC) between the 2 treatment arms;
2. To examine health-related QoL, disease-related symptoms, pain, and health status in subjects with durable clinical activity;
3. To examine biomarkers and their association with tremelimumab treatment and clinical outcome.

Exploratory objectives evaluated in this study will be reported in a research report or if available in the clinical study report.

3 STUDY DESIGN

3.1 Overview of Study Design

This is a Phase 2b, randomized, double-blind, placebo-controlled study. Subjects with unresectable pleural or peritoneal malignant mesothelioma will be randomized in a 2:1 ratio to receive either tremelimumab or placebo. Randomization will be stratified by EORTC status (low-risk vs high-risk; see Figure 3.1-1), line of therapy (second vs third), and anatomical site (pleural vs peritoneal). This study plans to use the EORTC status to stratify subjects into high or low risk groups in order to ensure balanced randomization to the different treatment groups. For subjects in whom pemetrexed was contraindicated or not tolerated or not an approved therapy (eg, peritoneal mesothelioma), prior therapy with a first-line platinum-based regimen is required. Though the number of subjects not receiving prior pemetrexed is expected to be small, the proportion of such subjects enrolled in the study will be capped at 20%. Approximately 564 subjects will be enrolled at approximately 180 study centers in multiple countries.

The study consists of a screening period, a treatment period, and a 90-day follow-up period (Figure 3.1-1). The treatment period will consist of 6 doses Q4W followed by doses Q12W unless permanent discontinuation criteria are met (see Section 4.2.3).

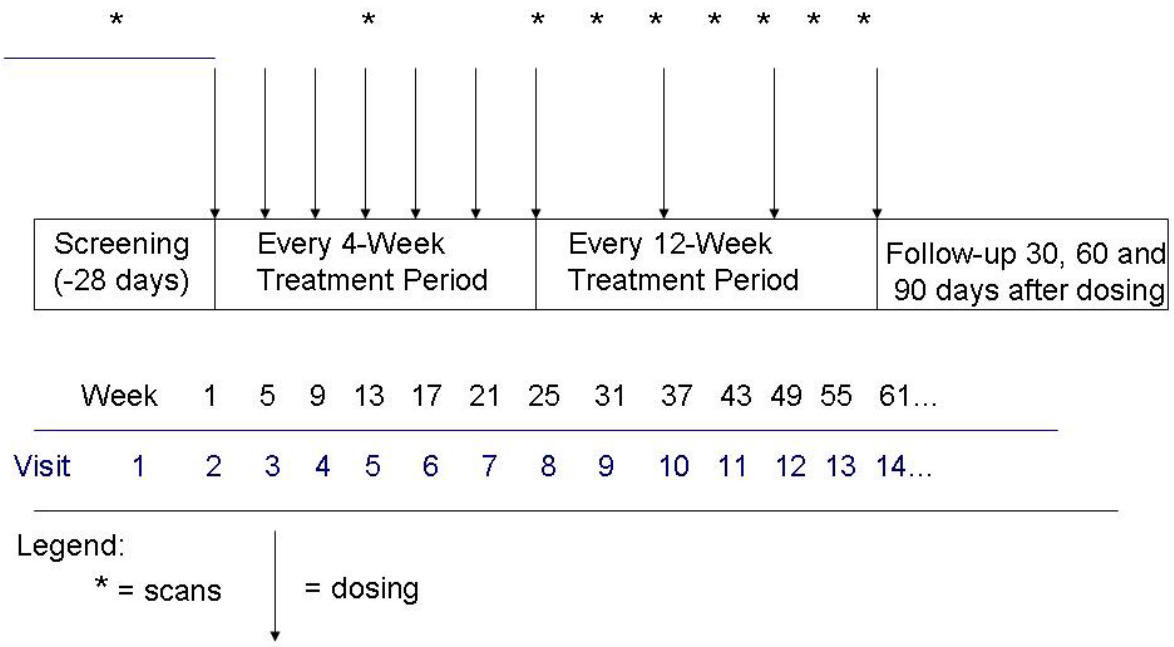

Figure 3.1-1 Study Flow Diagram

The endpoints to be measured in this study are described in Section 7.3.

3.2 Estimated Duration of Subject Participation

This study will consist of:

- A screening period of up to 28 days;
- A treatment period
  - Six doses Q4W unless confirmed disease progression, initiation of alternative cancer treatment, unacceptable toxicity, withdrawal of consent, or other reason for treatment discontinuation occurs;
  - Starting at 4 weeks after the 6th dose (Week 25), study treatment will be given Q12W unless permanent discontinuation criteria are met (see Section 4.2.3);
- A 90-day post-treatment safety follow-up period;
- A survival follow-up period with subjects being followed for survival until the end of the study.

The total subject participation time could be up to approximately 3 years.

3.3 Study-stopping Criteria

If the following occur, administration of investigational product will be stopped and no additional subjects will be randomized into the study:

- Any safety findings assessed as related to investigational product that, in the opinion of the sponsor in consultation with the Independent Data Monitoring Committee (IDMC), contraindicate further dosing of study subjects

If any such safety findings occur, further administration of the investigational product will be stopped and no further subjects will be randomized into the study. Thereafter the regulatory authorities and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) will be notified and a prompt cumulative review of safety data and the circumstances of the event in question will be conducted (see Section 6.5). The findings will be shared with the regulatory authorities and the IRB/IEC. If it is deemed appropriate by the sponsor after consulting with the Independent Data Monitoring Committee (IDMC) to resume the study, justification will be sent to the regulatory authorities and the IRBs/IECs as required.

Any subjects who have already received investigational product and are currently in the study at the time study-stopping criteria are met will continue to be followed by the investigator for safety.

Withdrawal criteria for individual subjects are provided in Section 4.2.3.

3.4 Rationale for Study Design, Doses, and Control Groups

Study Design

A placebo-controlled, double-blind study is appropriate since there are no agents approved for mesothelioma after failure of first-line therapy. Moreover, there is no consistent standard of care for subjects having this tumor in this setting, with treatments ranging from best supportive care to various single-agent chemotherapies including vinorelbine, pemetrexed, and gemcitabine. Second-line chemotherapy has been used in clinical practice because patients frequently still have a good performance status at the time of disease progression, but to date, no randomized Phase 3 study has demonstrated any significant improvement in OS or QoL in subjects with relapsed disease (Vogelzang et al, 2000; Jassem et al, 2008; Krug et al, 2011). Median OS in these studies ranged from approximately 6 to 10 months. Some of the randomized studies were conducted against placebo and failed to demonstrate any clinically meaningful or statistically significant benefits (Scherpereel et al, 2011; Stebbing et al, 2009; Ramalingam et al, 2009; Zucali et al, 2008; Okuno et al, 2008; Jänne et al, 2006; Taylor et al, 2008). Based on these data, chemotherapy has failed to demonstrate evidence of clinical benefit and is associated with severe toxicities. Thus, the National Comprehensive Cancer Network and European Society for Medical Oncology guidance propose clinical trials as the recommended option after first-line therapy. The available data suggest, therefore, that placebo is the appropriate comparator for the proposed Phase 2 study. Accordingly, the proposed study will employ a placebo-controlled study design with a 2:1 (tremelimumab:placebo) randomization scheme to ensure that proportionally more subjects receive potentially active tremelimumab treatment. Subjects in both treatment arms will receive best supportive care.

The efficacy, safety, PK, and immunogenicity endpoints to be examined in this study are common outcome measures in oncology studies. An exploratory analysis will also look at PFS using the irRC that have been proposed for use in patients being treated with immunotherapies (Wolchok et al, 2009). The irRC account for the types of early progression and late response that are seen with anti-CTLA-4 and other immunotherapies. Subjects who have evidence of progression at any disease evaluation and in the absence of clinical deterioration will continue to receive randomized therapy until PD is confirmed by a second tumor assessment at least 4 weeks later. This will allow subjects the potential for the maximum benefit from treatment if responses only occur late and prevent the early discontinuation of therapy for subjects who could be benefitting from therapy.

Doses

The tremelimumab dose employed in this study will be 10 mg/kg Q4W for the first 6 months, after which tremelimumab will be given Q12W at the same dose, as long as the subjects continues to derive clinical benefit. The selected dose and schedule is informed by safety and efficacy data on tremelimumab, and by data showing a relationship between exposure and survival in the advanced melanoma studies with tremelimumab.

Tremelimumab has been administered to approximately 1,000 subjects at doses ranging from 10 mg/kg Q4W to 15 mg/kg Q12W. A Phase 1b/2 clinical study in melanoma (A3671002; Camacho et al, 2009) has shown comparable efficacy and overall AE rates at the 2 dosing levels, although more Grade 3/4 AEs were seen at a dose of 10 mg/kg Q4W (27% Q4W vs 13% 15 mg/kg Q12W). The difference in Grade 3-4 AEs was largely due to differences in the incidence of ≥ Grade 3 diarrhea (21% vs 9%). Nevertheless, all Grade 3 or 4 AEs and SAEs were manageable and reversible when appropriate intervention was applied. Subsequent large Phase 2 and 3 studies with tremelimumab in melanoma used the regimen of 15 mg/kg Q12W. However, re-assessment of both the safety and the efficacy conclusions regarding the dosing regimen comparisons in Study A3671002 is warranted. The incidence of diarrhea might be reduced with the implementation of current clinical practice guidelines for the management of immune-related toxicity (Kaehler et al, 2010; Weber, 2012; see Section 4.5.7). In addition, there was an imbalance between the treatment arms of the Phase 2 portion of Study A3671002. A greater proportion of subjects in the 10-mg/kg arm had baseline characteristics that were associated with poor prognosis (eg, metastatic burden [M1c], lactate dehydrogenase [LDH] > upper limit of normal [ULN], Eastern Cooperative Oncology Group [ECOG] performance status > 0, and C-reactive protein [CRP] > 1.5 × ULN), which could have influenced the survival outcome in this small study. Cox-proportional hazard modeling, accounting for imbalances in prognostic factors, resulted in hazard ratios favoring the 10-mg/kg Q4W group, ranging from 0.7 to 0.8, although the differences were not significant ($p > 0.05$).

A retrospective exposure and survival analysis of 293 subjects treated with tremelimumab in a Phase 3 study in melanoma showed better OS in subjects with higher exposure. The median OS was 18.4 months for the high-AUC (≥ 123,665 µg.hr/mL) group compared to 9.0 months for the low-AUC (< 123,665 µg.hr/mL) group (HR 0.5; $p < 0.001$). Similar results were observed in a large Phase 2 study in patients with refractory or relapsed melanoma.

The target trough concentration of tremelimumab is estimated to be ~ 30 µg/mL based on enhanced IL-2 release (in vitro) and antitumor activity (in vivo) in preclinical studies. Pharmacokinetic simulations indicate that following tremelimumab at a dose of 10 mg/kg Q4W,

approximately 90% of subjects are expected to be above the target concentration of ~ 30 µg/mL compared to ~ 50% with 15 mg/kg Q12W. Therefore, the current study in malignant mesothelioma will use a dosing regimen of 10 mg/kg Q4W over 6 doses followed by dosing of 10 mg/kg Q12W in order to maximize exposure to tremelimumab while managing safety according to the established guidelines which have been published on anti-CTLA-4 AE management (Weber et al, 2012).

4 SUBJECT SELECTION, TREATMENT, AND WITHDRAWAL

4.1 Subject Participation and Identification

Study participation begins once written informed consent is obtained (see Section 10.3 for details). Once informed consent is obtained, a subject identification (SID) number will be assigned by a central system (eg, an interactive voice or web response system [IXRS]), and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The SID number will be used to identify the subject during the screening process and throughout study participation, if applicable.

A master log of all consented subjects will be maintained at the site and will document all screening failures (ie, subjects who are consented but do not meet study eligibility criteria and/or are not randomized), including the reason(s) for screening failure (see Section 9.1 for details).

4.2 Subject Selection and Withdrawal

The subjects in this study will be male or female adults with unresectable pleural or peritoneal malignant mesothelioma who have progressed after previous receipt of 1 or 2 previous lines of treatment including at least one platinum- and/or antifolate-based regimen.

This study will use dedicated clinical study units. The sites will use their subject database and possibly some form of advertising to recruit and identify subjects. The investigator (physician) or qualified designee will discuss the study with a subject/the legal representative of a subject who is considered a potential candidate for the study and provide the subject/legal representative with the study-specific Informed Consent Form(s) (ICF[s]) approved by the IRB/IEC. The investigator or designee will address any questions and/or concerns that the subject/legal representative may have and, if there is continued interest, will secure written informed consent for participation in the study. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act [HIPAA] authorization in the USA, European Union [EU] Data Privacy Directive authorization in the EU), will be obtained prior to conducting any protocol-specific procedures, including screening evaluations or medication washouts. See Section 10.3 for additional details concerning informed consent.

4.2.1 Inclusion Criteria

Subjects must meet *all* of the following criteria:

1. Histologically and/or cytologically confirmed pleural or peritoneal malignant mesothelioma;
2. Disease not amenable to curative surgery;
3. Age 18 and over at the time of consent;
4. ECOG Performance status 0-1;
5. Progressed after previous receipt of 1-2 prior systemic treatments for advanced disease that included a first-line pemetrexed (or anti-folate)-based regimen in combination with platinum agent. For subjects in whom pemetrexed was contraindicated or not tolerated or not an approved therapy (eg, peritoneal mesothelioma), prior therapy with a first-line platinum-based regimen is required;
6. Recovered from all toxicities associated with prior treatment, to acceptable baseline status, or a National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade of 0 or 1, except for toxicities not considered a safety risk, such as alopecia or vitiligo;
7. Measurable disease, defined as at least 1 lesion (measurable) that can be accurately assessed at baseline by computed tomography (CT) or magnetic resonance imaging (MRI) and is suitable for repeated assessment (modified RECIST for pleural mesothelioma or RECIST v1.1 for peritoneal mesothelioma);
8. Adequate bone marrow, hepatic, and renal function determined within 14 days prior to randomization defined as:
   - Platelet count $\geq 75{,}000/mm^3$;
   - Absolute neutrophil count $\geq 1{,}000/mm^3$;
   - Hemoglobin ≥ 9 g/dL;
   - Total bilirubin $\leq 1.5 \times$ ULN except subjects with documented Gilbert's syndrome ($> 5 \times$ ULN) or liver metastasis, who must have a baseline total bilirubin ≤ 3.0 mg/dL;
   - Aspartate transaminase (AST) and alanine transaminase (ALT) $\leq 3 \times$ ULN ($\leq 5 \times$ ULN if documented liver metastasis are present);
   - Serum creatinine ≤ 2.0 mg/dL or calculated creatinine clearance ≥ 50 mL/min as determined by the Cockcroft-Gault equation;
9. Negative screening test results for human immunodeficiency virus (HIV), hepatitis A, B and C. If positive results are not indicative of true active or chronic infection, the subjects can enter the study after discussion and agreement between the investigator and the contract research organization (CRO) medical monitor;
10. Written informed consent and any locally required authorization (eg, HIPAA in the USA, EU Data Privacy Directive authorization in the EU) obtained from the subject/legal representative prior to performing any protocol-related procedures, including screening evaluations;
11. Females of childbearing potential who are sexually active with a nonsterilized male partner must use a highly effective method of contraception for 28 days prior to the first dose of investigational product, and must agree to continue using such precautions for 6 months after

the final dose of investigational product; cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. They must also refrain from egg cell donation for 6 months after the final dose of investigational product;

- Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause);
- A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The acceptable methods of contraception are described in Table 4.2.1-1;

12. Nonsterilized males who are sexually active with a female partner of childbearing potential must use a highly effective method of contraception (see Table 4.2.1-1) from Days 1 through 90 post last dose. In addition, they must refrain from sperm donation for 90 days after the final dose of investigational product.

Table 4.2.1-1 Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
• Male condom with or without spermicide [a] • Copper T intrauterine device • Levonorgesterel-releasing intrauterine system (eg, Mirena®) [b]	• Implants • Hormone shot or injection • Combined pill • Minipill • Patch

[a] If male condom without spermicide is used, another form of contraception is required to meet the definition of a highly effective method of contraception with a failure rate of less than 1%.

[b] This is also considered a hormonal method.

4.2.2 Exclusion Criteria

Any of the following would exclude the subject from participation in the study:

1. Subjects who failed more than 2 prior systemic treatment regimens for advanced malignant mesothelioma;
2. Received any prior mAb against CTLA-4, programmed cell death 1 (PD1) or programmed cell death 1 ligand 1 (PD-L1);
3. History of chronic inflammatory or autoimmune disease (eg, Addison's disease, multiple sclerosis, Graves' disease, Hashimoto's thyroiditis, rheumatoid arthritis, hypophysitis, uveitis, etc) with symptomatic disease within the last 3 years prior to randomization. Note: Active vitiligo or alopecia or a history of vitiligo will not be a basis for exclusion;
4. Active, untreated central nervous system (CNS) metastasis (subjects with brain metastases who are identified at screening may be rescreened after the lesion[s] have been appropriately treated and subjects are off corticosteroids);

5. Any serious uncontrolled medical disorder or active infection that would impair the subject's ability to receive investigational product, such as conditions associated with frequent diarrhea;
6. History of other malignancy unless the subject has been disease-free for at least 3 years. Non-invasive cancer history (such as carcinoma in situ [CIS] that has been resected) is allowed;
7. Pregnant or breast feeding at time of consent;
8. Any condition that would prohibit the understanding or rendering of information and consent and compliance with the requirements of this protocol;
9. Active or history of diverticulitis. Note that diverticulosis is permitted;
10. Active or history of inflammatory bowel disease (eg, colitis, Crohn's), irritable bowel disease, celiac disease or other serious gastrointestinal chronic conditions associated with diarrhea. Active or history of systemic lupus erythematosis or Wegener's granulomatosis;
11. History of sarcoidosis syndrome;
12. Currently receiving systemic corticosteroids or other immunosuppressive medications or has a medical condition that requires the chronic use of corticosteroids. Note: inhaled and topical steroids are permitted;
13. Subjects should not be vaccinated with live attenuated vaccines within one month prior to starting tremelimumab treatment;
14. The last dose of prior chemotherapy or radiation therapy (with the exception of palliative radiotherapy) was received less than 2 weeks prior to randomization;
15. Any unresolved toxicity NCI CTCAE Grade ≥ 2 from previous anticancer therapy with the exception of vitiligo and alopecia;
16. Any condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of subject safety or study results;
17. Concurrent enrollment in another clinical study or receipt of an investigational product within the last 4 weeks (participation in the survival follow-up period of a study is not an exclusion criterion);
18. Employees of the study site directly involved with the conduct of the study, or immediate family members of any such individuals;
19. Subjects with a history of hypersensitivity to compounds of similar biologic composition to tremelimumab or any constituent of the product.

4.2.3 Withdrawal Criteria

Permanent discontinuation of investigational product: An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

1. Withdrawal of consent from study;
2. Withdrawal of consent from treatment;
3. Lost to follow-up;

4. Adverse event or laboratory abnormality that meets the permanent discontinuation criteria (see Table 4.5.7-3) and in the opinion of the investigator or the sponsor, contraindicates further dosing;
5. Subject is determined to have met one or more of the exclusion criteria for study participation and continuing investigational therapy might constitute a safety risk;
6. Pregnancy or intent to become pregnant;
7. Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; eg, refusal to adhere to scheduled visits;
8. Initiation of alternative anticancer therapy including another investigational product;
9. Confirmation of progressive disease;
10. Subject who skips 2 consecutive doses because of ongoing treatment-related toxicity;
11. Subject who has received any amount of infliximab or other tumor necrosis factor alpha (TNF-α) inhibitor.

The study medical monitor should be notified of any ongoing AE that may delay treatment or necessitate permanent discontinuation of treatment.

Subjects who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent from study, withdrawal of consent from treatment, due to an AE, other), will be identified as having permanently discontinued treatment. Subjects who permanently discontinue treatment may either be considered to have completed the study or not to have completed the study (see Section 4.7).

Subjects who are permanently discontinued because of toxicity or withdrawal of consent from treatment and in the absence of disease progression, will be asked to come in for every protocol-specified visit and will follow all protocol procedures with the exception of dosing. For subjects refusing to return to the site, they should be contacted every 3 months by phone to assess for survival unless consent is withdrawn.

Subjects who are permanently discontinued from receiving investigational product will be followed for safety per Section 6.4, including the collection of any protocol-specified blood, or urine specimens, unless consent is withdrawn.

Withdrawal of consent: If consent is withdrawn, the subject will not receive any further investigational product or further study observation. Note that the subject may need to undergo additional tests or tapering of treatment to withdraw safely.

Lost to follow-up: Subjects will be considered lost to follow-up only if no contact has been established by the time the study is completed (as defined in Section 4.9) such that there is insufficient information to determine the subject's status at that time.

- Note: For subjects refusing to continue participation in the study, they should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing subjects throughout the study period. If contact with a missing subject is re-established, the subject should not be considered lost to follow-up and any evaluations should resume according to the protocol.

4.2.4 Replacement of Subjects

Subjects will not be replaced in this study.

4.3 Treatment Assignment

An IXRS will be used for randomization to a treatment arm and assignment of blinded investigational product kit numbers to each subject.

Subjects will be randomized in a 2:1 ratio to receive either tremelimumab or placebo. The randomization will be stratified by EORTC status (low-risk vs high-risk) (see Appendix 3), line of therapy (second vs third), and anatomical site (pleural vs peritoneal). Enrollment of subjects without prior first-line pemetrexed-based treatment will be capped at 20%.

The procedure for using IXRS is as follows:

- The investigator or designee contacts the IXRS and provides the SID number and subject's baseline characteristic(s) used to verify that it is the same subject.
- The IXRS assigns a blinded treatment arm and investigational product kit number(s) to the subject.
- Confirmation of this information is sent to the investigator/designee who dispenses the investigational product to the subject per the response system and records the appropriate information in the subject's medical records and investigational product accountability log.

Investigational product (tremelimumab or placebo) must be administered within 24 hours after the investigational product is assigned and prepared. If there is a delay in the administration of investigational product such that it will not be administered within the specified timeframe, the study monitor must be notified *immediately*.

4.4 Blinding

This is a double-blind study in which tremelimumab and placebo are identically labeled and indistinguishable in appearance. As such, neither the subject/legal representative nor any of the investigator or sponsor/CRO staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received (International Conference on Harmonisation

[ICH] E9). In the event that treatment allocation for a subject becomes known to the investigator or other study staff involved in the management of study subjects, the sponsor must be notified *immediately*. If the treatment allocation for a subject needs to be known to treat an individual subject for an AE, the investigator should notify the sponsor/CRO *immediately* and, if possible, before unblinding the treatment allocation.

4.4.1 Unblinding in the Event of a Medical Emergency

In the event of a medical emergency, the investigator may unblind an individual subject's investigational product allocation. Instructions for unblinding an individual subject's investigational product allocation are contained in the IXRS manual. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received investigational product. In the majority of cases, the management of a medical emergency would be the same whether or not investigational product was received by the subject. If this was the case, the investigational product allocation should not be unblinded.

4.4.2 Unblinding for Interim Analyses

To ensure the blinding of each subject's treatment assignment throughout the study, the unblinded analyses will be performed by an independent third party biostatistician who is not involved in the conduct of the study. For the interim analysis, an IDMC will review unblinded interim data and inform the sponsor whether the interim boundaries specified in Section 7.5 are crossed.

MedImmune staff, CRO staff (including site monitors), site staff (investigators and study site staff), and study subjects will remain blinded until the database lock for the primary analysis of OS.

4.5 Study Medications

4.5.1 Investigational Products

The sponsor will provide the investigator(s) with investigational product (Table 4.5.1-1) using designated distribution centers.

Table 4.5.1-1 Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
Tremelimumab	MedImmune	Formulated at a nominal concentration of 20 mg/mL in 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, and 0.27 mM disodium edetate dihydrate (EDTA), pH 5.5.
Placebo	MedImmune	Placebo contains the same excipients, in the same concentration only lacking tremelimumab.

Both tremelimumab and placebo vials should be stored at refrigerated temperatures (2°C to 8°C), and should not be frozen.

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines (such as GMP Annex 13 requirements for labeling). Label text will be translated into local languages, as required.

Investigational product (active and placebo) will be supplied to the site in containers with identical appearances in coded kits. Each kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each vial within the carton).

4.5.1.1 Investigational Product Accountability

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to the sponsor. All unused investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorization by the sponsor.

4.5.1.2 Reporting Product Complaints

Any defects with the investigational product must be reported *immediately* to the the sponsor Product Complaint Department by the site with further notification to the site monitor. All defects will be communicated to the sponsor and investigated further with the Product Complaint Department. During the investigation of the product complaint, all investigational products must be stored at labeled conditions unless otherwise instructed.

Product defects may be related to component, product, or packaging and labeling issues. The list below includes, but is not limited to, descriptions of product complaints that should be reported.

- **Component Issue:** Defect in container or dosing mechanism of the investigational product. The component defect may be damaged, missing, or broken. Component examples include vials, stoppers, caps, spray barrels, spray nozzles, or plungers.
- **Product Issue:** Defect in the product itself. The product appearance has visual imperfections such as foreign particles, crystallization, discoloration, turbidity, insufficient volume, or anything that does not apply to the product description.
- **Packaging/Labeling Issue:** Defect in the packaging or labeling of the product. The packaging or labeling defects may be damaged or unreadable, or the label may be missing.

When reporting a product complaint, site staff must be prepared to provide the following information:

1. Customer information: reporter name, address, contact number, and date of complaint
2. Product information: product name, packaging kit number or lot number, expiry date, and clinical protocol number
3. Complaint information: complaint issue category and description

MedImmune contact information for reporting product complaints:

Email:

4.5.2 Other Study Medications

No other study medications are specified for use in this clinical protocol. Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management [including palliative radiotherapy, etc]) should be used when necessary for all subjects with the exception of prohibited concomitant medications (see Section 4.6.2). Opioids can be used but with caution and under medical control after discussion with the medical monitor.

4.5.3 Treatment Regimen

Tremelimumab is to be administered as an IV solution of 10 mg/kg at a rate of 250 mL/hr, followed by observation. Subjects will receive one dose of investigational product Q4W for 6 doses, followed by dosing starting 4 weeks after Dose 6 (Week 25) with one dose Q12W unless permanent discontinuation criteria are met (see Section 4.2.3).

4.5.4 Investigational Product Dose Preparation

Tremelimumab is supplied as a sterile IV solution, filled in 20 mL clear glass vials with a rubber stopper and aluminum seal. Each vial contains 20 mg/mL (with a nominal fill of 20 mL accounting to 400 mg/vial) of tremelimumab, in an isotonic solution at pH 5.5. Vials containing tremelimumab must be stored in the refrigerator at 2-8^{o}C. The 20 mg/mL solution will be diluted into a saline bag for IV infusion. Vials containing tremelimumab may be gently inverted for mixing, but should not be shaken.

Placebo is supplied as a sterile IV solution, filled in 20 mL clear glass vials with a rubber stopper and aluminum seal. Each vial is filled with 20 mL (nominal fill) placebo in an isotonic solution at pH 5.5. Vials containing placebo must be stored in the refrigerator at 2-8^{o}C. The placebo solution will be diluted into a saline bag for IV infusion. Vials containing placebo may be gently inverted for mixing, but should not be shaken.

For dose preparation steps, the following ancillary items are required:

- IV infusion bags of 0.9% sodium chloride injection (250 mL size). Saline bags must be latex-free and can be made of polyvinyl chloride (PVC) or polyolefins (eg, polyethylene), manufactured with bis (2-ethylhexyl) phthalate (DEHP) or DEHP-free.
- IV infusion lines made of PVC/DEHP or PVC/tri octyl trimellitate (TOTM) or polyethylene or polyurethane. All DEHP-containing or DEHP-free lines are acceptable. Lines should contain a 0.22 or 0.2 µm in-line filter. The in-line filter can be made of polyethersulfone (PES) or polyvinylidene fluoride DRF (PVDF). Lines containing cellulose-based filters should not be used with tremelimumab.
- Catheters/infusion sets made of polyurethane or fluoropolymer with silicone and stainless steel and/or PVC components.
- Syringes made of polypropylene and latex-free. Polycarbonate syringes should not be used with tremelimumab.
- Needles made of stainless steel.

4.5.4.1 Dose Calculation

Subject weight at baseline should be used for dosing calculations unless there is a ≥ 10% change in weight. Alternatively, the dose can be calculated based on body weight measured prior to each dose.

The dose will be calculated using the following formula:

$$\text{Dose (mL)} \quad \frac{[\text{subject weight (kg)} \times \text{dose level (10 mg/kg)}]}{\text{drug concentration (20 mg/mL)}}$$

The corresponding volume of investigational product should be rounded to the nearest tenth of a mL (0.1 mL). Each vial contains a small amount of overage and the overage should be utilized as much as possible before using another vial.

The number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

$$\text{Number of vials} \quad \text{Dose (mL)} \div 20 \text{ (mL/vial)}$$

4.5.4.2 Investigational Product Inspection

Each vial selected for dose preparation should be inspected.

If there are any defects noted with the investigational product, the investigator and site monitor should be notified immediately. Refer to the Product Complaint section for further instructions (Section 4.5.1.2).

During the inspection if the solution is not clear or any turbidity, discoloration or particulates are observed, notify your site monitor and store the vial(s) in QUARANTINE at refrigerated (2-8ºC) temperature for drug accountability and potential future inspection.

Notify the IXRS that the unusable vials are damaged. The IXRS will indicate the replacement vials. Select appropriate replacement vials for the preparation of the subject's dose, and perform the same inspection on the newly selected vials. For accountability, record the total number of vials removed from site inventory. Used vials can be held for accountability purposes at ambient storage temperature.

4.5.4.3 Dose Preparation Steps

Tremelimumab does not contain preservatives and any unused portion must be discarded. Preparation of tremelimumab and preparation of the IV bag are to be performed aseptically.

Total in-use storage time for the prepared final IV bag should not exceed 24 hours at 2-8°C or 4 hours at room temperature (25°C). However, it is recommended that the prepared final IV bag be stored in the dark at 2-8°C until needed. The refrigerated infusion solutions in the prepared final IV bag should be equilibrated at room temperature for about 2 hours prior to administration. If storage time exceeds these limits, a new dose must be prepared from new vials.

The investigational product manager or qualified personnel will be responsible for preparing the IV doses using the following steps:

1. Select the IXRS-assigned number of vials of investigational product required to prepare the subject's dose.
2. All investigational product vials should be equilibrated to room temperature for 30 minutes prior to dose preparation.
3. To prepare the IV bag, first, calculate the dose volume of investigational product required. Second, remove the volume of 0.9% sodium chloride IV solution equivalent to the calculated dose volume of investigational product from the IV bag. Lastly, add the calculated dose volume of investigational product to the IV bag. Gently mix the solution in the bag by inverting up and down. Avoid shaking the IV bag to prevent foaming.

Example: A subject weighing 85 kg will require 42.5 mL (3 vials) of investigational product. Remove 42.5 mL of saline from the commercial IV bag. Add the 42.5 mL of investigational product to the IV bag and gently mix by inverting up and down.

4.5.5 Treatment Administration

The first day of dosing is considered Day 1. Each dose of investigational product should be administered using the following guidelines:

1. Investigational product must be administered at room temperature (25°C) by controlled infusion via an infusion pump into a peripheral vein. Prior to the start of the infusion, ensure that the bag contents are at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.
2. A physician must be present at the site or immediately available to respond to emergencies during all administrations of investigational product. Fully functional resuscitation facilities should be available.
3. Investigational product must not be administered via IV push or bolus but as a slow IV infusion. The entire content of each IV bag will be infused using an infusion pump.
4. The infusion lines should be attached only at time of use. Lines used for infusion during dose administration will need to be equipped with 0.22 or 0.2 μm in-line filters.
5. If there are no requirements to slow, interrupt, or permanently stop the infusion, the anticipated infusion time to deliver each dose (250 mL) is anticipated to be at least 60 minutes.

6. Some investigational product may remain in the IV line after the infusion has completed. Fifteen to 30 mL of 0.9% sodium chloride IV solution should be added to the infusion bag after the investigational product has been administered to flush the line. The infusion rate should not be changed.

The duration of the investigational product administration will be recorded.

4.5.6 Monitoring of Dose Administration

Vital signs will be collected before investigational product infusion, every 30 minutes during infusion, at completion of infusion, and 30 and 60 minutes post infusion.

As with any antibody, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis, as per local institutional guidelines.

4.5.7 Dose Modification for Toxicity Management

No dose reduction is allowed. Dosing may be delayed up to + 3 days during the treatment phase to allow recovery from treatment-related toxicity. Toxicity management guidelines for anti-CTLA-4 monoclonal antibodies have been developed and published in the past 5 years (Kaehler and Hauschild, 2011; Weber et al, 2012). Specific detailed management guidelines have been created for diarrhea and/or colitis-related events (Appendix 4). However, for management of most other toxicities follow the guideline in Table 4.5.7-1.

Table 4.5.7-1 General Toxicity Management Guidelines

Condition	Management
Onset of any toxicity	• Rule out alternative etiology • In case of doubt, investigator should consult with study medical monitor promptly
NCI CTCAE Grade 1	• Provide symptomatic treatment • Possible topical steroids if applicable • If symptoms persist > 10 days, treat as NCI CTCAE Grade 2
NCI CTCAE Grade 2	• Provide symptomatic treatment • Do not give scheduled dose; dosing may be resumed at next scheduled dose if symptoms are resolved • Dosing delays are not permitted (except per protocol-specified window of + 3 days in the treatment phase) • Consider oral or IV steroids at the onset of symptoms. Taper steroid over at least 4 weeks if symptoms improve • For persistent NCI CTCAE Grade 2 events: treat as NCI CTCAE Grade 3 event, start high-dose IV steroids
NCI CTCAE Grade 3	• Start high-dose IV steroids at the onset of the symptoms • Provide symptomatic treatment • Permanent discontinuation [a] of tremelimumab for NCI CTCAE Grade 3 events thought to be drug-related • Exception are endocrinopathies that are asymptomatic and controlled with hormone replacement therapy, and rash or other skin disorders
NCI CTCAE Grade 4	• Start high-dose IV steroids at the onset of the symptoms • Provide symptomatic treatment • Permanent discontinuation [a] of tremelimumab for all NCI CTCAE Grade 4 events
Steroid refractory toxicity (no improvement after 5 days on high-dose IV steroids) or relapse after reducing high-dose steroids	• Continue symptomatic treatment and steroids • Possible infliximab [b] 5 mg/kg IV for GI toxicities unless contraindicated [consult with GI specialist]. Caution: rule out bowel perforation and refer to label before using infliximab • For subjects with increased AST/ALT, or total bilirubin levels, consider mycophenolate mofetil

ALT = alanine transaminase; AST = aspartate transaminase; GI = gastrointestinal; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

[a] Subjects will not receive any subsequent dose, but will remain on study and follow the other procedures required from the study (eg, follow-up procedures, disease assessment scans, blood sample collections).

[b] Use will result in discontinuation of treatment.

Guidelines for Skipping the Next Scheduled Dose for Drug-related AEs

The following guidance (see Table 4.5.7-2) must be followed when determining whether to skip/hold the next scheduled dose of investigational product during management of drug-related

toxicities. If it appears that an ongoing AE will necessitate the omitting of a dose, the study medical monitor must be contacted.

When a scheduled dose of investigational product is skipped, dosing may be resumed at the next scheduled dose if the symptoms have resolved to NCI CTCAE Grade ≤ 1. Dose delays are not allowed (except within the protocol-specified window of + 3 days during the treatment phase).

Table 4.5.7-2 Guidelines for Skipping a Dose

Condition	Action
For persistent NCI CTCAE Grade 1 treatment-related toxicities (> 10 days).	**Consult** with study medical monitor and manage as a NCI CTCAE Grade 2
Subjects with AST/ALT 5-8 × ULN or total bilirubin 3-5 × ULN. Subjects with any NCI CTCAE Grade 2 treatment-related laboratory abnormalities. For ongoing NCI CTCAE Grade 2 related toxicities. Dosing may be resumed at next scheduled dose if the event is resolving and at Grade ≤ 1. Exceptions to this are: • Investigational product may be dosed for NCI CTCAE Grade ≤ 3 endocrine disorders, if asymptomatic and controlled with hormone replacement therapy. Skip investigational product dose for Grade ≥ 2 endocrinopathies that are under treatment and remain symptomatic. • For hypersensitivity reactions and infusion reactions NCI CTCAE Grade ≤ 2: slow the infusion rate or temporally pause the infusion, medicate the subject with symptomatic therapies (ie, anti-histaminic drugs), and consider pre-medication per institutional guidelines. Consult with the medical monitor as needed. • Investigational product may be dosed for NCI CTCAE Grade 2 rash or other skin disorders; skip dose for Grade 3 skin disorders, except investigational product may be dosed for vitiligo any grade.	**Skip** scheduled tremelimumab dose

ALT = alanine transaminase; AST = aspartate transaminase; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ULN = upper limit of normal.

During the study, subjects may require immunosuppressive medications such as steroids for management of underlying disease, treatment-related toxicity, or unrelated conditions. If symptoms resolved to NCI CTCAE Grade ≤ 1, tremelimumab dosing may be resumed during steroid taper. Subjects with adrenal insufficiency may take daily prednisone or equivalent therapy for their endocrinopathy while receiving tremelimumab treatment. Topical and inhaled steroids in standard doses are allowed.

Guideline for Permanent Dosing Discontinuation (Safety Related)

Table 4.5.7-3 lists the safety related conditions under which subjects must be permanently discontinued from tremelimumab treatment. Additionally, tremelimumab should be permanently discontinued for any AE that, in the opinion of the investigator or sponsor, contraindicates further dosing. If it appears that an ongoing AE will necessitate permanent discontinuation of treatment, the study medical monitor must be contacted. When tremelimumab dosing is permanently discontinued, continue to follow the subject (eg, the subject should undergo the other procedures required in the study; follow-up procedures, imaging follow-up, blood sample collection, etc).

Table 4.5.7-3 Guidelines for Permanent Discontinuation of Investigational Product

Action	Condition
Permanent Discontinuation	NCI CTCAE ≥ Grade 3 treatment-related diarrhea or colitis
	AST or ALT > 8 × ULN or total bilirubin > 5× ULN
	NCI CTCAE ≥ Grade 3 hypersensitivity reaction or infusion reaction; Recurrent/persistent CTCAE Grade 2 hypersensitivity despite optimal premedication
	NCI CTCAE ≥ Grade 3 endocrine disorders, if symptomatic and not controlled with hormone replacement therapy. Tremelimumab may be dosed for CTCAE Grade ≤ 3 endocrine disorders, if asymptomatic and controlled with hormone replacement therapy
	NCI CTCAE Grade 4 rash or other skin disorders (with the exception of vitiligo, which may be dosed regardless of severity)
	Any other CTCAE ≥ Grade 3 events thought to be drug-related
	Any subject who receives infliximab or any other TNF-α inhibitor
	If 2 consecutive doses are missed due to on-going treatment-related toxicities
	Begins new investigational therapy, chemotherapy, cytokine therapy, or immunotherapy (including vaccines) must withdraw from treatment
	Subject becomes pregnant

ALT = alanine transaminase; AST = aspartate transaminase; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; TNF-α = tumor necrosis factor alpha; ULN = upper limit of normal.

Management of Diarrhea/Colitis

A diarrhea management flow chart can be found in Appendix 4.

4.5.8 Treatment Compliance

Investigational product is administered by study site personnel, who will monitor compliance.

4.6 Concomitant Medications

Concomitant medication status will be collected by study site staff from signing of the ICF to 90 days post last dose of investigational product.

4.6.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care (see Section 4.5.2) but do not include anti-cancer therapy. Subjects are allowed to take existing medications (eg, cardiac, diabetes, vascular disease).

Use of nonsteroidal anti-emetics, paracetamol (acetaminophen), or aspirin is permitted.

4.6.2 Excluded Concomitant Medications

The following medications are to be considered exclusionary by the investigator and are not permitted from signing of the ICF through the periods indicated. The investigator and sponsor must be notified if a subject receives any of the following during the study:

1. Monoclonal antibodies against CTLA-4, PD1, or PD-L1 through 90 days post last dose during the study
2. Immunosuppressive doses of steroids or other immunosuppressive medication through 90 days post last dose during the study. Note however, that inhaled and topical steroids when medically indicated as treatment for an acute illness or as pretreatment before CT scans (for contrast allergies) are allowed. The investigator is permitted to use corticosteroids as treatment for infusion reactions.
3. Drugs with laxative properties and herbal or natural remedies for constipation should be avoided through 90 days post last dose during the study because of the potential for exacerbation of diarrhea which is an identified risk for tremelimumab
4. Live attenuated vaccinations during the study or up to 6 months post last dose of investigational product
5. Inactivated vaccinations ± 30 days around any dose of investigational product

4.7 Subject Completion

An individual subject will be considered to have completed the study if the subject was followed up through the end of the study as defined in Section 4.9, regardless of the number of doses of investigational product that was received.

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up (see Section 4.2.3).

After the primary analysis of the study, subjects who are still receiving tremelimumab treatment and who in the opinion of the investigator are considered to be gaining benefit will be provided with an option for continued treatment (eg, rollover study). These patients can continue to receive study treatment until a study discontinuation criterion (eg, withdrawal of consent) has been met as assessed by the investigator. Investigators will report all SAEs to the sponsor until 90 days after receipt of their last dose of study treatment. Drug accountability data will also be collected.

Patients who have discontinued tremelimumab who have completed the 90-day safety follow-up are to be withdrawn from study at the earliest opportunity and no further data will be collected from these patients after withdrawal.

Patients currently receiving placebo or those who have discontinued placebo are expected to withdraw from the study. Investigators will report all serious adverse events to the sponsor until date of withdrawal from study.

4.8 Site Completion

Site completion is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study at the given site. All materials or supplies provided by the sponsor will be returned to the sponsor or designee upon site completion of the study, as directed by the site monitor. The investigator will notify the IRB/IEC when the study has been completed at his/her site.

4.9 End of the Study

The end of the study (“study completion”) will be declared after the primary analysis of the study (ie, study is stopped based on a positive interim analysis or after the final analysis of the study has occurred) or the date the sponsor stops the study, and at which no patients are exposed to study related procedures. Patients who, in the opinion of the investigator, are receiving clinical benefit will be given the option to continue to receive study treatment until a study discontinuation criterion (eg, withdrawal of consent) has been met as assessed by the investigator.

5 STUDY PROCEDURES

5.1 Schedule of Study Procedures

All subjects who are assigned an SID number and receive any investigational product will be followed according to the protocol regardless of the number of doses received, unless consent is

withdrawn. The investigator must notify the sponsor or designee of deviations from protocol visits or evaluations and these evaluations, if applicable, must be rescheduled or performed at the nearest possible time to the original schedule. Protocol deviations will be recorded on the source document with an explanation for the deviation. The investigator must comply with the applicable requirements related to the reporting of protocol deviations to the IRB/IEC.

Subjects/legal representatives will be instructed to call study personnel to report any abnormalities during the intervals between study visits and to come to the study site if medical evaluation is needed and the urgency of the situation permits. For emergency and other unscheduled visits to a medical facility other than the study site, medical records will be obtained by the investigator and made available to the sponsor or designee during monitoring visits.

A schedule of study procedures is presented in Table 5.1-1 and Table 5.1.2, followed by a description of each visit. A description of the study procedures is included in Section 5.2. Following the primary analysis of Study D4880C00003, patients will have the option to discontinue study treatment and withdraw from the study, or continue on the study as detailed in Section 5.1.6 and Table 5.1-3 (for patients remaining on tremelimumab treatment only post primary analysis of Study D4880C00003 and approval of Protocol Amendment 5).

Table 5.1-1 Schedule of Study Procedures for Screening and Every 4-Week Treatment Period

Study Period	Screening	Q4W Treatment Period						Protocol Section for Details
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	
Procedure / Study Week	**Day -28 to Day -1**	**Week 1**	**Week 5 ± 3 Days**	**Week 9 ± 3 Days**	**Week 13 ± 3 Days**	**Week 17 ± 3 Days**	**Week 21 ± 3 Days**	
Written informed consents/ assignment of SID number	X							4.1
LCSS-Meso questionnaire (ePRO)	X	X	X	X	X	X	X	5.2.8.3
EQ-5D-3L questionnaire (ePRO)	X	X	X	X	X	X	X	5.2.8.3
BPI-sf questionnaire (ePRO)	X	X	X	X	X	X	X	5.2.8.3
Medical history	X							5.2.1
Physical examination, weight	X	X	X	X	X	X	X	5.2.1
Height	X							5.2.1
Vital signs	X	X	X	X	X	X	X	5.2.1
Serum chemistry	X	X	X	X	X	X	X	5.2.2
Hematology	X	X	X	X	X	X	X	5.2.2
Serum pregnancy test	X							5.2.2
Urine pregnancy test		X	X	X	X	X	X	5.2.2
Hepatitis A, B, C, HIV virologies	X							5.2.2
Urinalysis	X	X	X	X	X	X	X	5.2.2
ECOG performance status	X	X	X	X	X	X	X	5.2.8.2
ECG	X	X (post dose)	X (post dose)		X (post dose)			5.2.1
Obtain archival tissue sample if consent provided	X							5.2.5
Central safety laboratory sample	X	X	X	X	X	X	X	5.2.2
PK blood sample		X	X		X			5.2.3

Table 5.1-1 Schedule of Study Procedures for Screening and Every 4-Week Treatment Period

Study Period	Screening	Q4W Treatment Period						Protocol Section for Details
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	
Procedure / Study Week	**Day -28 to Day -1**	**Week 1**	**Week 5 ± 3 Days**	**Week 9 ± 3 Days**	**Week 13 ± 3 Days**	**Week 17 ± 3 Days**	**Week 21 ± 3 Days**	
Immunogenicity blood sample		X	X		X			5.2.4
Flow cytometry samples	X	X	X		X			5.2.5
Cryopreserved PBMCs	X	X	X		X			5.2.5
Circulating soluble factors	X	X	X	X	X		X	5.2.5
Circulating apoptosis markers	X		X	X				5.2.5
RNA samples		X			X		X	5.2.5
DNA samples (optional)	X							5.2.5
Disease evaluations (CT or MRI if CT is contraindicated)	X				X			5.2.6
Assessment of AEs/SAEs	X	X	X	X	X	X	X	6.3
Concomitant medications	X	X	X	X	X	X	X	4.6
Verify eligibility criteria	X	X						4.2
Randomization		X						4.3
Investigational product administration		**X**	**X**	**X**	**X**	**X**	**X**	4.5.3, 4.5.5
Obtain core needle tumor biopsy if feasible and consent provided	X							

AE = adverse event; BPI-sf = brief pain inventory-short form; CT = computed tomography; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ePRO = electronic patient reported outcome; EQ-5D-3L = EQ-5D 3 level version; HIV = human immunodeficiency virus; LCSS-Meso = Lung Cancer Symptom Scale-mesothelioma; MRI = magnetic resonance imaging; PBMCs = peripheral blood mononuclear cells; PK = pharmacokinetics; Q4W = every 4 weeks; RNA = ribonucleic acid; SAE = serious adverse event; SID = subject identification; V = visit; W= week.

Table 5.1-2 Schedule of Study Procedures for Every 12-Week Treatment, End of Treatment, and Follow-up Period

Study Period	Q12W Treatment Period		End of Treatment	Short Term Follow-up Visits			Long Term Follow-up Period	Protocol Section for Details
Visit Number	Dosing Visits V8, V10, V12...	Non-dosing Visits V9, V11, V13						
Procedure / Study Week	W25 (± 3 Days) & Q12W (± 3 Days) Thereafter (W37, W49...)	W31 (± 3 Days), W43, and W55		30 Days (± 3 Days) After Last Dose	60 Days (± 3 Days) After Last Dose	90 Days (± 3 Days) After Last Dose	Every 3 Months After 90 Day (± 14 Days) Follow-up Visit	
LCSS-Meso questionnaire (ePRO)	X		X					5.2.8.3
EQ-5D-3L questionnaire (ePRO)	X		X					5.2.8.3
BPI-sf questionnaire (ePRO)	X		X					5.2.8.3
Physical examination, weight	X	X	X	X	X	X		5.2.1
Vital signs	X	X	X	X	X	X		5.2.1
Serum chemistry	X	X	X	X	X	X		5.2.2
Hematology	X	X	X	X	X	X		5.2.2
Urine pregnancy test	X		X					5.2.2
Urinalysis	X	X	X	X	X	X		5.2.2
ECOG performance status	X	X	X					5.2.8.2
ECG every 3 months the 1st year & every 6 months starting in the 2nd year (V14-W61)	X (post dose)		X			X		5.2.1
Central safety laboratory sample	X	X	X	X	X	X		5.2.2
PK blood sample	X (V8; V10 pre-dose only)		X			X		5.2.3
Immunogenicity blood sample	X (V8 and V10 pre-dose only)		X			X		5.2.4

Table 5.1-2 Schedule of Study Procedures for Every 12-Week Treatment, End of Treatment, and Follow-up Period

Study Period	Q12W Treatment Period		End of Treatment	Short Term Follow-up Visits			Long Term Follow-up Period	Protocol Section for Details
Visit Number	Dosing Visits V8, V10, V12...	Non-dosing Visits V9, V11, V13						
Procedure / Study Week	W25 (± 3 Days) & Q12W (± 3 Days) Thereafter (W37, W49...)	W31 (± 3 Days), W43, and W55		30 Days (± 3 Days) After Last Dose	60 Days (± 3 Days) After Last Dose	90 Days (± 3 Days) After Last Dose	Every 3 Months After 90 Day (± 14 Days) Follow-up Visit	
Flow cytometry samples	X (V8 only)							5.2.5
Cryopreserved PBMCs	X (V8 only)		X					5.2.5
Circulating soluble factors	X (V8 only)		X					5.2.5
Circulating apoptosis markers			X					5.2.5
RNA samples			X					5.2.5
Disease evaluations (CT or MRI if CT is contraindicated)	X	X	X			X	X	5.2.8.1
Assessment of AEs/SAEs	X	X	X	X	X	X		6.3
Concomitant medications	X	X	X	X	X	X		4.6
Investigational product administration	**X**							4.5.3, 4.5.5
Obtain core needle tumor biopsy if feasible and consent provided	X							
New systemic anticancer treatment			X	X	X	X	X	
Assess for survival			X	X	X	X	X	

AE = adverse event; BPI-sf = brief pain inventory-short form; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ePRO = electronic patient reported outcome; EQ-5D-3L = EQ-5D 3 level version; LCSS-meso = Lung Cancer Symptom Scale-mesothelioma; MRI = magnetic resonance imaging; PBMCs = peripheral blood mononuclear cells; PK = pharmacokinetic; Q12W = every 12 weeks; RNA = ribonucleic acid; SAE = serious adverse event; V = visit; W = week.

Table 5.1-3 Schedule of Study Procedures for Post Primary Analysis Period

Study Period	Post Primary Analysis	Protocol Section for Details
Visit Number	**Dosing Visits V8, V10, V12...**	
Procedure / Study Week	**W25 (± 3 Days) & Q12W (± 3 Days) Thereafter (W37, W49...)**	
Mandated assessments		
Assessment of AEs/SAEs[a]	X	6.3
Suggested assessments per Investigators discretion		
Physical examination, weight	X	5.2.1
Vital signs	X	5.2.1
Serum chemistry	X	5.2.2
Hematology	X	5.2.2
Urine pregnancy test	X	5.2.2
Urinalysis	X	5.2.2
ECG	X (post dose)	5.2.1
Disease evaluations (CT or MRI if CT is contraindicated)	X	5.2.8.1
Investigational product administration (mandatory)	**X**	4.5.3, 4.5.5

AE = adverse event; AZ DES = AstraZeneca Data Entry Site; CT = computed tomography; ECG = electrocardiogram; MRI = magnetic resonance imaging; Q12W = every 12 weeks; SAE = serious adverse event; ; V = visit; W = week.

[a] Investigators will report all SAEs to the sponsor until 90 days after receipt of their last dose of study treatment. Serious adverse event data will be collected via paper and emailed (preferably) or faxed directly to also known as AZ DES (see Section 6.4.2.2 for further information).

5.1.1 Screening (Visit 1)

All screening procedures must be performed within 28 days before randomization (Day -28 to Day -1), unless otherwise specified. The screening evaluations may be carried out over more than one visit. Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening evaluations. However, if evaluations that have been performed for other purposes prior to informed consent are otherwise suitable for use as screening evaluations, those evaluations need not be repeated if the subject/legal representative consents to allow use.

1. Obtain written informed consents (master ICF, DNA ICF, and future use ICF) and appropriate privacy act document authorization
2. Obtain an SID number from IVRS/IWRS
3. Administer questionnaires
    a. Lung Cancer Symptom Scale-mesothelioma (LCSS-Meso; collected with electronic patient-reported outcome [ePRO] device)
    b. EQ-5D 3 level version (EQ-5D-3L; collected with ePRO device)
    c. Brief pain inventory-short form (BPI-sf; collected with ePRO device)
4. Perform medical history
5. Perform physical examination including height and weight
6. Collect vital signs
7. Collect blood for screening samples:
    a. Serum chemistry
    b. Hematology
    c. Serum β-hCG (for females of childbearing potential only)
    d. Hepatitis A, B and C, HIV virologies
    e. Central safety labs
    f. Biomarker samples
        i. Flow cytometry
        ii. Cryopreserved peripheral blood mononuclear cells (PBMC)
        iii. Circulating soluble factors
        iv. Circulating apoptosis markers
        v. Deoxyribonucleic acid (DNA; optional)
8. Collect urine for urinalysis
9. Assess ECOG performance status
10. Perform electrocardiogram (ECG)
    a. The first 100 subjects will have triplicate ECGs (at least 1 minute apart)
    b. The remaining subjects will have a single ECG
11. Collect tissue for archival tumor sample, if consent provided

12. Evaluate disease via CT or MRI scan if CT is contraindicated. If for any reason a subject has undergone disease evaluation in the last 45 days, these scans are acceptable and do not need to be repeated; however if scan are clinically indicated, scans may be repeated
13. Assess for AEs and serious adverse events (SAEs)
14. Record concomitant medications
15. Calculate EORTC status (Appendix 3)
16. Determine line of therapy
17. Determine anatomical site
18. Determine if prior line of pemetrexed treatment was received
19. Verify eligibility criteria

5.1.2 Every 4-Week Treatment Period

5.1.2.1 Week 1: First Infusion (Visit 2)

Pre-dose

1. Administer questionnaires
   a. LCSS-Meso (collected with ePRO device)
   b. EQ-5D-3L (collected with ePRO device)
   c. BPI-sf (collected with ePRO device)
2. Perform physical examination including weight (if applicable, record new findings as AEs or SAEs). Subject weight at baseline should be used for dosing calculations unless there is a ≥ 10% change in weight. Alternatively, the dose can be calculated based on body weight measured prior to each dose
3. Take vital signs before administration of investigational product
4. Collect blood samples for:
   a. Serum chemistry
   b. Hematology
   c. Central safety labs
   d. PK
   e. Immunogenicity
   f. Biomarker samples
      i. Flow cytometry
      ii. Cryopreserved PBMC
      iii. Circulating soluble factors
      iv. Ribonucleic acid (RNA)
5. Collect urine for:
   a. Pregnancy test; ensure result is negative (serum pregnancy test may be substituted)
   b. Urinalysis
6. Assess ECOG performance status

7. Assess for AEs and SAEs
8. Update concomitant medications
9. Calculate EORTC status (Appendix 3)
10. Determine line of therapy
11. Determine anatomical site
12. Determine if prior line of pemetrexed treatment was received
13. Verify eligibility criteria
14. Contact IVRS/IWRS to randomize subject and obtain assigned study product kit number

Dosing and post-dose

1. Administer investigational product
2. Take vital signs every 30 minutes (± 5 minutes) during infusion, at completion of infusion (± 5 minutes), and 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post infusion
3. Assess for AEs and SAEs during and subsequent to infusion
4. Perform ECG (between 2 and 6 hours after treatment administration)
   a. The first 100 subjects will have triplicate ECGs (at least 1 minute apart)
   b. The remaining subjects will have a single ECG
5. Collect blood for post dose PK samples (end of infusion) (± 5 minutes)

5.1.2.2 Weeks 5, 9 and 17 (+/- 3 Days): Every 4-Week Treatments (Visits 3, 4, and 6)

Pre-dose

1. Administer questionnaires
   a. LCSS-Meso (collected with ePRO device)
   b. EQ-5D-3L (collected with ePRO device)
   c. BPI-sf (collected with ePRO device)
2. Perform physical examination including weight (if applicable, record new findings as AEs or SAEs). Subject weight at baseline should be used for dosing calculations unless there is a ≥ 10% change in weight. Alternatively, the dose can be calculated based on body weight measured prior to each dose
3. Take vital signs before administration of investigational product
4. Collect blood samples for:
   a. Serum chemistry
   b. Hematology
   c. Central safety labs
   d. PK (Visit 3)
   e. Immunogenicity (Visit 3)
   f. Biomarker samples

i. Flow cytometry (Visit 3)
ii. Cryopreserved PBMC (Visit 3)
iii. Circulating soluble factors (Visits 3 and 4)
iv. Circulating apoptosis markers (Visits 3 and 4)

5. Collect urine for:
   a. pregnancy test; ensure result is negative (serum pregnancy test may be substituted)
   b. urinalysis
6. Assess for ECOG performance status
7. Assess for AEs and SAEs
8. Update concomitant medications

Dosing and post-dose

1. Administer investigational product;
2. Take vital signs every 30 minutes (± 5 minutes) during infusion, at completion of infusion (± 5 minutes), and 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post infusion
3. Perform ECG (Visit 3 only between 2 and 6 hours after treatment administration)
   a. The first 100 subjects will have triplicate ECGs (at least 1 minute apart)
   b. The remaining subjects will have a single ECG
4. Assess for AEs and SAEs

5.1.2.3 Week 13 (+/- 3 Days): Every 4-Week Treatments (Visit 5)

Pre-dose

1. Administer questionnaires
   a. LCSS-Meso (collected with ePRO device)
   b. EQ-5D-3L (collected with ePRO device)
   c. BPI-sf (collected with ePRO device)
2. Perform physical examination including weight (if applicable, record new findings as AEs or SAEs). Subject weight at baseline should be used for dosing calculations unless there is a ≥ 10% change in weight. Alternatively, the dose can be calculated based on body weight measured prior to each dose.
3. Take vital signs before administration of investigational product
4. Collect blood samples for:
   a. Serum chemistry
   b. Hematology
   c. Central safety labs
   d. PK
   e. Immunogenicity

f. Biomarker samples
   i. Flow cytometry
   ii. Cryopreserved PBMC
   iii. Circulating soluble factors
   iv. RNA

5. Collect urine for:
   a. Pregnancy test; ensure result is negative (serum pregnancy test may be substituted)
   b. Urinalysis
6. Assess for ECOG performance status
7. Evaluate disease via CT or MRI scan
8. Assess for AEs and SAEs
9. Update concomitant medications

Dosing and post-dose

1. Administer investigational product
2. Take vital signs every 30 minutes (± 5 minutes) during infusion, at completion of infusion (± 5 minutes), and 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post infusion
3. Assess for AEs and SAEs
4. Collect blood for post-dose PK samples (end of infusion ± 5 minutes)
5. Perform ECG (between 2 and 6 hours after treatment administration)
   a. The first 100 subjects will have triplicate ECGs (at least 1 minute apart)
   b. The remaining subjects will have a single ECG

5.1.2.4 Week 21 (+/- 3 Days): Every 4-Week Treatments (Visit 7)

Pre-dose

1. Administer questionnaires
   a. LCSS-Meso (collected with ePRO device)
   b. EQ-5D-3L (collected with ePRO device)
   c. BPI-sf (collected with ePRO device)
2. Perform physical examination including weight (if applicable, record new findings as AEs or SAEs). Subject weight at baseline should be used for dosing calculations unless there is a ≥ 10% change in weight. Alternatively, the dose can be calculated based on body weight measured prior to each dose
3. Take vital signs before administration of investigational product
4. Collect blood samples for:
   a. Serum chemistry
   b. Hematology

c. Central safety labs
d. Biomarker samples
    i. Circulating soluble factors
    ii. RNA

5. Collect urine for:
    a. Pregnancy test; ensure result is negative (serum pregnancy test may be substituted)
    b. Urinalysis
6. Assess for ECOG performance status
7. Assess for AEs and SAEs
8. Update concomitant medications

Dosing and post-dose

1. Administer investigational product
2. Take vital signs every 30 minutes (± 5 minutes) during infusion, at completion of infusion (± 5 minutes), and 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post infusion
3. Assess for AEs and SAEs

5.1.3 Every 12-Week Treatment Period

5.1.3.1 Treatment Visits: Week 25 (+/- 3 days), Weeks 37, 49 (+/- 3 days); Visits 8, 10, 12, 14, 15 and 16

The first dose of 12-Week treatment (Week 25 ± 3 days) is 4 weeks after the last dose of the 4-Week treatment phase. All subsequent visits will be 12 weeks (± 3 days) later starting on Week 37.

Pre-dose

1. Administer questionnaires
    a. LCSS-Meso (collected with ePRO device)
    b. EQ-5D-3L (collected with ePRO device)
    c. BPI-sf (collected with ePRO device)
2. Perform physical examination including weight (if applicable, record new findings as AEs or SAEs). Subject weight at baseline should be used for dosing calculations unless there is a ≥ 10% change in weight. Alternatively, the dose can be calculated based on body weight measured prior to each dose
3. Take vital signs before administration of investigational product
4. Collect blood samples for:
    a. Serum chemistry
    b. Hematology

c. Central safety labs
d. PK (Visits 8 and 10)
e. Immunogenicity (Visits 8 and 10)
f. Biomarker samples
   iii. Flow cytometry (Visit 8 only)
   iv. Cryopreserved PBMC (Visit 8 only)
   v. Circulating soluble factors (Visit 8 only)

5. Collect urine for:
   a. Pregnancy test; ensure result is negative (serum pregnancy test may be substituted)
   b. Urinalysis
6. Evaluate disease via CT or MRI scan
7. Assess for AEs and SAEs
8. Update concomitant medications

Dosing and post-dose

1. Administer investigational product
2. Take vital signs every 30 minutes (± 5 minutes) during infusion, at completion of infusion (± 5 minutes), and 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post infusion
3. Assess for AEs and SAEs
4. Perform ECG (between 2 and 6 hours after treatment administration; every 3 months the 1st year and every 6 months the 2nd year starting at Visit 14 (Week 61)
   a. The first 100 subjects will have triplicate ECGs (at least 1 minute apart)
   b. The remaining subjects will have a single ECG
5. Collect blood for post-dose PK samples (end of infusion, Visit 8 only) (± 5 minutes)

5.1.3.2 Non-dosing Study Visits: Week 31, 43, and 55 (+/- 3 days); Visits 9, 11, and 13

During the Every 12-Week Treatment Period, subjects will have non-dosing study visits every 6 weeks after dosing during the first year of treatment (ie, months 6-12). The first non-dosing study visit will take place Week 31 ± 3 days.

1. Perform physical examination including weight (if applicable, record new findings as AEs or SAEs)
2. Take vital signs
3. Collect blood samples for:
   c. Serum chemistry
   d. Hematology
   e. Central safety labs

4. Collect urine for urinalysis
5. Assess for ECOG performance status
6. Evaluate disease via CT or MRI scan
7. Assess for AEs and SAEs
8. Update concomitant medications

5.1.4 End of Treatment Visit

End of treatment evaluations need not be repeated at the end of treatment visit if they have been performed within the previous 14 days.

1. Administer questionnaires
   a. LCSS-Meso (collected with ePRO device)
   b. EQ-5D-3L (collected with ePRO device)
   c. BPI-sf (collected with ePRO device)
2. Perform physical examination including weight (if applicable, record new findings as AEs or SAEs)
3. Take vital signs
4. Collect blood samples for:
   a. Serum chemistry
   b. Hematology
   c. Central safety labs
   d. PK
   e. Immunogenicity
   f. Biomarker samples
      i. Circulating soluble factors
      ii. Circulating apoptosis markers
      iii. RNA
      iv. Cryopreserved PMBC
5. Collect urine for:
   a. Pregnancy test; ensure result is negative
   b. Urinalysis
6. Assess for ECOG performance status
7. Perform ECG
   a. The first 100 subjects will have triplicate ECGs (at least 1 minute apart)
   b. The remaining subjects will have a single ECG
8. Evaluate disease via CT or MRI scan
9. Assess for AEs and SAEs
10. Update concomitant medications

11. Assess for new systemic anticancer treatments
12. Assess for survival

5.1.5 Follow-up Periods

All subjects will be followed for safety every 30 days (± 3 days) through 90 days after the last dose of investigational product or at the time of initiation of new systemic anticancer treatment. After 90 days, only subjects with investigational product-related SAEs will continue to be followed for safety. All subjects will be followed for survival every 3 months (± 14 days) until the end of the study (approximately 30 months from the date the last subject is randomized into the study or the sponsor stops the study).

5.1.5.1 Short Term Follow-up Visits (30 Days, 60 Days, and 90 Days [+/- 3 Days] Post Last Dose or at the Time of Initiation of New Systemic Anticancer Treatment)

1. Perform physical examination including weight (if applicable, record new findings as AEs or SAEs).
2. Take vital signs
3. Collect blood samples for:
   a. Serum chemistry
   b. Hematology
   c. Central safety labs
   d. PK (Day 90 visit only)
   e. Immunogenicity (Day 90 visit only)
4. Collect urine for urinalysis
5. Perform ECG (Day 90 visit only)
   a. The first 100 subjects will have triplicate ECGs (at least 1 minute apart)
   b. The remaining subjects will have a single ECG
6. Evaluate disease via CT or MRI scan (Day 90 visit only)
7. Assess for AEs and SAEs
8. Update concomitant medications
9. Assess for new systemic anticancer treatments
10. Assess for survival

5.1.5.2 Long Term Follow-up Period (Every 3 Months [+/- 14 Days] After 90-day Follow-up Visit Until the End of the Study)

1. Evaluate disease via CT or MRI scan until PD or initiation of subsequent anticancer therapy
2. Assess for study drug-related SAEs until the events have been resolved, returned to baseline, deemed irreversible by treating physicians, or until the subject dies
3. Assess for new and subsequent systemic anticancer treatments

4. Assess for survival

5.1.6 Study Procedures Following the Primary Analysis of Study D4880C00003

Following review of the primary analysis data from Study D4880C00003 which demonstrated no statistically significant improvement in overall survial of tremelimumab compared with placebo in subjects with unresectable malignant mesothelioma, the sponsor recommended that all patients remaining on study treatment were unblinded. After unblinding , all patients will have the option to discontinue study treatment and withdraw from the study, or continue on the study as detailed below, depending on the study arm that they were originally on.

Patients currently receiving tremelimumab, who in the opinion of the investigator are receiving clinical benefit, will be given the option to continue to receive tremelimumab. These patients can continue to receive study treatment until a study discontinuation criterion (eg, withdrawal of consent) has been met as assessed by the investigator (see Section 4.2.3). Investigators will report all SAEs to the sponsor until 90 days after receipt of their last dose of study treatment, see Section 5.1.6.1 and Table 5.1-3 for further details. Drug accountability data will also be collected.

Patients who have discontinued tremelimumab and who have completed the 90-day safety follow-up are to be withdrawn from study at the earliest opportunity and no further data will be collected from these patients after withdrawal. At any time after completion of the study, if an investigator or qualified designee becomes aware of an SAE that is suspected by the investigator or qualified designee to be related to investigational product, the event must be reported to also known as AZ Data Entry Site (AZ DES), which will be responsible for processing all SAEs onto the AZ global safety database.

Patients currently receiving placebo or those who have discontinued placebo are expected to withdraw from the study. Investigators will report all SAEs to the sponsor until date of withdrawal from the study. No further data will be collected for these patients after withdrawal. Treatment and assessments will revert to standard of care at their particular site.

All safety data produced by all ongoing patients up to the time of approval of protocol amendment 5 will continue to be entered into the web based data capture (WBDC) system.

Following approval of protocol amendment 5, the WBDC system will be decommissioned and SAE data will be collected via paper and emailed (preferably) or faxed directly to (also known as AZ DES) (see Section 6.4.2.2 for further information), which will be responsible for

processing all SAEs onto the AZ global safety database. Drug accountability information will be stored in the patient notes at site.

5.1.6.1 Tremelimumab Treatment Continuation

For those patients continuing on tremelimumab, the following assessments (with the exception to assessing for SAEs) will be performed at the discretion of the investigator and in the best interest of the patient and their safety:

Pre-dose

1. Perform physical examination including weight (if applicable, record new findings as AEs or SAEs). Subject weight at baseline should be used for dosing calculations unless there is a ≥ 10% change in weight. Alternatively, the dose can be calculated based on body weight measured prior to each dose
2. Take vital signs before administration of tremelimumab
3. Collect blood samples for:
   a. Serum chemistry
   b. Hematology
4. Collect urine for:
   a. Pregnancy test; ensure result is negative (serum pregnancy test may be substituted)
   b. Urinalysis
5. Evaluate disease via CT or MRI scan, as clinically indicated
6. Assess for AEs and SAEs (SAEs require reporting)

Dosing and post-dose

1. Administer tremelimumab
2. Take vital signs every 30 minutes (± 5 minutes) during infusion, at completion of infusion (± 5 minutes), and 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post infusion
3. Assess for AEs and SAEs (SAEs require reporting)
4. Perform ECG (between 2 and 6 hours after treatment administration, if clinically indicated)

5.2 Description of Study Procedures

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study.

5.2.1 Medical History and Physical Examination, Weight, Vital Signs, and ECG

A medical history will be recorded at screening.

A complete physical examination will be conducted including height and weight. Findings from medical history and physical exam will be given a baseline grade according to the procedure for AEs. Increases in severity of preexisting conditions during the study will be considered AEs, with resolution occurring when the grade returns to at or below the pre-study baseline.

Vital signs will be monitored at screening and at every visit during the study. Vital signs include temperature, blood pressure, pulse rate, respiratory rate, and pulse oximetry. Vital signs will also be collected every 30 minutes (± 5 minutes) during infusion, at completion of infusion (± 5 minutes), and 30 and 60 minutes (± 5 minutes) post infusion. Pulse oximetry is required on dosing days only during infusion and 30 and 60 minutes post infusion.

In order to evaluate the potential risk for QTc (the time between the start of the Q wave and the end of the T wave corrected for heart rate) prolongation with tremelimumab, subjects will have ECGs collected at specified time points noted in the schedule of events. All ECGs performed during the study will be 12-lead and will be obtained at screening, following the first dose on Week 1, Week 5, Week 13, and every 3 months thereafter during the first year of treatment (Visits 1, 2, 3, 5, 8, 10, and 12). Beginning with the second year of treatment (starting at Visit 14), ECGs will be performed every 6 months until discontinuation of treatment. All ECGs on dosing days must be performed between 2 and 6 hours after treatment administration. The first 100 subjects will have ECGs obtained in triplicate and within a 5-minute time period for all time points (at least 1 minute apart). The remaining subjects will have a single ECG performed for all time points. In case of clinically significant ECG abnormalities including an ECG that demonstrates a QTc value > 500 msec, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 min) to confirm prolongation.

5.2.2 Clinical Laboratory Tests

Clinical laboratory safety tests will be performed in a licensed local clinical laboratory. Urine pregnancy tests may be performed at the site using a licensed test (dipstick). A serum pregnancy test is required at screening and may be performed in place of a urine pregnancy test for all dosing visits. Abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

The following clinical laboratory tests will be performed (see Table 5.1-1 and Table 5.1-2 for the schedule of tests):

Serum Chemistry

- Calcium
- Chloride
- Magnesium
- Potassium
- Sodium
- Bicarbonate
- AST
- ALT
- Alkaline phosphatase (ALP)
- Total bilirubin
- Amylase [a]
- Thyroid stimulating hormone (TSH)
- Gamma glutamyl transferase (GGT)
- Lactic dehydrogenase (LDH)
- Uric acid
- Creatinine
- Blood urea nitrogen (BUN)
- Glucose
- Albumin
- Total protein
- Triglycerides
- Cholesterol
- Lipase [a]
- C-reactive protein (CRP) [b]

[a] To be analyzed at local and central lab.

[b] To be analyzed at central lab only.

Note for serum chemistries: Tests for AST, ALT, ALP, and total bilirubin must be conducted concurrently and assessed concurrently.

Hematology

- White blood cell (WBC) count with differential
- Red blood cell (RBC) count
- Hematocrit
- Hemoglobin
- Platelet count
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin concentration (MCHC)

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Blood
- Bilirubin
- Microscopy including WBC/high power field (HPF), RBC/HPF

Pregnancy Test (females of childbearing potential only)

- Urine human chorionic gonadotropin (hCG)
- Serum β-hCG (at screening only)

Other Safety Tests

- Hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody
- HIV antibodies (eg, HIV-1 or HIV-2)

5.2.3 Pharmacokinetic Evaluation and Methods

The time points for PK sampling are described in Table 5.1-1 and Table 5.1-2. A validated enzyme-linked immunosorbent assay (ELISA) will be used for the quantitative determination of tremelimumab in human blood. Details of PK sample collection are provided in the Laboratory Manual.

5.2.4 Immunogenicity Evaluation and Methods

The time points for the assessment of anti-tremelimumab antibodies are described in Table 5.1-1 and Table 5.1-2. A validated electrochemiluminescence assay (ECLA) using a Meso Scale Discovery (MSD) platform will be used for the detection of anti-tremelimumab antibodies in human blood. Details for sample collection will be provided in the Laboratory Manual.

5.2.5 Biomarker Evaluation and Methods

Blood samples will be collected and analyzed to evaluate cellular, protein, and nucleic acid biomarkers that relate to tremelimumab treatment.

The numbers of T cells, B cells, and other immune cells as well as subsets of T cells will be evaluated in whole blood by flow cytometry. The activation status of T cells will also be assessed in the same study. Whole blood samples will be collected pre-infusion on Visits 1, 2, 3, 5, and 8. Additionally, absolute lymphocyte count at baseline and in response to tremelimumab treatment will be evaluated for any relationship with treatment outcome. Peripheral blood mononuclear cells will be isolated from blood samples and cryopreserved for further exploratory analysis such as quantification of myeloid-derived suppressor cells.

Blood samples will be collected for analysis of circulating levels of soluble factors such as CRP, cytokines, and chemokines. They may include but are not limited to soluble CTLA-4, soluble PD-L1, soluble B7.1/B7.2, soluble IL-6R, vascular endothelial growth factor, fibroblast growth factor, IL-1 IL-2, IL-4, IL-6, IL-8, IL-10, cancer biomarkers (alpha fetoprotein, carcinoembryonic antigen, cancer antigen 125, prostate specific antigen, soluble mesothelin-related protein [SMRP]), granzyme B, IFN, C-X-C motif chemokine 10 (CXCL10), suppressor of cytokine signaling 3 (SOCS3), a proliferation inducing ligand, B-cell activating factor, insulin-like growth factor (IGF)-1, IGF-2, and autoantibodies to host and tumor antigens and antibodies to endogenous pathogens to explore their association with tremelimumab treatment and clinical outcome. Additionally, levels of circulating nucleosomal DNA as a marker of apoptosis may be evaluated in response to treatment and relationship with clinical outcome.

Whole blood samples will be collected in PAXgene tubes and stored frozen for RNA and/or micro ribonucleic acid (miRNA)/RNA sample preparation. Ribonucleic acid may be used in the analyses of transcript and/or miRNA expression and stored for future analyses. Messenger ribonucleic acid (mRNA) levels of selected inflammatory/immune and cytokine pathways that may include but not limited to IL-6, IL-8, tissue inhibitor of metalloproteinase 1 (TIMP1), Fc gamma receptor 2 B (FCGR2B), leukemia inhibitory factor (LIF), IFN, CXCL10, SOCS3 and their association with tremelimumab treatment outcome. Ribonucleic acid analyses may be conducted to generate hypotheses associated with the mechanisms of action of tremelimumab and identify subsets of subjects responsive to tremelimumab.

Archival tumor samples, when available, may be evaluated for the immunosuppressive biomarker PD-L1 protein on tumor cells and the expression level and localization of other markers of inflammatory/immune signature that may include but not be limited to CTLA-4, CD3, CD4, CD8, protein tyrosine phosphatase receptor type C (CD45RO), forkhead box P 3 (FOXP3), and granzyme by immunohistochemistry analysis to evaluate any relationship with subject response to treatment with tremelimumab. Additionally, genetic alterations, such as tumor mutations and polymorphisms, may be analyzed in archival tumor tissue and/or blood samples through relevant methodologies that may include gene sequencing in order to evaluate the relationship of genetic variations in mesothelioma with treatment outcome to tremelimumab. Finally, mRNA expression levels of selected inflammatory/immune signatures may be evaluated to determine if there is a gene signature that can predict for tremelimumab treatment outcome.

Details for sample collection, processing, storage, and shipment will be provided in the Laboratory Manual.

5.2.6 Tumor Biopsies

During the screening period and following informed consent, the optional image-guided core needle tumor biopsy may be performed according to institutional practice if deemed clinically feasible. Tumor lesions used for biopsy should not be lesions used as RECIST target lesions, unless there are no other lesions suitable for biopsy. If needed or in case of doubt, consult with the medical monitor prior to performing the biopsy. If a RECIST target lesion is used for biopsy the lesion must be ≥ 2 cm in longest diameter. Additional tumor biopsies are permitted as clinically indicated (eg, for mixed responses or upon PD). If clinically practical, subjects will undergo 4 core biopsies, but a minimum of at least 3 core biopsies are required. The first and third core biopsies will be placed in formalin and processed for formalin fixed paraffin embedded, while the second and fourth core biopsies (fourth biopsy, if available) will be immediately frozen in liquid nitrogen or equivalent method and then stored at -60°C or below. In

exceptional cases, excisional or punch biopsies are permitted and may be substituted for the required minimum of 3 core biopsies if sufficiently large (4 mm or greater in diameter).

5.2.7 Other Fluids/Tissues

If fluids and/or tissue are collected from subjects in the course of standard clinical management, any residual material left over after all necessary medical assessment (if any) have been made will be refrigerated and shipped to the sponsor for further processing.

5.2.8 Disease Evaluation and Methods

5.2.8.1 Response Assessments

Imaging assessments will be performed at baseline (within 28 days before randomization with an exception discussed in Section 5.1.1) and every 3 months during the 4-week treatment period, every 6 weeks during Weeks 25-61, and every 3 months thereafter until confirmed objective disease progression irrespective of whether the subject has discontinued investigational product. In the absence of progression, the next assessment should be performed at the next scheduled visit. In addition, when available, scans done after disease progression in subjects who permanently discontinue investigational product will be obtained when possible to determine if there was any delayed tremelimumab activity unless consent is withdrawn or the subject is lost to follow-up or starts receiving another anticancer therapy. Subjects who discontinue treatment without radiographic evidence of disease progression (eg, clinical deterioration), should undergo an imaging assessment as soon as possible to provide radiographic evidence of disease progression, if feasible. Additional scans can also be done at any time based on investigator discretion.

- An initial increase in tumor burden or the appearance of new lesions could precede immunotherapy-induced tumor regression (Wolchok et al, 2009). According to this model of response, subjects initially assessed as PD by modified RECIST criteria for mesothelioma, in the absence of significant clinical deterioration warranting discontinuation of study treatment will continue treatment and receive a confirmatory scan at least 4 weeks later. The following criteria will be used to determine if study treatment is continued:
  - If the tumor burden at the confirmatory scan is more than 20% larger than the tumor burden at the initial PD scan, the subject will be considered to have confirmed PD and will be discontinued from study treatment
  - If the tumor burden at the confirmatory scan is within 20% of the tumor burden at the initial PD scan, the subject will be considered to have SD and will continue treatment until the next scheduled scan 3 months after the initial PD. Any subsequent scheduled tumor assessment visit showing that the tumor burden is more than 20% larger than the tumor burden at the initial PD scan will be considered as confirmed PD, and the subject will be discontinued from study treatment

- It is important to maintain the schedule of assessments every 3 months and subjects having confirmatory scans for PD must return for the next scheduled visit per protocol.

Pleural Mesothelioma

Modified RECIST criteria for mesothelioma (Byrne and Nowak, 2004) will be used to assess pleural mesothelioma using CT (with contrast) scans of the chest, abdomen, and pelvis. Where CT is contraindicated MRI may be used. At the level of the pleura, tumor thickness perpendicular to the chest wall or mediastinum is measured in 2 positions at 3 separate levels on transverse cuts of CT scans. The sum of six measurements defines a pleural unidimensional measure. Transverse cuts, at least 1 cm apart and related to anatomical landmarks in the thorax, 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. Nodal, subcutaneous, and other bidimensionally measurable lesions are measured unidimensionally as per the RECIST criteria. Unidimensional measurements are added to obtain the total tumor measurement.

Modified RECIST criteria for pleural mesothelioma are as follows:

- **Complete Response**: Complete response (CR) is defined as the disappearance of all target lesions with no evidence of tumor elsewhere.
- **Partial Response**: Partial response is defined as at least a 30% reduction in the total tumor measurement.
- **Stable Disease**: Stable disease is defined as subjects who fulfilled the criteria for neither PR nor PD.
- **Progressive Disease**: Progressive disease is defined as an increase of at least 20% in the total tumor measurement over the nadir measurement, or the appearance of one or more new lesions.

Peritoneal Mesothelioma

Peritoneal mesothelioma will be assessed using RECIST criteria v 1.1(Eisenhauer et al, 2009). To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion (10 mm by CT scan [CT scan slice thickness no greater than 5 mm], 10 mm caliper measurement by clinical exam, or 20 mm by chest x-ray). When more than one measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all

involved organs should be identified as target lesions and will be recorded and measured at baseline. Remaining lesions will be considered as non-target lesions.

The RECIST criteria for peritoneal mesothelioma are as follows:

- **Complete Response:** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- **Partial Response:** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease:** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- **Stable Disease:** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Immune-related Response Criteria

Central tumor scan review will be used to assess durable DCR, PFS, ORR, and duration of response based on irRC (Wolchok et al, 2009). Response will be assessed by an independent review committee consisting of qualified experts in malignancies. All images will be collected and stored for possible future central re-analysis.

5.2.8.2 ECOG Performance Status

The standard ECOG performance status scales and criteria (Oken et al, 1982) will be used. A copy is provided in Appendix 2.

5.2.8.3 Patient-reported Outcome Assessments

The LCSS-Meso, BPI-sf, and EQ-5D-3L are self-administered questionnaires and are to be completed by the subject without the assistance of the investigational site personnel. These questionnaires are completed using an ePRO device. All questionnaires should be completed before any other study procedures are conducted.

Lung Cancer Symptom Scale-mesothelioma

The LCSS-Meso is an 8-item subject-completed questionnaire (Appendix 5) designed to assess the impact of 5 major symptoms experienced by the subject in the past 24 hours prior to completing the questionnaire. The symptoms captured in the LCSS-Meso are appetite loss,

fatigue, cough, dyspnea, and pain. Responses range from 0 “Not at all” to 100 “Very Much” using visual analogue scales (VAS; 100 mm horizontal line). Normally subjects put a mark on the 100 mm line on a pen and paper version of the instrument corresponding to the intensity of response to the items in question (0 lowest rating; 100 highest rating). Each item is given an individual score equal to the length of the line marked by the subject, with zero corresponding to the lowest (best) rating and 100 representing the highest (worst) rating (ie, highest degree of severity of symptoms). The aggregate score (an average of all 8 items), the average symptom burden index (the mean of all 5 major symptoms), and individual items are used to evaluate specific areas of change (Hollen et al, 1995). Subjects will be provided with the ePRO device at screening and will complete the questionnaire once during screening, daily during the 4-Week treatment phase, and daily during the 12-Week treatment phase, and at the end of treatment. Since the study will use an ePRO device and not a pen and paper, a shorter length VAS line will be displayed due to the screen size. The length of the VAS on the ePRO device will be calculated, and scores will be transformed back to a 0-100 scale. The subjects will be instructed to bring the ePRO device to each visit and investigational site personnel will check compliance.

Brief Pain Inventory-short Form (BPI-sf)

The BPI-sf is a widely used, self-administered questionnaire (Appendix 6) developed to assess the severity of pain and the impact of pain on functioning (Cleeland, 2006). The BPI-sf is a 2-page questionnaire that includes front and back body diagrams, 4 pain severity items and 7 pain interference items rated on a 0-10 scale, and an item for rating pain relief from analgesics. The 4 items of pain severity domain, which assess pain at its “worst,” “least,” “average,” and “now” (current pain) on an 11-point numeric rating scale from 0 (No Pain) to 10 (Pain as bad as you can imagine). Studies document good to excellent psychometric performance across different patient populations including patients with cancer pain (eg, Seidman et al, 1995; Wu et al, 2010). This questionnaire will be completed using the ePRO device prior to any study procedures at screening, at or before the 4-Week treatment study visits, at or before study visits during the 12-Week treatment phase, and at the end of treatment. The “worst” pain item will be collected on a daily basis using the ePRO device. Item 7 will be removed from the questionnaire and an additional question on any change in the subject’s pain medications or treatment will be collected on a daily basis using the ePRO device. The investigational site personnel will check compliance at each visit.

EQ-5D 3 Level Version (EQ-5D-3L)

The EQ-5D is a standardized measure of health status (Appendix 7) to provide a simple, generic measure of health for clinical and economic appraisal (The EuroQol Group, 1990). The

EQ-5D-3L essentially consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled "Best imaginable health state" and "Worst imaginable health state." It is cognitively undemanding, taking only a few minutes to complete. This questionnaire will be completed on an ePRO device prior to any study procedures at screening, at or before 4-Week treatment study visits, at or before study visits during the 12-Week treatment phase, and at the end of treatment. Since the study will use an ePRO device and not a pen and paper, a shorter length EQ-VAS line will be displayed due to the screen size. The length of the EQ-VAS on the ePRO device will be calculated, and scores will be transformed back to a 0-100 scale. The investigational site personnel will check compliance at each visit.

5.2.9 Estimate of Volume of Blood to Be Collected

No more than 50 mL of blood will be drawn from any subject per day across all tests combined on days in which blood is collected. The estimated volume of blood to be collected during the 4-Week treatment phase is approximately 175 mL. Approximately 100 mL will be collected during the 12-Week treatment phase. Approximately 70 mL will be collected during the remaining visits (end of treatment and follow-up visits). The total volume to be collected in any subject will depend upon the number of treatment visits administered and the duration of safety follow-up.

6 ASSESSMENT OF SAFETY

6.1 Safety Parameters

6.1.1 Adverse Events

The ICH Guideline for Good Clinical Practice (GCP) E6 (R1) defines an AE as:

> Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

Adverse events may be treatment emergent (ie, occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

6.1.2 Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
  This term refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that may have led to death.

- Requires inpatient hospitalization or prolongation of existing hospitalization
  In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in an outpatient setting.

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

- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

  Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive

treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

6.1.3 Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to the understanding of the investigational product and requires close monitoring and communication by the investigator to the sponsor. An AESI may be serious or nonserious. The reporting of AESIs allows ongoing subject health care and analysis of these events in order to characterize and understand them in association with the use of this investigational product. The mechanism of action of tremelimumab involves activation of the immune system and therefore the most common AEs associated with tremelimumab therapy are inflammatory in nature and can be seen in any organ. All events, regardless of their designation of special interest, will continue to be closely monitored and reviewed. A full list of possibly related AEs based on the totality of data evaluated to date is available in the Investigator's Brochure. Moreover, as per Section 4.5.7, toxicity management guidelines have been developed according to what has been published recently on the toxicity profile of the anti-CTLA-4 compounds (Kaehler and Hauschild, 2011; Weber et al, 2012).

6.1.3.1 Gastrointestinal Disorders

Diarrhea/colitis is the most commonly observed treatment emergent SAE. In rare cases colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome if not properly managed. Diarrhea and colitis should be managed as per Tremelimumab Guidelines for the Management of Diarrhea and Colitis (Appendix 4).

6.1.3.2 Hepatic Function Abnormality

Adverse events of hepatic function abnormality of special interest to the sponsor are defined as any increase in laboratory liver function tests; ALT or AST to greater than 3 × ULN **and concurrent** increase in bilirubin to greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. In the event of hepatic function abnormality where the etiology is unknown, timely follow-up investigations and inquiries should be initiated by the investigational site, based on medical judgment, to make an informed decision regarding the etiology of the event.

6.1.3.3 Infusion Reactions

Adverse events of infusion reactions (also termed infusion-related reactions) are of special interest to the sponsor and are defined, for the purpose of this protocol, as all AEs occurring from

the start of the study treatment infusion up to 48 hours after the infusion start time. For all infusion reactions, the case report form (CRF) should be completed as instructed in Section 6.3, and all SAEs should be reported to (also known as AZ DES) as described in Section 6.4.

6.1.3.4 Hypersensitivity Reactions

In case of hypersensitivity reactions, the investigator should institute treatment measures deemed medically appropriate per institutional guidelines and notify the study medical monitor of the event.

- Grade 1 Transient flushing or rash; drug fever < 38°C
- Grade 2 Rash; flushing; urticaria; dyspnea; drug fever ≥ 38°C
- Grade 3 Symptomatic bronchospasm with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension; anaphylaxis
- Grade 4 Anaphylaxis
- Grade 5 Death

6.1.3.5 Autoimmunity

If a subject experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis, hepatitis, pancreatitis, thrombocytopenia, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing and immediate consideration of endocrinology consultation. If specific auto-antibodies are present, the blood sample taken for storage at baseline can be tested for the presence of auto-antibodies. Further dosing should be delayed until the etiology of the event is established. Continuation of investigational product in the presence of immune-mediated events should be done by the investigator with consideration to risk-benefit analysis.

6.1.3.6 Cardiovascular: QTc Prolongation

Past medical history of tremelimumab has indicated that the risk of QTc prolongation with tremelimumab therapy is extremely low. Subjects on this study will have repeat ECGs assessed in order to provide data on prolongation of the ECG QTc interval. In addition, the first 100 subjects will be assessed with more intensive ECG monitoring: triplicate ECGs (at least 1 minute apart) will be obtained at baseline, following the first dose on Day 1, Visit 3, Visit 5, subsequently every 3 months for the first year of dosing and every 6 months for the second year of dosing.

Resting 12-lead ECG

At screening, a 12-lead ECG must be performed to establish a baseline. For the first 100 subjects, baseline QTc will be determined by the average of 3 consecutive ECGs within a 5-minute time period for all time points (at least 1 minute apart) at the screening visit (prior to randomization). In the event of QTc prolongation (> 500 msec) at any visit, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 min) to confirm prolongation.

Electrocardiograms will be performed after the first dose and once Q12W thereafter for the first year of treatment. Electrocardiograms will be performed every 6 months after the first year of treatment or until discontinuation from treatment. Prior to discontinuation, all ECGs must be performed within 2 to 6 hours of the dosing. The final ECG will be performed at the short term follow-up visit.

For this study QTc prolongation is defined as:

- A single QTc value of ≥ 550 msec OR
- Repeat QTc measurements, within 48 hours of one another, where the average QTc interval is > 500 msec, but < 550 msec on both sets of ECGs

Any clinically significant abnormal findings or QTc prolongations during this period will be recorded as AEs.

At the conclusion of the study, a CRO to be selected by the sponsor will evaluate the first 100 subject's ECGs. A cardiologist at the CRO will review all ECGs for the presence of QTc prolongation or other abnormalities, in particular any changes in the T-wave morphology that would suggest a higher likelihood for the development of any arrhythmia.

6.2 Assessment of Safety Parameters

6.2.1 Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE 3.0. The determination of severity for all other events not listed in the NCI CTCAE should be made by the investigator based upon medical judgment (and documented in the CRF) using the severity categories of Grades 1 to 5 as listed below.

Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2 (moderate)	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Grade 3 (severe)	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
Grade 4 (life threatening)	An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).
Grade 5 (fatal)	Death (loss of life) as a result of an AE.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.1.2. A Grade 3 AE is not necessarily considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

6.2.2 Assessment of Relationship

6.2.2.1 Relationship to Investigational Product

The investigator is required to provide an assessment of relationship of all AEs and SAEs to the investigational product(s).

An event will be considered “not related” to use of the investigational product if any of the following tests are met:

- An unreasonable temporal relationship between administration of the investigational product and the onset of the event (eg, the event occurred either before, or too long after administration of the investigational product for the AE to be considered product-related)

- A causal relationship between the investigational product and the event is biologically implausible (eg, death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the event is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related event)

Individual AE/SAE reports will be considered "related" to use of the investigational product if the "not related" criteria are not met.

"Related" implies that the event is considered to be "associated with the use of the drug" meaning that there is "a reasonable possibility" that the event may have been caused by the product under investigation (ie, there are facts, evidence, or arguments to suggest possible causation).

6.2.2.2 Relationship to Protocol Procedures

The investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE Report Form. This includes nontreatment-emergent SAEs (ie, SAEs that occur prior to the administration of investigational product) as well as treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection, washout of an existing medication). The following guidelines should be used by investigators to assess the relationship of SAEs to the protocol:

Protocol-related:	The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative etiology present in the subject's medical record.
Not protocol-related:	The event is related to an etiology other than the procedure/ intervention that was described in the protocol (the alternative etiology must be documented in the study subject's medical record).

6.3 Recording of Safety Parameters

6.3.1 Recording of Adverse Events and Serious Adverse Events

Adverse events will be recorded on the CRF using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, relationship to the study procedure, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to (also known as AZ DES). See Section 6.1.2 for the definition of SAEs, and Section 6.2.1 and Section 6.2.2 for guidelines for assessment of severity and relationship,

respectively. If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE Report Form.

6.3.2 Recording of Adverse Events of Special Interest

All events of special interest (as defined in Section 6.1.3) will be recorded in the CRF according to the definitions of AE and SAE (Section 6.1.1 and Section 6.1.2, respectively). All AESIs that are regarded as serious (as per seriousness criteria defined in Section 6.1.2) must also be reported in an SAE Report Form.

6.3.2.1 Recording of Hepatic Function Abnormality

Events of hepatic function abnormality (as defined in Section 6.1.3.2) should be recorded in the CRF according to the definitions of AE and SAE (Section 6.1.1 and Section 6.1.2, respectively):

- If the underlying diagnosis for the hepatic function abnormality is known (including progression of pre-existing disease such as primary or metastatic malignancy), the diagnosis should be recorded as an AE/SAE per Section 6.3.1.
- If the underlying diagnosis for the hepatic function abnormality remains unknown, the term "hepatic function abnormal" should be used to report the AE/SAE per Section 6.4.3.2.

6.4 Reporting Requirements for Safety Parameters

6.4.1 Study Reporting Period and Follow-up for Adverse Events

The reporting period for AEs is the period immediately following the time that written informed consent is obtained through 90 days post investigational product administration.

New (nonserious) AEs that start after the reporting period has ended will not be collected. All AEs that start during the reporting period will be followed to resolution until the end of subject participation in the study even if the resolution date extends beyond the AE reporting period.

6.4.2 Reporting of Serious Adverse Events

6.4.2.1 Study Reporting Period and Follow-up for Serious Adverse Events

The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through the end of subject participation in the study. After submitting an initial SAE report for a subject (to also known as AZ DES), the investigator is required to follow the subject until the resolution of the SAE and provide further information on the subject's condition to or designee ( ).

, also known as AZ DES, will be responsible for processing all SAEs onto the AZ global safety database.

At any time after completion of the study, if an investigator or qualified designee becomes aware of an SAE that is suspected by the investigator or qualified designee to be related to investigational product, the event must be reported to (also known as AZ DES).

The investigator is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

6.4.2.2 Notifying the Sponsor of Serious Adverse Events

Within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational product, the investigator or qualified designee must complete the SAE Report Form and email it to or designee.

or designee contact information:

The sponsor is responsible for reporting certain SAEs as expedited safety reports to appropriate regulatory authorities, all study ethics committees, and all participating investigators, in accordance with ICH Guidelines and/or local regulatory requirements (see Section 6.4.2.3). The sponsor may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that investigators submit additional information requested by the sponsor as soon as it becomes available.

Investigators should provide all available information at the time of SAE Report Form completion. Investigators should not wait to collect additional information to fully document the event before notifying of an SAE. When additional information becomes available, investigators should submit a follow-up SAE Report Form (separate from the initial report form) with the new information. Any follow-up information to an SAE also needs to be provided to within 24 hours of learning of the new information.

6.4.2.3 Safety Reporting to Investigators, Institutional Review Boards or Independent Ethics Committees, and Regulatory Authorities

The sponsor is responsible for timely reporting of all applicable SAEs to regulatory authorities, investigators, and IRBs/IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. The sponsor will also prepare an expedited report for

other safety issues where these might materially alter the current benefit-risk assessment of an investigational product or that would be sufficient to consider changes in the administration of the investigational product or in the overall conduct of the study.

For all investigators located in the European Economic Area, the sponsor will be responsible for reporting suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities including the European Medicines Agency (EMA), investigators, and IRBs/IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. The SUSARs will be submitted within 7 days for fatal and life-threatening events and within 15 days for other serious events, unless otherwise required by national regulations.

For all other investigators, the sponsor will prepare an expedited report for all SAEs that are unexpected and potentially related to the investigational product, and copies will be distributed to all concerned regulatory authorities, investigator(s), and IRBs/IECs according to applicable laws and regulations. The investigational site also will forward a copy of all expedited reports to the site's applicable IRB/IEC. Investigators must also submit safety information provided by the sponsor to the IRB/IEC as detailed in Section 10.1 and Section 10.2.

6.4.3 Other Events Requiring Immediate Reporting

Immediately reportable events (IREs) are event that are required to be reported within 24 hours of knowledge of the event to the sponsor.

6.4.3.1 Overdose

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study subject with the investigational product, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to (also known as AZ DES) or designee ( ) using the Safety Fax Notification Form (see Section 6.4.2.2 for contact information). If the overdose results in an AE, the AE must also be recorded on the AE CRF (see Section 6.3.1). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be reported as an SAE (see Section 6.3.1 and Section 6.4.2).

6.4.3.2 Hepatic Function Abnormality

Hepatic function abnormality (as defined in Section 6.1.3) of unknown etiology, or which is considered attributable to investigational product, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to (also known as AZ DES) using the SAE Report Form, even if the event is considered to be nonserious (see Section 6.4.2.2 for contact information). The investigator will review the data with the study medical monitor. The investigator should then use clinical judgment to establish the cause based on local standard of care and follow the subject by conducting testing as clinically indicated.

- If, after appropriate workup, in the opinion of the investigator, the underlying diagnosis for the abnormality remains unexplained, or is considered attributable to investigational product, discontinuation of dosing for the study subject should be considered.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor. If the etiology of the event remains unconfirmed and/or is considered related to investigational product (see Section 6.2.2.1), a prompt cumulative review of safety data and the circumstances of the event in question will be conducted and assessed by the MedImmune Safety Monitoring Committee (SMC; see Section 6.5) to determine whether continued dosing of current study subjects and/or study randomization should be interrupted, whether the protocol will be modified, or whether the study will be discontinued permanently. Review and approval by the SMC and IDMC are required for resumption of subject dosing or study randomization in the event that the study is interrupted. Where applicable, regulatory authorities and IRBs/IECs will be notified of any actions taken with the study.

6.4.3.3 Pregnancy

Pregnancy in a female subject who has received investigational product is required to be reported ***within 24 hours of knowledge of the event*** to (also known as AZ DES) or designee) using the Safety Fax Notification Form (see Section 6.4.2.2 for contact information).

Subjects who become pregnant during the study period must not receive additional doses of investigational product but will not be withdrawn from the study. If the subject requests to know which treatment she received, this information will be provided to her. After obtaining the subject's consent, the pregnancy will be followed for outcome of the mother and child (including any premature terminations) and should be reported to (also known as AZ DES) or designee) after outcome.

Should the investigator become aware of a pregnancy in the partner of a male study subject who has received investigational product this should be reported ***within 24 hours of knowledge of the event*** to (also known as AZ DES) or designee using the Safety Fax Notification Form (see Section 6.4.2.2 for contact information). The sponsor will endeavor to collect follow-up information on such pregnancies provided the partner of the study subject provides consent.

6.4.3.4 Events Meeting Study-stopping Criteria

Events that meet any of the study-stopping criteria (Section 3.3), with or without associated AEs or SAEs, are required to be reported ***within 24 hours of knowledge of the event*** to (also known as AZ DES) using the Safety Fax Notification Form (see Section 6.4.2.2 for contact information). The occurrence of these events does not automatically make an AE serious, but if the consequences of the event are serious, for example hospitalization, the event is serious and must be reported as an SAE (see Section 6.3.1 and Section 6.4.2).

6.5 Safety Management During the Study

The study medical monitor has primary responsibility for the ongoing medical review of safety data throughout the study. This includes review of SAEs and timely review of AEs and "other events" reported during the study. (also known as AZ DES) is responsible for the receipt, immediate review, investigation, and follow-up of SAEs and other IREs (eg, overdose and pregnancies) reported from the clinical study sites.

The SMC provides safety surveillance, guidance, and oversight for all clinical development studies in which MedImmune has sponsor accountabilities. The SMC members include the heads of Patient Safety, Clinical Development, and Regulatory Affairs, and external physician members with expertise in relevant therapeutic areas. The SMC reviews protocol-specific safety data at regularly scheduled meetings and ad hoc meetings, and provides oversight for individual study protocol safety committees, such as those specified for early-phase dose-escalation studies. Based on review of safety data, the SMC may suspend enrollment or subject dosing in clinical studies, request modification of study documents, or take other actions as deemed necessary. An IDMC will also be used in the study (see Section 7.7).

7 STATISTICAL CONSIDERATIONS

7.1 General Considerations

Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be

summarized by descriptive statistics, including mean, standard deviation, median, minimum, and maximum. Confidence intervals will be 2-sided, unless otherwise stated. Details of endpoint analyses will be described in the Statistical Analysis Plan.

Note: Following the primary analysis of overall survival of the study, no further formal statistical analysis of the data will be conducted. All safety data collected after the primary analysis, up until the approval of protocol amendment 5 at the site, will be listed and/or summarised as appropriate.

7.2 Analysis Populations

The Intent-to-treat (ITT) Population includes all subjects who are randomized into the study. Treatment arms will be assigned according to the initial randomization, regardless of whether subjects receive any investigational product or receive an investigational product different from that to which they were randomized.

The Safety Population includes all subjects who receive any amount of investigational product. Treatment arms will be assigned according to actual investigational product received.

7.3 Endpoints

7.3.1 Primary Endpoint

The primary endpoint is OS which is defined as the time from randomization until death due to any cause. For subjects who are alive at the time of data cutoff for the primary analysis or lost to follow-up, OS will be censored on the last date when subjects are known to be alive. The distribution of OS times will be estimated using the Kaplan-Meier method (Kaplan and Meier, 1958). The primary comparison of the 2 treatment arms will be performed after 456 OS events (deaths) have been observed by a stratified log-rank test with 3 stratification factors specified in Section 4.3, at the overall 2-sided α 0.05 significance level. In addition, the hazard ratio (HR) of tremelimumab vs placebo and its 95% confidence interval (based on profile-likelihood method) will be estimated using a stratified Cox regression model with ties handled by the Efron method (Efron, 1977). The primary analysis will be based on the ITT Population. The patterns of censoring between the 2 arms will be assessed. Where available, public tumor registries and/or vital records reports will be used to collect survival data, according to and respectful of country specific laws.

7.3.2 Secondary Endpoints

7.3.2.1 Efficacy

The secondary efficacy endpoints include OS rate at 18 months, PROs as well as durable DCR, PFS, ORR, and duration of response, based on modified RECIST criteria for pleural mesothelioma and RECIST criteria v 1.1 for peritoneal mesothelioma. The analysis of these secondary endpoints will be based on investigator-determined response data.

A hierarchical gate keeping strategy will be applied to control the overall type 1 error at 2-sided 0.05 for testing the primary endpoint of OS and key secondary efficacy endpoints. The details will be described in the Statistical Analysis Plan.

Overall Survival Rate at 18 Months

The OS rate at 18 months will be estimated using the Kaplan-Meier method (Kaplan and Meier, 1958). The comparison of OS at 18 months between the 2 treatment arms will be performed by a normal approximation under cloglog transformation (Klein et al, 2007).

Durable Disease Control Rate

Durable DCR is defined as the proportion of subjects with best response of CR, PR, or SD of ≥ 6 months duration. The 95% confidence interval for durable DCR will be estimated using an exact probability method.

Progression-free Survival

Progression-free survival will be measured from randomization to the first documentation of disease progression or death due to any cause, whichever occurs first. The PFS will be censored on the date of the last tumor assessment documenting absence of tumor progression for subjects who have no documented progression and are still alive prior to data cutoff or dropout. Subjects having no tumor assessments after randomization will have PFS censored on the date of randomization.

Patient-reported Outcomes

Patient-reported outcomes as measured by the LCSS-Meso (for disease-related symptoms and health-related QoL), EQ-5D-3L (for health status), and BPI-sf (for pain) will be summarized descriptively; the change from baseline for total score and individual domain scores by treatment arm at each time point will be explored. Change or improvement in overall disease-related symptoms will be measured using the symptoms burden scale of LCSS-Meso. The change from

baseline to total score will be summarized and statistically compared between the 2 treatment arms. The change from baseline in scores of individual items/symptoms for symptom burden scale of LCSS-Meso will be summarized.

Time to deterioration of disease-related symptoms will be analyzed using the same methods as those described for the primary endpoint described in Section 7.3.1. The definition of deterioration for each disease-related symptom will be specified in the Statistical Analysis Plan.

Overall Response Rate

Overall response rate is defined as the proportion of subjects with CR or PR. The 95% confidence intervals of ORR will be estimated using the exact probability method.

Duration of Response

Duration of response will be defined as the duration from the first documentation of objective response (CR or PR) to the first documented disease progression. Duration of response will be censored on the date of last tumor assessment documenting absence of disease progression for subjects who have no documented progression prior to data cutoff, dropout, or initiation of alternate anticancer treatment. Duration of response will be evaluated using the Kaplan-Meier method (Kaplan and Meier, 1958) for the subgroup of subjects with an objective response.

Progression-free survival and duration of response will be analyzed using the same methods as for primary endpoint described in Section 7.3.1. Cochran-Mantel-Haenszel test adjusting for 3 stratification factors specified in Section 4.3 will be used to compare the durable DCR and ORR between 2 treatment arms.

7.3.2.2 Safety

The safety endpoints include AEs and SAEs, changes from baseline in clinical laboratory evaluations, ECGs, and vital signs. Adverse events, treatment-related AEs, and SAEs will be summarized by system organ class and the Medical Dictionary for Regulatory Activities (MedDRA) preferred term, severity, and relationship to investigational product. The safety analysis will be descriptive in nature and no formal statistical comparison will be made.

7.3.2.3 Pharmacokinetics and Immunogenicity of Tremelimumab

PK Non-compartmental Analysis

Tremelimumab concentration data and summary statistics will be tabulated. Individual and mean blood tremelimumab concentration-time profiles will be generated and included in the report.

The PK of tremelimumab will be assessed using parameters including peak concentration (C_{max}), trough concentration (C_{min}) and time to peak concentration (T_{max}) after the first dose. Tremelimumab steady-state PK parameters including peak concentration ($C_{max,ss}$), trough concentration ($C_{min,ss}$), and time to peak concentration ($T_{max,ss}$) will be estimated. All PK parameters will be estimated by non-compartmental analysis. Accumulation to steady state will be assessed as the ratio of $C_{max,ss}$:C_{max} and $C_{min,ss}$:C_{min}. The trough concentrations observed during the 12-Week treatment phase will also be summarized.

Immunogenicity Analysis

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of subjects who develop detectable anti-tremelimumab antibodies. The immunogenicity titer will be reported for samples confirmed positive for the presence of anti-tremelimumab antibodies. The effect of immunogenicity on PK, pharmacodynamics, efficacy, and safety will be evaluated.

Population PK and Exposure-response Analysis

A population PK model will be developed using a non-linear mixed-effects modeling approach in subjects with malignant mesothelioma. The impact of physiologically-relevant subject characteristics (covariates) and disease on PK will be evaluated. The relationship between tremelimumab blood exposure and OS or safety will be evaluated.

7.3.3 Exploratory Endpoints

The variables to be included in the exploratory analyses may include:

1. To estimate and compare durable DCR, PFS, ORR, and duration of response based on irRC determined by central review data;
2. To evaluate changes in total score and individual scores in health-related QoL and disease-related symptoms (using LCSS-Meso), subject pain symptoms (using BPI-sf), and health status (using EQ-5D-3L) from baseline to each time point in subjects with durable clinical activity such as durable DCR (details of the statistical analysis will be provided in the SAP);
3. To evaluate the number of T cells, B cells, and other immune cells as well as subsets and activation status of T cells in whole blood by flow cytometry and explore their association with tremelimumab treatment and clinical outcome;
4. To evaluate absolute lymphocyte count (ALC) at baseline and in response to tremelimumab treatment with clinical outcome;
5. To evaluate levels of selected circulating soluble factors, that may include but are not limited to CRP, chemokines, cytokines, soluble CTLA-4, soluble PD-L1, cancer biomarkers,

nucleosomal DNA as a marker for apoptosis and autoantibodies to host and tumor antigens, and to explore their association with tremelimumab treatment and clinical outcome;

6. To evaluate mRNA or miRNA levels of selected inflammatory immune and cytokine pathways including but not limited to IL-6, IL-8, TIMP1, FCGR2B, LIF, IFN, CXCL10, SOCS3 and their association with tremelimumab treatment outcome;
7. To analyze tumor mutations and polymorphisms in archival tumor tissue when available and/or blood samples using relevant methodologies that could include gene sequencing in order to evaluate genetic variations in mesothelioma and their relationship with treatment outcome to tremelimumab;
8. To evaluate archival tumor samples when available for expression level and localization of immunosuppressive proteins, such as PD-L1 protein on tumor cells and/or markers of inflammatory/immune signature which may include but are not limited to CTLA-4, CD3, CD4, CD8, CD45RO, FOXP3 and granzyme, by immunohistochemistry analysis and explore any relationship with subject response to treatment with tremelimumab.

Progression-free survival based on the irRC will be analyzed using the same methods as for primary endpoint described in Section 7.3.1. The other exploratory endpoints will be summarized by descriptive statistics when possible. Depending on the nature of the data, geometric mean and other appropriate statistical summaries might be used as well.

7.4 Subgroup Analysis

The subgroup analyses of the primary and secondary efficacy endpoints will be performed for each of the 3 stratification factors specified in Section 4.3. Planned subgroup analyses also include age (≤ 60 vs > 60 years), race (White vs not-White), CRP (≤ 1.5 vs > 1.5 ULN), gender (male vs female), and country (USA vs other). Additional subgroup analysis may be performed if deemed necessary.

7.5 Interim Analysis

Two interim analyses are planned to assess futility and superiority of OS. The first interim analysis will be performed after 128 OS events (deaths) are observed from the first 180 subjects randomized, with the futility analysis based on these 180 subjects and efficacy analysis based on all subjects randomized up to this time. The second interim analysis will be performed after 342 OS events (75% of the total 456 OS events) have been observed. The futility boundary at the first interim is based on predictive power being less than 10% (corresponding approximately to HR 1). The interim and final efficacy boundaries are based on O'Brien-Fleming type flexible alpha spending methods (Jennison and Turnbull, 1999) and are presented in the following table if the two interim analyses occur at exactly 50% and 75% information time, respectively
( ).

Table 7.5-1 Futility and Efficacy Boundaries at Interim and Final Analyses

Analysis	# of OS events (% of information)	Futility and Efficacy Boundary
Interim 1	Futility: 128 OS events from first 180 subjects	Futility boundary: predictive power < 10% (HR ≈1)
	Efficacy: all OS events (≈ 228 [50]) from all randomized subjects at this time	Efficacy boundary: 2-sided p < 0.0030 (HR ≈ 0.66)
Interim 2	342 (75)	2-sided p < 0.0184 (HR ≈ 0.76)
Final	456 (100)	2-sided p < 0.0440 (HR ≈ 0.82)

The actual efficacy boundaries at 2 interim and final analyses will be adjusted according to the actual number of observed events at each analysis time so that the overall type I error is controlled at 2-sided 0.05 level.

7.6 Sample Size and Power Calculations

The planned sample size for this study is approximately 564 subjects, which is based on the group sequential design with 2 planned interim analyses. Subjects will be randomly assigned to the tremelimumab and placebo arms in a 2:1 ratio. If the interim boundaries specified in Section 7.5 are not crossed, then the final analysis will take place after observing a total of 456 OS events (deaths). The 2-sided significance level for the final analysis will be determined by O'Brien-Fleming type flexible alpha spending function. For example it is 0.0440 (corresponding approximately to HR 0.82) under the scenario presented in Table 7.5-1.

The sample size and power calculations are based on simulation method under a non-proportional hazard model that accounts for the potential delayed treatment effect for immunotherapy. Assuming exponential distribution of OS with median time of 7 months for placebo (Krug et al, 2011) and 4-month delayed effect (ie, HR 1 for the first 4 months and HR 0.56 thereafter) for tremelimumab (Roberts et al, 2011), a total of 456 OS events (deaths) are required to provide approximately 90% power and to control the overall 2-sided alpha level of 0.05 with 2 planned interim analyses specified in Section 7.5. The assumptions correspond to a hazard ratio of 1 for the first 4 months and 0.56 thereafter. Under these assumptions, the 1000 simulations generate a mean 0.71 for HR and a mean of 7 and 9.3 months for median time for placebo and tremelimumab arms, respectively. The detailed simulation description will be provided in the Statistical Analysis Plan.

With a planned accrual period of 32 months (approximately 15 subjects/months for first 12 months and 19 subjects/months thereafter), it is expected that a total of 564 subjects are needed in order to achieve 456 OS events at an approximate follow-up period of approximately

10 months. The 128 OS events from the first 180 subjects needed for the first interim analysis are expected to be reached after approximately 12 months of accrual and 11 months of follow-up. The 342 OS events for the second interim analysis are expected to be reached after approximately 32 months of accrual.

7.7 Independent Data Monitoring Committee

An IDMC will be established prior to the first subject being enrolled in the study. The first meeting will occur after 30 subjects have been randomized in the study and followed for 3 months. Subsequent meetings will be held every 6 months with responsibility for safeguarding the interests of study participants via review of accumulated safety data. In addition, two interim analyses are planned and the IDMC will review the unblinded interim data and inform the sponsor whether the interim boundaries specified in Section 7.5 are crossed. The IDMC will comprise a minimum of 2 independent physicians and 1 independent biostatistician, each of whom will be free from any material interest in the study. The IDMC members will be experts in the disease area and in immunotherapy. Each IDMC meeting will start with an open session, during which representatives from the sponsor (MedImmune) will update the IDMC on study progress and relevant operational issues. This will be followed by a closed session for IDMC members only, to review summaries of key aggregate safety data (and efficacy data at 2 interims) by treatment group which will have been prepared by an independent biostatistician, who is not involved in the conduct of the study, from the CRO. Recommendations for study conduct (continue as planned, continue with modifications, terminate) will be conveyed to the sponsor by the IDMC chair. Further details will be described in a separate IDMC charter.

8 DIRECT ACCESS TO SOURCE DOCUMENTS

The study will be monitored by the sponsor or designee on a regular basis throughout the study period. During monitoring visits, the investigator will provide direct access to all source documentation relevant to the subject's participation in the study. Source documentation includes, but is not limited to, the subject's clinic and/or office chart, hospital chart, ICFs, treatment notes, laboratory reports, pharmacy records, radiographs, recorded data from automated instruments, and any other records maintained to conduct and evaluate the clinical study. The investigator must also ensure that direct access to study documents be made available for study-related audits, IRB/IEC review, or regulatory inspection.

9 QUALITY CONTROL AND QUALITY ASSURANCE

9.1 Data Collection

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate and accurate case histories for the subjects treated under this protocol. Case histories include CRFs and supporting data including, but not limited to, signed and dated ICFs, progress notes, hospital charts, nurse's notes, diary cards or other worksheets provided to subjects, laboratory reports, ECG strips, etc.

Subject demographics and key/essential disease baseline characteristics thought to affect outcome, ie, stratification variables and other prognostic factors, may be collected, as available, for all subjects who provide written informed consent. For subjects who provide informed consent and were not entered/randomized into the study, the reason the subject was not entered/randomized, ie, did not meet one or more inclusion criteria, met one or more exclusion criteria, or other (eg, lost to follow-up, consent withdrawn), may also be collected.

9.2 Study Monitoring

The primary source document for this study will be the subject's medical record. If separate research records are maintained by the investigator(s), both the medical record and the research records will be monitored/audited for the purposes of the study.

The investigator and institutions involved in the study will permit study-related monitoring and provide direct access to all study records and facilities. Adequate time and space for monitoring visits should be made by the investigator or other investigator site staff.

The site monitor will visit study facilities at periodic intervals, in addition to maintaining necessary contact through telephone, e-mail, and letter, to ensure that the study is conducted and documented in accordance with the protocol, GCP, and applicable regulations. The site monitor will assess subject enrollment and informed consent procedures; investigational product storage, dispensing, administration and accountability; compliance with protocol procedures; completeness and accuracy of data entered onto validated data collection instruments (paper CRF or electronic data screen) against original source documents; the continued acceptability of the facilities and qualifications of the site staff; and the occurrence of AEs/SAEs. All aspects of the study will be carefully monitored for compliance with the protocol, applicable regulatory requirements, GCP, and the site's standard operating procedures.

The site monitor will discuss the conduct and progress of the study with the investigator and other site staff. The investigator must cooperate with the site monitor to ensure that corrective

action is taken to resolve any problems noted in the course of the monitoring, and that the preventative measures are put into place to prevent recurrence of issues. In cases where compliance is not achieved, shipment(s) of investigational product to the investigator will be discontinued and study participation by that investigator will be terminated.

9.3 Audit and Inspection of the Study

During and after the study, the sponsor or its representative may conduct audits of any data and any facility participating in the study. The investigator and institutions involved in the study will permit such study-related audits and provide direct access to all study records and facilities. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by the sponsor or its designated monitors, auditors, or regulatory agency representatives. The investigator agrees to participate in audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also perform inspections either during or after the study. In the event of an inspection by any regulatory authority, the investigator should promptly notify the sponsor. The investigator agrees to cooperate fully with inspections conducted by regulatory authorities and to allow representatives of the regulatory authority access to all study records. The investigator will forward to the sponsor a copy of any inspection records received.

10 ETHICS

10.1 Regulatory Considerations

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the ICH Guidelines on GCP, any applicable laws and requirements, and any conditions required by a regulatory authority and/or IRB/IEC that approves this study to be conducted in its territory. Good Clinical Practice is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical studies in a way that provides assurance that the data and reported results are credible and accurate, and that the rights, safety, and well-being of study subjects are protected.

Per GCP, the protocol will be reviewed and approved by the IRB or IEC of each participating center prior to study initiation. Serious adverse events regardless of causality will be reported to (also known as AZ DES) or designee, and the investigator will keep the IRB/IEC informed as to the progress of the study.

The investigator will explain the nature of the study and will inform the subject/legal representative that participation is voluntary and that the subject can withdraw or be withdrawn

from the study at any time. Written informed consent will be obtained from each subject/legal representative prior to the screening procedures to determine if study eligibility criteria are met. A copy of the signed ICF(s) will be given to every subject/legal representative, and the original(s) will be maintained with the subject's records.

10.2 Institutional Review Board or Independent Ethics Committee

A list of IRB/IEC members or a Statement of GCP Compliance should be obtained by the investigator and provided to the sponsor.

Any documents that the IRB/IEC may need to fulfill its responsibilities, such as protocol amendments, and information concerning subject recruitment, payment, or compensation procedures, or information from the sponsor will be submitted to the IRB/IEC. The IRB/IEC's written unconditional approval of the study protocol, the ICF(s), and any other written materials to be provided to subjects will be in the possession of the investigator and the sponsor before the study is initiated. The IRB/IEC's unconditional approval statement will be transmitted by the investigator to the sponsor prior to shipment of investigational product supplies to the site. This approval must refer to the study by exact protocol title and number, and should identify the documents reviewed and the date of review.

Protocol modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted should be obtained.

The IRB/IEC must be informed by the investigator of ICF changes or revisions of other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study (as applicable according to local regulations); new information that may affect adversely the safety of the subjects or the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

10.3 Informed Consent

Freely given informed consent will be obtained and documented for all subjects under this protocol (or a subject's legal representative, if the subject is unable to provide informed consent) in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the ICH Guidelines on GCP, any applicable laws and requirements, and any conditions required by a regulatory authority and/or IRB/IEC.

Information should be given in both oral and written form, and subjects or their legal representatives must be given ample opportunity to inquire about details of the study. Written informed consent will additionally be obtained for the conduct of certain protocol-specified procedures archival tumor tissue, genetic, and future use using separate ICFs. If the study will enroll subjects who are unable to give written informed consent, such as children or incapacitated subjects, informed consent will be obtained according to the site's standard operating procedures.

The ICF(s) generated by the investigator must be approved by the IRB/IEC and be acceptable to the sponsor. Informed consent forms must be written so as to be understood by the prospective subject/legal representative. Informed consent will be documented by the use of a written ICF(s) approved by the IRB/IEC and signed and dated by the subject or the subject's legal representative, and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. Each subject's signed ICF(s) must be kept on file by the investigator for possible inspection by the sponsor or its designated monitors, auditors, or regulatory agency representatives. The subject or the subject's legal representative should receive a copy of the signed and dated written ICF(s) and any other written information provided to the subject, and should receive copies of any signed and dated ICF updates and any amendments to the written information provided to subjects.

10.4 Withdrawal of Consent for Continued Study Participation

Data and Samples Obtained for the Main Study

Study data are protected by the use of an SID number, which is a number specific to the subject. The investigator is in control of the information that is needed to connect a study sample to a subject. A subject's consent to the use of data does not have a specific expiration date, but the subject may withdraw consent at any time by notifying the investigator. If consent is withdrawn, any data collected prior to that time may still be given to and used by the sponsor but no new data or samples will be collected unless specifically required to monitor safety of the subject.

Samples Obtained for Genetic Research or Future Research

Samples obtained for archival tumor tissue, genetic research, or future research will be labeled with a sample identification number but will not be labeled with personal identifiers such as the subject's name. A file linking this sample identification number with the SID number will be kept in a secure place at the sponsor with restricted access. If the subject withdraws consent for participating in the genetic research or future research, this link will allow the sponsor to locate

the subject's sample and destroy it. The coding of samples and results is to ensure that these research results are kept confidential by keeping the subject's identity and these results separate.

If the subject consents to have his/her samples used for genetic research or future research, this additional research may not start immediately and may start at any time during the storage period. The subject's sample(s) including any specimens of extracted DNA will be stored by the sponsor with similar samples from other subjects at a secure central laboratory. The subject's samples will not be kept for more than 25 years after the end of the study in which they were collected. If the subject chooses not to allow his/her study samples to be used for genetic research or future research, the samples will be destroyed by the sponsor once they are no longer required for the main study.

If consent is withdrawn after a sample has been taken but before the subject's sample is sent to the sponsor for genetic research or future research, the investigator will arrange to have it destroyed. If consent is withdrawn after the subject's sample(s) have been sent to the sponsor for genetic research or future research, the sponsor and the investigator will ensure that these sample(s) are destroyed unless the sample identification number has been removed and the subject can no longer be linked to any sample(s). However, if the subject's samples have already been used for research, the sponsor is not required to destroy results of this research. In this case only the remaining sample(s) will be destroyed.

11 DATA HANDLING AND RECORD KEEPING

To maintain confidentiality, all laboratory specimens, evaluation forms, reports, and other records transmitted outside the clinical site will be identified by a subject's identification number or coded number. All study records, source medical records, and code sheets or logs linking a subject's name to an SID number will be kept in a secure location. Study records such as CRFs may be maintained electronically and require the same security and confidentiality as paper. Clinical information will not be released without written permission of the subject/legal representative, except as specified in the ICF(s) (eg, necessary for monitoring by regulatory authorities or the sponsor of the clinical study). The investigator must also comply with all applicable privacy regulations (eg, HIPAA 1996, EU Data Protection Directive 95/46/EC).

The study site (and the investigator) will retain the essential documents specified in the ICH GCP (eg, source document such as medical records, contract, signed ICF). Essential documents should be retained at the study site for at least 15 years following completion of the study, or per regulatory obligations if longer, and thereafter destroyed only after agreement with the sponsor. However this is not always applied to those that are not preservable such as blood samples. In the event of any inconsistency between the above-mentioned contents and the contract with the

study site, the contract shall prevail. These documents should be retained for a longer period however if needed by the sponsor, and the specific period and method of retention will be separately discussed between the study site and the sponsor. The sponsor should notify the head of the study site in writing when the study-related records are no longer needed. The records should be managed by a responsible person appointed by the head of the study site.

12 FINANCING AND INSURANCE

Financing and insurance are addressed in the individual site contracts.

13 PUBLICATION POLICY

Publication by the site of any data from this study must be carried out in accordance with the clinical study site agreement.

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Appendix 1 Signatures

Sponsor Signature

A Phase 2b Randomized, Double-blind Study Comparing Tremelimumab to Placebo in Second- or Third-line Treatment of Subjects with Unresectable Pleural or Peritoneal Malignant Mesothelioma

I agree to the terms of this protocol and all amendments/administrative changes.

Signature and date:

Signature of Principal Investigator

A Phase 2b, Randomized, Double-blind Study Comparing Tremelimumab to Placebo in Second- or Third-line Treatment of Subjects with Unresectable Pleural or Peritoneal Malignant Mesothelioma

I, the undersigned, have reviewed this protocol and all amendments, and I agree to conduct this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP), any applicable laws and requirements, and any conditions required by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

I understand that the protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the applicable regulatory authority and IRB/IEC, and must be approved by the IRB/IEC prior to implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the sponsor, involves only logistical or administrative changes. Documentation of IRB/IEC approval must be sent to the sponsor immediately upon receipt.

Signature and date: _____

Name and title: _____

Address including postal code: _____

_____

Telephone number: _____

Site/Center Number (if available)_____

Appendix 2 ECOG Performance Scale

Table 14-1 ECOG Performance Status

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

ECOG = Eastern Cooperative Oncology Group.

(Oken et al, 1982).

Appendix 3 EORTC Criteria

The EORTC prognostic factors will be used.

Prognostic indices of survival for advanced mesothelioma in EORTC studies

EORTC studies				
Study	**Response (percent)**	**MST (months)**		
Mitoxantrone	2.4	7.5		
Epidoxorubicin	13.5	8.9		
Etoposide (IV)	4.2	6.7		
Etoposide (PO)	7.3	8.7		
Paclitaxel	0	9.3		
Poor prognostic factors in multivariate analysis				
	Variable	**MST (months)**		
Performance status (PS)	Good (0)	10.7		
	Poor (1-2)	7.2		
WBC count	High (>8.3)	6		
	Low (<8.3)	10.4		
Hemoglobin (HGB)	High* (>1 g/dL)	7.3		
	Low* (<1 g/dL)	9.6		
Histologic diagnosis	Definite	9.8		
	Possible	6		
Sarcomatous subtype	Present	5		
	Other subtype	8.4-9.1		
EORTC prognostic groups				
Group characteristics		**MST (months)**	**1 yr OS**	**2 yr OS**
Low risk (prognostic score <1.27)		10.8	40 percent	14 percent
Equivalent to having 0-2 poor prognostic factors				
High risk (prognostic score >1.27)		5.5	12 percent	0 percent
Equivalent to having three or more poor prognostic factors				

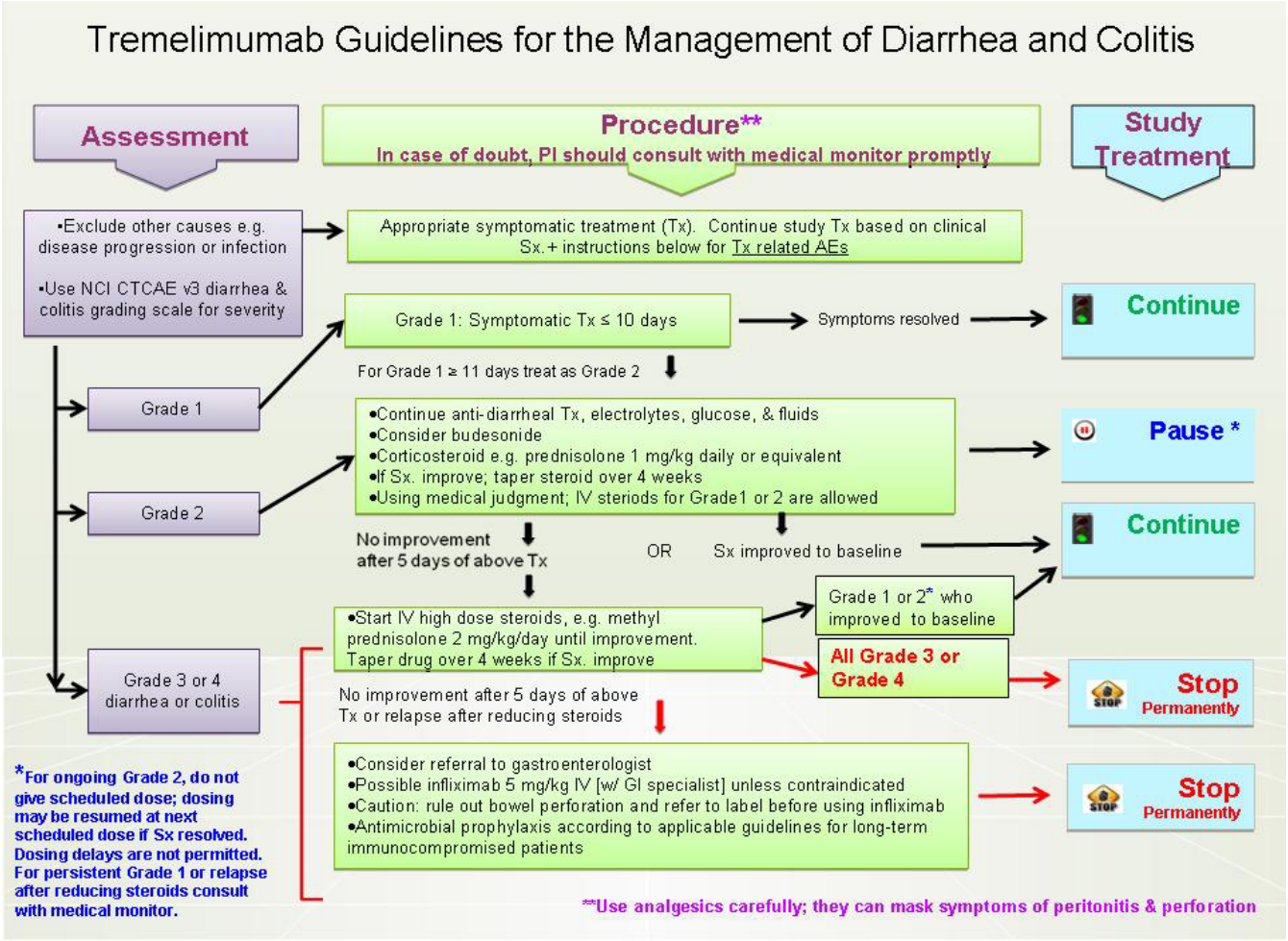
EORTC: European Organization for Research and Treatment of Cancer; MST: median survival time; WBC: white blood cell count, X 1000/µl.
* Hemoglobin abnormalities expressed as difference relative to 16 g/dL in men and 14 g/DL in women.

The formula for calculation of the EPS is:

EPS 0.55 (if the WBC count is > 8.3 10^9/L) + 0.60 (if the ECOG performance status ≥ 1) + 0.52 (if the histological diagnosis is possible) + 0.67 (if the histology subtype is sarcomatous tissue) + 0.60 (if the sex is male)

The EPS cut-off value for high-risk is > 1.27 (Curran et al, 1998).

Appendix 4 Diarrhea Management Flowchart



* For ongoing Grade 2, do not give scheduled dose; dosing may be resumed at next scheduled dose if symptoms resolved. Dosing delays are not permitted. For persistent Grade 1 or relapse after reducing steroids, consult with medical monitor.

** Use analgesics carefully; they can mask symptoms of peritonitis and perforation.

AE = adverse event; GI = gastrointestinal; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PI = principal investigator; Sx = symptom; Tx = treatment.

Appendix 5 Sample LCSS-Meso Questionnaire

LCSS-Meso: Patient Scale

Directions: Please place a mark along each line where it would best describe the symptoms of your lung illness DURING THE PAST DAY (within the last 24 hours).

Example Question:

How good is the weather?

As good as it could be ——— As bad as it could be

1. How good is your appetite?

As good as it could be ——— As bad as it could be

2. How much fatigue do you have?

None ——— As much as it could be

3. How much coughing do you have?

None ——— As much as it could be

4. How much shortness of breath do you have?

None ——— As much as it could be

5. How much pain do you have?

None |_____| As much as it could be

6. How bad are your symptoms from lung illness?

I have none |_____| As bad as they could be

7. How much has your lung illness affected your ability to carry out normal activities?

Not at all |_____| So much that I can do nothing for myself

8. How would you rate the quality of your life today?

Very high |_____| Very low

LCSS-Meso
Patient Scale
Page 2 of 2

Appendix 6 Sample BPI-sf Questionnaire

STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: _____/_____/_____ Time: _____

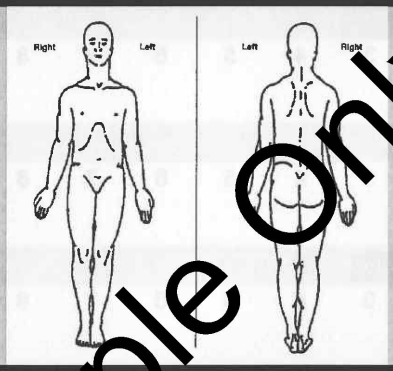
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

   1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one nuimber that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Appendix 7 Sample EQ-5D-3L Questionnaire

Health Questionnaire

By placing a check-mark in one box in each group below, please indicate which statements best describe your own state of health today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain/Discomfort

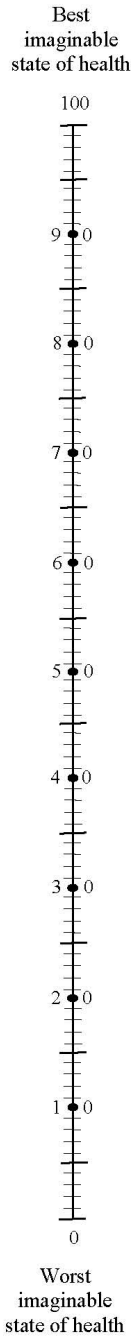
I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

To help people say how good or bad their state of health is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your state of health is today.



Your own state of health today

3

Appendix 8 Changes to the Protocol

All changes described below have been incorporated into the current version of the protocol.

Protocol Amendment 1

Change #1: Section Cover Page

Previous text:

Medical Monitors:

Contract Research

Organization:

Revised text:

Primary Medical Monitors:

_____

_____

Contract Research

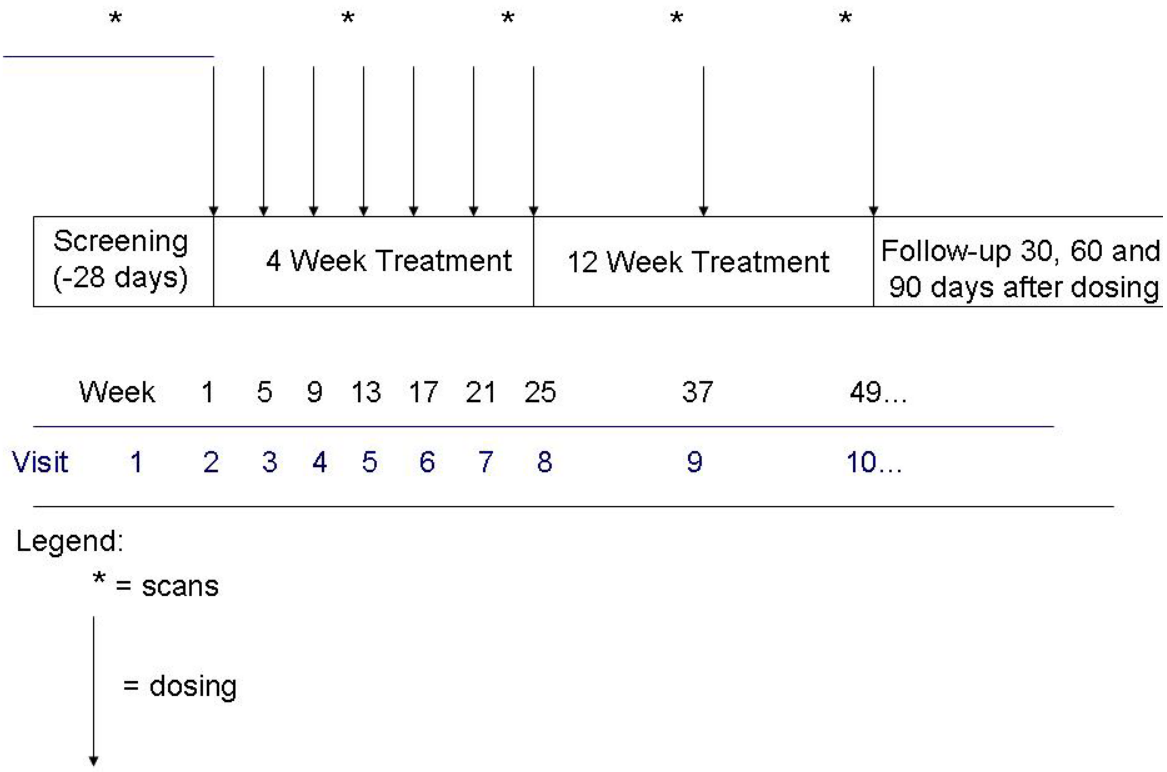
Organization:

Reason for change:

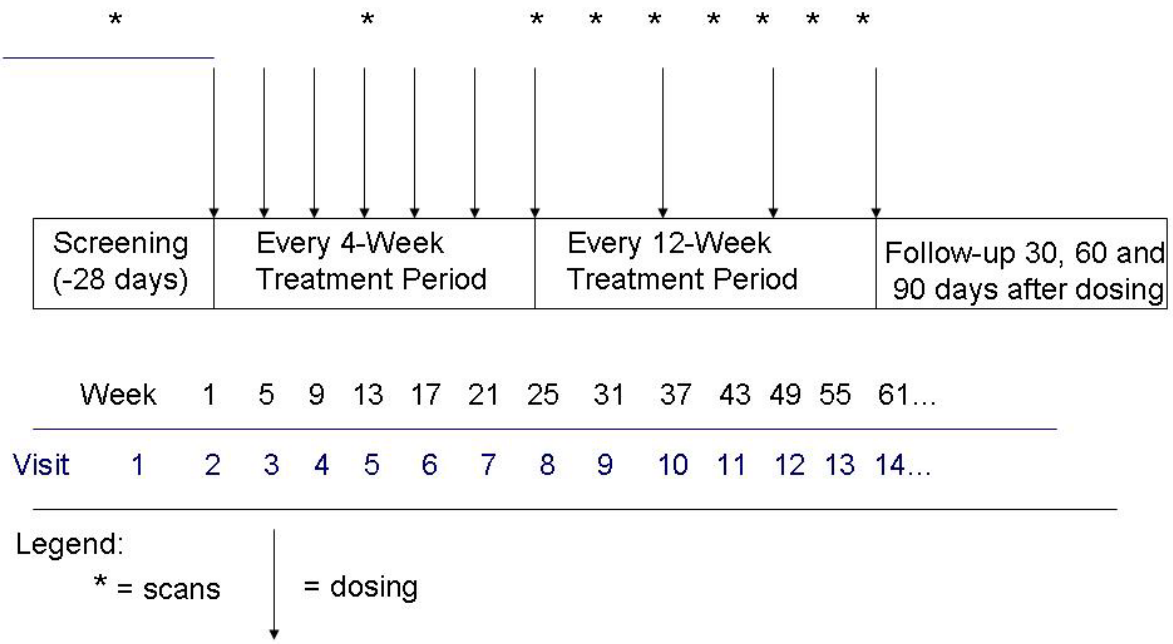
The contract research organization has changed its name and we received the fax number for the US medical monitor.

Change #2: Section 3.1 Overview of Study Design (Figure 3.1-1)

Previous figure:



Revised figure:



Reason for change:

The figure was updated to add the non-dosing study visits (visits 9 and 11) and the related scans per the United States Food and Drug Administration (US FDA) request.

Change #3: Section 4.7 Subject Completion

Previous text:

After the end of study, subjects who are still receiving treatment and considered to be gaining benefit will be provided with an option for continued treatment.

Revised text:

After the end of study, subjects who are still receiving treatment and considered to be gaining benefit will be provided with an option for continued treatment **(eg, rollover study)**.

Reason for change:

A description of one possible option for treatment continuation was added for clarity.

Change #4: Section 4.9 End of Study

Previous text:

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study or 12 months after the last subject is randomized.

Revised text:

The end of the study ("study completion") is defined as the date ~~of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study~~ **when the prespecified number of death events have been reached for the primary endpoint** ~~or a minimum of 12 months after the last subject is randomized~~ **or the date the sponsor stops the study**.

Reason for change:

The definition for end of study was revised to better describe when the study would be completed.

Change #5: Section 5.1 Schedule of Study Procedures (Table 5.1-1)

Previous table:

Table 5.1-1 Schedule of Study Procedures for Screening and 4-Week Treatment Period

Study Period	Screening	Q4W Treatment Period						Protocol Section for Details
Visit Number	V1	V2	V3	V4	V5	V6	V7	
Procedure / Study Week	Day -28 to Day -1	Week 1	Week 5 ± 3 Days	Week 9 ± 3 Days	Week 13 ± 3 Days	Week 17 ± 3 Days	Week 21 ± 3 Days	
Written informed consents/ assignment of SID number	X							4.1
LCSS-Meso questionnaire (ePRO)	X	X	X	X	X	X	X	5.2.8.3
EQ-5D-3L questionnaire (ePRO)	X	X	X	X	X	X	X	5.2.8.3
BPI-sf questionnaire (ePRO)	X	X	X	X	X	X	X	5.2.8.3
Medical history	X							5.2.1
Physical examination, weight	X	X	X	X	X	X	X	5.2.1
Height	X							5.2.1
Vital signs	X	X	X	X	X	X	X	5.2.1
Serum chemistry	X	X	X	X	X	X	X	5.2.2
Hematology	X	X	X	X	X	X	X	5.2.2
Serum pregnancy test	X							5.2.2
Urine pregnancy test		X	X	X	X	X	X	5.2.2
Hepatitis A, B, C, HIV virologies	X							5.2.2
Urinalysis	X	X	X	X	X	X	X	5.2.2
ECOG performance status	X	X	X	X	X	X	X	5.2.8.2
ECG	X	X (post dose)			X (post dose)			5.2.1
Central safety laboratory sample	X	X	X	X	X	X	X	5.2.2
		X	X		X			5.2.3
Immunogenicity blood sample		X	X		X			5.2.4

Table 5.1-1 Schedule of Study Procedures for Screening and 4-Week Treatment Period

Study Period	Screening	Q4W Treatment Period						Protocol Section for Details
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	
Procedure / Study Week	**Day -28 to Day -1**	**Week 1**	**Week 5 ± 3 Days**	**Week 9 ± 3 Days**	**Week 13 ± 3 Days**	**Week 17 ± 3 Days**	**Week 21 ± 3 Days**	
Flow cytometry samples	X	X	X		X			5.2.5
Circulating soluble factors	X	X	X	X	X		X	5.2.5
Circulating apoptosis markers	X		X	X				5.2.5
RNA samples		X			X		X	5.2.5
DNA samples (optional)	X							5.2.5
Disease evaluations (CT or MRI if CT is contraindicated)	X				X			5.2.6
Assessment of AEs/SAEs	X	X	X	X	X	X	X	6.3
Concomitant medications	X	X	X	X	X	X	X	4.6
Verify eligibility criteria	X	X						4.2
Randomization		X						4.3
Investigational product administration		**X**	**X**	**X**	**X**	**X**	**X**	4.5.3, 4.5.5

AE = adverse event; BPI-sf = brief pain inventory-short form; CT = computed tomography; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ePRO = electronic patient reported outcome; EQ-5D-3L = EQ-5D 3 level version; HIV = human immunodeficiency virus; LCSS-Meso = Lung Cancer Symptom Scale-mesothelioma; MRI = magnetic resonance imaging; PK = pharmacokinetics; Q4W = every 4 weeks; RNA = ribonucleic acid; SAE = serious adverse event; SID = subject

Table 5.1-1 Schedule of Study Procedures for Screening and 4-Week Treatment Period

Study Period	Screening	Q4W Treatment Period						Protocol Section for Details
Visit Number	V1	V2	V3	V4	V5	V6	V7	
Procedure / Study Week	Day -28 to Day -1	Week 1	Week 5 ± 3 Days	Week 9 ± 3 Days	Week 13 ± 3 Days	Week 17 ± 3 Days	Week 21 ± 3 Days	
identification; V = visit; W= week.								

Revised table:

Table 5.1-2 Schedule of Study Procedures for Screening and Every 4-Week Treatment Period

Study Period	Screening	Q4W Treatment Period						Protocol Section for Details
Visit Number	V1	V2	V3	V4	V5	V6	V7	
Procedure / Study Week	Day -28 to Day -1	Week 1	Week 5 ± 3 Days	Week 9 ± 3 Days	Week 13 ± 3 Days	Week 17 ± 3 Days	Week 21 ± 3 Days	
Written informed consents/ assignment of SID number	X							4.1
LCSS-Meso questionnaire (ePRO)	X	X	X	X	X	X	X	5.2.8.3
EQ-5D-3L questionnaire (ePRO)	X	X	X	X	X	X	X	5.2.8.3
BPI-sf questionnaire (ePRO)	X	X	X	X	X	X	X	5.2.8.3

Table 5.1-2 Schedule of Study Procedures for Screening and Every 4-Week Treatment Period

Study Period	Screening	Q4W Treatment Period						Protocol Section for Details
Visit Number	V1	V2	V3	V4	V5	V6	V7	
Procedure / Study Week	Day -28 to Day -1	Week 1	Week 5 ± 3 Days	Week 9 ± 3 Days	Week 13 ± 3 Days	Week 17 ± 3 Days	Week 21 ± 3 Days	
Medical history	X							5.2.1
Physical examination, weight	X	X	X	X	X	X	X	5.2.1
Height	X							5.2.1
Vital signs	X	X	X	X	X	X	X	5.2.1
Serum chemistry	X	X	X	X	X	X	X	5.2.2
Hematology	X	X	X	X	X	X	X	5.2.2
Serum pregnancy test	X							5.2.2
Urine pregnancy test		X	X	X	X	X	X	5.2.2
Hepatitis A, B, C, HIV virologies	X							5.2.2
Urinalysis	X	X	X	X	X	X	X	5.2.2
ECOG performance status	X	X	X	X	X	X	X	5.2.8.2
ECG	X	X (post dose)	**X (post dose)**		X (post dose)			5.2.1
Obtain archival tissue sample if consent provided	X							5.2.5
Central safety laboratory sample	X	X	X	X	X	X	X	5.2.2
PK blood sample		X	X		X			5.2.3
Immunogenicity blood sample		X	X		X			5.2.4
Flow cytometry samples	X	X	X		X			5.2.5
Circulating soluble factors	X	X	X	X	X		X	5.2.5
Circulating apoptosis markers	X		X	X				5.2.5
RNA samples		X			X		X	5.2.5
DNA samples (optional)	X							5.2.5

Table 5.1-2 Schedule of Study Procedures for Screening and Every 4-Week Treatment Period

Study Period	Screening	Q4W Treatment Period						Protocol Section for Details
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	
Procedure / Study Week	**Day -28 to Day -1**	**Week 1**	**Week 5 ± 3 Days**	**Week 9 ± 3 Days**	**Week 13 ± 3 Days**	**Week 17 ± 3 Days**	**Week 21 ± 3 Days**	
Disease evaluations (CT or MRI if CT is contraindicated)	X				X			5.2.6
Assessment of AEs/SAEs	X	X	X	X	X	X	X	6.3
Concomitant medications	X	X	X	X	X	X	X	4.6
Verify eligibility criteria	X	X						4.2
Randomization		X						4.3
Investigational product administration		**X**	**X**	**X**	**X**	**X**	**X**	4.5.3, 4.5.5

AE = adverse event; BPI-sf = brief pain inventory-short form; CT = computed tomography; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ePRO = electronic patient reported outcome; EQ-5D-3L = EQ-5D 3 level version; HIV = human immunodeficiency virus; LCSS-Meso = Lung Cancer Symptom Scale-mesothelioma; MRI = magnetic resonance imaging; PK = pharmacokinetics; Q4W = every 4 weeks; RNA = ribonucleic acid; SAE = serious adverse event; SID = subject identification; V = visit; W= week.

Reason for change:

An additional ECG was added at Visit 3 for safety assessment.

Change # 6 Section 5.1 Schedule of Study Procedures (Table 5.1-2)

Previous table:

Table 5.1-2 Schedule of Study Procedures for 12-Week Treatment, End of Treatment and Follow-up Period

Study Period	Q12W Treatment Period		Short Term Follow-up Visits			Long Term Follow-up Period	
Visit Number	V8, V9, V10...						
Procedure / Study Week	W25 (± 3 Days) and Q12W (± 14 Days) Thereafter (W37, W49...)	End of Treatment	30 Days (± 3 Days) After Last Dose	60 Days (± 3 Days) After Last Dose	90 Days (± 3 Days) After Last Dose	Every 3 Months After 90 Day (± 14 Days) Follow-up Visit	Protocol Section for Details
LCSS-Meso questionnaire (ePRO)	X	X					5.2.8.3
EQ-5D-3L questionnaire (ePRO)	X	X					5.2.8.3
BPI-sf questionnaire (ePRO)	X	X					5.2.8.3
Physical examination, weight	X	X	X	X	X		5.2.1
Vital signs	X	X	X	X	X		5.2.1
Serum chemistry	X	X	X	X	X		5.2.2
Hematology	X	X	X	X	X		5.2.2
Urine pregnancy test	X	X					5.2.2
Urinalysis	X	X	X	X	X		5.2.2
ECOG performance status	X	X					5.2.8.2

Table 5.1-2 Schedule of Study Procedures for 12-Week Treatment, End of Treatment and Follow-up Period

Study Period	**Q12W Treatment Period**		**Short Term Follow-up Visits**			**Long Term Follow-up Period**	
Visit Number	**V8, V9, V10...**						
Procedure / Study Week	**W25 (± 3 Days) and Q12W (± 14 Days) Thereafter (W37, W49...)**	**End of Treatment**	**30 Days (± 3 Days) After Last Dose**	**60 Days (± 3 Days) After Last Dose**	**90 Days (± 3 Days) After Last Dose**	**Every 3 Months After 90 Day (± 14 Days) Follow-up Visit**	**Protocol Section for Details**
ECG every 3 months the 1st year & every 6 months starting in the 2nd year (V11-W51)	X (post dose)	X			X		5.2.1
Central safety laboratory sample	X	X	X	X	X		5.2.2
PK blood sample	X (V8; V9 pre-dose only)	X			X		5.2.3
Immunogenicity blood sample	X (V8 and V9 pre-dose only)	X			X		5.2.4
Flow cytometry samples	X (V8 only)						5.2.5
Circulating soluble factors	X (V8 only)						5.2.5
Circulating apoptosis markers		X					5.2.5
RNA samples		X					5.2.5
Disease evaluations (CT or MRI if CT is contraindicated)	X	X			X	X	5.2.8.1
Assessment of AEs/SAEs	X	X	X	X	X		6.3
Concomitant medications	X	X	X	X	X		4.6
Investigational product administration	**X**						4.5.3, 4.5.5
New systemic anticancer treatment		X	X	X	X	X	
Assess for survival		X	X	X	X	X	

AE = adverse event; BPI-sf = brief pain inventory-short form; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ePRO = electronic patient reported outcome; EQ-5D-3L = EQ-5D 3 level version; LCSS-meso = Lung Cancer Symptom Scale-mesothelioma; MRI = magnetic resonance imaging; PK = pharmacokinetic; Q12W = every 12 weeks; RNA = ribonucleic acid; SAE = serious adverse event; V = visit; W = week.

Revised table:

Table 5.1-2 Schedule of Study Procedures for Every 12-Week Treatment, End of Treatment and Follow-up Period

Study Period	Q12W Treatment Period		End of Treatment	Short Term Follow-up Visits			Long Term Follow-up Period	Protocol Section for Details
Visit Number	Dosing Visits V8, V10, V12...	Non-dosing Visits V9, V11, V13 only						
Procedure / Study Week	W25 (± 3 Days) and Q12W (± 14 Days) Thereafter (W37, W49...)	W31 (± 3 Days), W43, and W55		30 Days (± 3 Days) After Last Dose	60 Days (± 3 Days) After Last Dose	90 Days (± 3 Days) After Last Dose	Every 3 Months After 90 Day (± 14 Days) Follow-up Visit	
LCSS-Meso questionnaire (ePRO)	X		X					5.2.8.3
EQ-5D-3L questionnaire (ePRO)	X		X					5.2.8.3
BPI-sf questionnaire (ePRO)	X		X					5.2.8.3
Physical examination, weight	X	**X**	X	X	X	X		5.2.1
Vital signs	X	**X**	X	X	X	X		5.2.1
Serum chemistry	X	**X**	X	X	X	X		5.2.2
Hematology	X	**X**	X	X	X	X		5.2.2
Urine pregnancy test	X		X					5.2.2
Urinalysis	X	**X**	X	X	X	X		5.2.2
ECOG performance status	X	**X**	X					5.2.8.2
ECG every 3 months the 1st year & every 6 months starting in the 2nd year (V14-W61)	X (post dose)		X			X		5.2.1
Central safety laboratory sample	X	**X**	X	X	X	X		5.2.2
PK blood sample	X (V8; V10 pre-dose only)		X			X		5.2.3
Immunogenicity blood sample	X (V8 and V10 pre-dose		X			X		5.2.4

Table 5.1-2 Schedule of Study Procedures for Every 12-Week Treatment, End of Treatment and Follow-up Period

Study Period	Q12W Treatment Period		End of Treatment	Short Term Follow-up Visits			Long Term Follow-up Period	Protocol Section for Details
Visit Number	Dosing Visits V8, V10, V12...	Non-dosing Visits V9, V11, V13 only						
Procedure / Study Week	W25 (± 3 Days) and Q12W (± 14 Days) Thereafter (W37, W49...)	W31 (± 3 Days), W43, and W55		30 Days (± 3 Days) After Last Dose	60 Days (± 3 Days) After Last Dose	90 Days (± 3 Days) After Last Dose	Every 3 Months After 90 Day (± 14 Days) Follow-up Visit	
	only)							
Flow cytometry samples	X (V8 only)							5.2.5
Circulating soluble factors	X (V8 only)							5.2.5
Circulating apoptosis markers			X					5.2.5
RNA samples			X					5.2.5
Disease evaluations (CT or MRI if CT is contraindicated)	X	X	X			X	X	5.2.8.1
Assessment of AEs/SAEs	X	X	X	X	X	X		6.3
Concomitant medications	X	X	X	X	X	X		4.6
Investigational product administration	**X**							4.5.3, 4.5.5
New systemic anticancer treatment			X	X	X	X	X	
Assess for survival			X	X	X	X	X	

AE = adverse event; BPI-sf = brief pain inventory-short form; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ePRO = electronic patient reported outcome; EQ-5D-3L = EQ-5D 3 level version; LCSS-meso = Lung Cancer Symptom Scale-mesothelioma; MRI = magnetic resonance imaging; PK = pharmacokinetic; Q12W = every 12 weeks; RNA = ribonucleic acid; SAE = serious adverse event; V = visit; W = week.

Reason for change:

The US FDA requested an additional visit take place between the every 12 weeks (Q12W) dosing visits for safety examination and disease assessment.

Change #7: Section 5.1.2.2 Weeks 5, 9, and 17 (+/- 3 days): Every 4-Week Treatments (Visits 3, 4, and 6)

Previous text:

Dosing and post-dose

1. Administer investigational product;
2. Take vital signs every 30 minutes (± 5 minutes) during infusion, at completion of infusion (± 5 minutes), and 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post infusion
3. Assess for AEs and SAEs

Revised text:

Dosing and post-dose

1. Administer investigational product;
2. Take vital signs every 30 minutes (± 5 minutes) during infusion, at completion of infusion (± 5 minutes), and 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post infusion
3. Perform ECG (Visit 3 only between 2 and 6 hours after treatment administration)
   a. The first 100 subjects will have triplicate ECGs
   b. The remaining subjects will have a single ECG
4. Assess for AEs and SAEs

Reason for change:

An additional ECG was added at Visit 3 for safety assessment.

Change #8 Section 5.1.3.1 Treatment Visits

Previous text:

Section 5.1.3 Treatment Visits: Week 25 (+/- 3 days), Weeks 37, 49 (+/- 14 days)...; Visits 8 to 16.

Revised text:

Section 5.1.3**.1** Treatment Visits: Week 25 (+/- 3 days), Weeks 37, 49 (+/- 14 days)...; Visits 8**, 10, 12, 14, 15 and** 16

Reason for change:

The section heading was updated to reflect the addition of the non-dosing study visits and the change in dosing visit numbers.

Change #9: Section 5.1.3.2 Non-dosing Follow-up Visits.

Previous text:

Not applicable. New section added.

Revised text:

Section 5.1.3.2 Non-dosing Study Visits: Week 31, 43, and 55 (+/- 3 days); Visits 9, 11, and 13

During the Every 12-Week Treatment Period, subjects will have non-dosing study visits every 6 weeks after dosing during the first year of treatment (ie, months 6-12). The first non-dosing study visit will take place Week 31 ± 3 days.

1. Perform physical examination including weight (if applicable, record new findings as AEs or SAEs)
2. Take vital signs
3. Collect blood samples for:
   a. Serum chemistry
   b. Hematology
   c. Central safety labs
4. Collect urine for urinalysis
5. Assess for ECOG performance status
6. Evaluate disease via CT or MRI scan
7. Assess for AEs and SAEs
8. Update concomitant medications

Reason for change:

This section was added to describe the procedures to be completed at each non-dosing visit during the Every 12-Week Treatment Period.

Change #10: Section 5.2.1 Medical History and Physical Examination, Weight, Vital Signs and ECG

Previous text:

All ECGs performed during the study will be 12-lead and will be obtained at baseline following the first dose on Day 1 and every 3 months for the first year of treatment (Visits 1, 2, 5, 8, 9, 10, and 11). Electrocardiograms will be performed every 6 months thereafter or until discontinuation of treatment (starting at Visit 13). Prior to discontinuation, all ECGs must be performed between 2 and 6 hours after treatment administration. The first 100 subjects will have ECGs obtained in triplicate and within a 5-minute time period to evaluate the risk of QTc (the time between the start of the Q wave and the end of the T wave corrected for heart heart) prolongation with tremelimumab. The remaining subjects will have a single ECG performed. The ECGs will be performed for all subjects at the timepoints noted in the schedule of events.

Revised text:

In order to evaluate the potential risk for QTc (the time between the start of the Q wave and the end of the T wave corrected for heart rate) prolongation with tremelimumab, subjects will have ECGs collected at specified time points noted in the schedule of events. All ECGs performed during the study will be 12-lead and will be obtained at baseline, following the first dose on Week 1, **Week 5,** Week 13 and every 3 months **thereafter during** ~~for~~ the first year of treatment (Visits 1, 2, **3,** 5, 8, ~~9,~~ 10, and 12). **Beginning with the second year of treatment (starting at Visit 14),** ECGs will be performed every 6 months until discontinuation of treatment. All ECGs on dosing days must be performed between 2 and 6 hours after treatment administration. The first 100 subjects will have ECGs obtained in triplicate and within a 5-minute time period **for all time points** ~~to evaluate the risk of QTc (the time between the start of the Q wave and the end of the T wave corrected for heart heart) prolongation with tremelimumab~~. The remaining subjects will have a single ECG performed for all time points. ~~The ECGs will be performed for all subjects at the timepoints noted in the schedule of events.~~

Reason for change:

Text was updated to reflect the change in visit numbers and to clarify the frequency of ECG collection during the study.

Change #11: Section 5.2.4 Immunogenicity Evaluation and Methods

Previous text:

A validated electrochemiluminescence assay (ECLA) using a Meso Scale Discovery (MSD) platform will be used for the detection of anti-tremelimumab antibodies in human plasma.

Revised text:

A validated electrochemiluminescence assay (ECLA) using a Meso Scale Discovery (MSD) platform will be used for the detection of anti-tremelimumab antibodies in human **blood**.

Reason for change:

To correct an error in the protocol.

Change #12: Section 5.2.6.3.3 EQ-5D 3 Level Version (EQ-5D-3L)

Previous text:

This questionnaire will be completed on an ePRO device prior to any study procedures at screening, at or before 4-Week treatment study visits, at or before study visits during the 12-Week treatment phase, and at the end of treatment. The investigational site personnel will check compliance at each visit.

Revised text:

This questionnaire will be completed on an ePRO device prior to any study procedures at screening, at or before 4-Week treatment study visits, at or before study visits during the 12-Week treatment phase, and at the end of treatment. **Since the study will use an ePRO device and not a pen and paper, a shorter length EQ-VAS line will be displayed due to the screen size. The length of the EQ-VAS on the ePRO device will be calculated, and scores will be transformed back to a 0-100 scale.** The investigational site personnel will check compliance at each visit.

Reason for change:

This information was mistakenly left out of the original protocol.

Change #13: Section 7.3.1 Primary Endpoint

Previous text:

The primary endpoint is OS which is defined as the time from randomization until death due to any cause. The primary analysis of OS will be performed after 124 deaths have occurred among the approximately 180 subjects randomized. For subjects who are alive at the end of the study or lost to follow-up, OS will be censored on the last date when subjects are known to be alive.

Revised text:

The primary endpoint is OS which is defined as the time from randomization until death due to any cause. The primary analysis of OS will be performed after 124 deaths have occurred among the approximately 180 subjects randomized. For subjects who are alive at the ~~end of study~~**time of the primary analysis** or lost to follow-up, OS will be censored on the last date when subjects are known to be alive.

Reason for change:

This was changed to correct an over sight in the text.

Change #14: Section 7.3.2.3.2 Immunogenicity Analysis

Previous text:

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of subjects who develop detectable anti-tremelimumab antibodies. The immunogenicity titer will be reported for samples confirmed positive for the presence of anti-tremelimumab antibodies. The effect of immunogenicity on PK, pharmacodynamics, and safety will be evaluated.

Revised text:

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of subjects who develop detectable anti-tremelimumab antibodies. The immunogenicity titer will be reported for samples confirmed positive for the presence of anti-tremelimumab antibodies. The effect of immunogenicity on PK, pharmacodynamics, **efficacy**, and safety will be evaluated.

Reason for change:

The word efficacy was added to explore the potential effect of immunogenicity on efficacy.

Change #15: Section 7.3.2.3.3 Population PK and Exposure-response Analysis

Previous text:

A population PK model will be developed using a non-linear mixed-effects modeling approach in subjects with malignant mesothelioma. The impact of physiologically-relevant subject characteristics (covariates) and disease on PK will be evaluated. The relationship between tremelimumab blood exposure and OS will be evaluated.

Revised text:

A population PK model will be developed using a non-linear mixed-effects modeling approach in subjects with malignant mesothelioma. The impact of physiologically-relevant subject characteristics (covariates) and disease on PK will be evaluated. The relationship between tremelimumab blood exposure and OS **or safety** will be evaluated.

Reason for change:

The section was modified to examine the potential relationship between tremelimumab blood exposure and safety.

Change #16: Section 7.3.3 Exploratory Endpoints

Previous text:

2) To evaluate changes in total score and individual scores in health-related QoL and disease-related symptoms (using LCSS-Meso), subject pain symptoms (using BPI-sf), and health status (using EQ5D-3L) from baseline to each time point in subjects with durable clinical activity such as DCR (details of the statistical analysis will be provided in the SAP);

Revised text:

2) To evaluate changes in total score and individual scores in health-related QoL and disease-related symptoms (using LCSS-Meso), subject pain symptoms (using BPI-sf), and health status (using EQ-5D-3L) from baseline to each time point in subjects with durable clinical activity such as **durable** DCR (details of the statistical analysis will be provided in the SAP);

Reason for change:

Text was modified to include the word durable in the endpoint to match the objective.

Protocol Amendment 2

Major changes to the protocol are described below. In addition, minor copyedits were made.

Change #1: Section Cover Page

Previous text:

Application Number:

Primary Medical Monitors:

Sponsor Medical Monitor:

Revised text:

Application Number:

Primary Medical Monitors:

_____

_____

Sponsor Medical Monitor:

_____

Reason for change:

To add NCT and UTN, and reflect change in primary and sponsor medical monitors

Change #2: Changes to the Protocol

Entire section was deleted from the beginning of the document and placed as a new appendix to the protocol (Appendix 8)

Reason for change:

To facilitate readability

Change #3: Abstract (Assessment of Endpoints), paragraph 6

Previous text:

Pharmacokinetics of tremelimumab will be assessed by estimating PK parameters after the first and steady-state doses using a non-compartmental analysis approach. A population PK model will be developed using a non-linear mixed-effects modeling approach in subjects with malignant mesothelioma. The impact of physiologically-relevant subject characteristics (covariates) and disease on PK will be evaluated. The relationship between tremelimumab blood exposure and OS will be evaluated.

Revised text:

Pharmacokinetics of tremelimumab will be assessed by estimating PK parameters after the first and steady-state doses using a non-compartmental analysis approach. A population PK model will be developed using a non-linear mixed-effects modeling approach in subjects with malignant mesothelioma. The impact of physiologically-relevant subject characteristics (covariates) and disease on PK will be evaluated. The relationship between tremelimumab blood exposure and OS **or safety** will be evaluated.

Reason for change:

Updated to match the body of the protocol

Change #4: Section 4.2.1 Inclusion Criteria

Previous text:

12) Nonsterilized males who are sexually active with a female partner of childbearing potential must use a highly effective method of contraception (see Table 4.2.1-1) from Day 1 through 90 post last dose. In addition, they must refrain from sperm donation for 6 months after the final dose of investigational product;

Table 4.2.1-1 Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
• Male condom plus spermicide • Copper T intrauterine device • Levonorgesterel-releasing intrauterine system (eg, Mirena®) [a]	• Implants • Hormone shot or injection • Combined pill • Minipill • Patch

[c] This is also considered a hormonal method.

Revised text:

12) Nonsterilized males who are sexually active with a female partner of childbearing potential must use a highly effective method of contraception (see Table 4.2.1-1) from Days 1 through 90 post last dose. In addition, they must refrain from sperm donation for ~~6 months~~ **90 days** after the final dose of investigational product;

Table 4.2.1-1 Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
• Male condom ~~plus~~ **with or without** spermicide • Copper T intrauterine device • Levonorgesterel-releasing intrauterine system (eg, Mirena®) [a]	• Implants • Hormone shot or injection • Combined pill • Minipill • Patch

[a] This is also considered a hormonal method.

Reason for change:

Change to 90 days after final dose of investigational product for sperm donation to align with a duration of approximately 5 half-lives for the elimination of tremelimumab;

Change in use of spermicide to align with global contraceptive policies

Change #5: Section 4.2.2 Exclusion Criteria

Previous text:

3) History of chronic inflammatory or autoimmune disease (eg, Addison's disease, multiple sclerosis, Graves' disease, Hashimoto's thyroiditis, rheumatoid arthritis, hypophysitis, etc) with symptomatic disease within the last 3 years prior to randomization. Note: Active vitiligo or a history of vitiligo will not be a basis for exclusion;

Revised text:

3) History of chronic inflammatory or autoimmune disease (eg, Addison's disease, multiple sclerosis, Graves' disease, Hashimoto's thyroiditis, rheumatoid arthritis, hypophysitis**, uveitis**, etc) with symptomatic disease within the last 3 years prior to randomization. Note: Active vitiligo or a history of vitiligo will not be a basis for exclusion;

Added the following criterion:

19) Subjects with a history of hypersensitivity to compounds of similar biologic composition to tremelimumab or any constituent of the product.

Reason for change:

Added uveitis to specify an autoimmune condition that might not be routinely investigated in the clinical practice;

Added criterion 19 to exclude subjects who might have previously shown hypersensitivity to any component of the investigational product

Change #6: Section 4.4 Blinding, last sentence

Previous text:

If the treatment allocation for a subject needs to be known to treat an individual subject for an AE, the investigator must notify the sponsor/CRO *immediately* and, if possible, before unblinding the treatment allocation.

Revised text:

If the treatment allocation for a subject needs to be known to treat an individual subject for an AE, the investigator ~~must~~ **should** notify the sponsor/CRO *immediately* and, if possible, before unblinding the treatment allocation.

Reason for change:

In order to facilitate the unblinding of treatment allocation for an individual subject in case of medical emergency, without deviating from the protocol

Change #7: Section 4.4.1 Unblinding in the Event of a Medical Emergency

Previous text:

In the event of a medical emergency, the investigator may unblind an individual subject's investigational product allocation. Prior to unblinding the investigational product allocation for an individual subject, the investigator must first attempt to contact the study monitor to discuss the medical emergency and the reason for wanting to unblind. Instructions for unblinding an individual subject's investigational product allocation are contained in the IXRS manual.

Revised text:

In the event of a medical emergency, the investigator may unblind an individual subject's investigational product allocation. ~~Prior to unblinding the investigational product allocation for an individual subject, the investigator must first attempt to contact the study monitor to discuss the medical emergency and the reason for wanting to unblind.~~ Instructions for unblinding an individual subject's investigational product allocation are contained in the IXRS manual.

Reason for change:

In order to facilitate the unblinding of treatment allocation for an individual subject in case of medical emergency, without deviating from the protocol

Change #8: Section 4.5.4.1 Dose Calculation

Previous text:

The subject's weight (in kilograms) must be measured prior to each dosing for dose calculation. Measurements can be taken in street clothes without shoes and a calibrated scale must be used for all measurements.

The dose will be calculated at each dosing visit using the following formula:

$$\text{Dose (mL)} \quad \frac{[\text{subject weight (kg)} \times \text{dose level (10 mg/kg)}]}{\text{drug concentration (20 mg/mL)}}$$

The corresponding volume of investigational product should be rounded to the nearest tenth of a mL (0.1 mL). Each vial contains a small amount of overage and the overage should be utilized as much as possible before using another vial.

The number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

Number of vials Dose (mL) ÷ 20 (mL/vial)

Revised text:

Subject weight at baseline should be used for dosing calculations unless there is a ≥ 10% change in weight. ~~The subject's weight (in kilograms) must be measured prior to each dosing for dose calculation. Measurements can be taken in street clothes without shoes and a calibrated scale must be used for all measurements.~~

The dose will be calculated ~~at each dosing visit~~ using the following formula:

$$\text{Dose (mL)} \quad \frac{[\text{subject weight (kg)} \times \text{dose level (10 mg/kg)}]}{\text{drug concentration (20 mg/mL)}}$$

The corresponding volume of investigational product should be rounded to the nearest tenth of a mL (0.1 mL). Each vial contains a small amount of overage and the overage should be utilized as much as possible before using another vial.

The number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

Number of vials Dose (mL) ÷ 20 (mL/vial)

Reason for change:

Not requiring a body weight assessment prior to each dose, except for subjects with a ≥ 10% change from baseline weight, will allow the physicians to schedule the subject's dosing visit in advance, according to the routine institutional practice.

Change #9: Section 4.5.7 Dose Modification for Toxicity Management, paragraph 1

Previous text:

No dose reduction is allowed. Dosing may be delayed up to + 3 days during the treatment phase to allow recovery from treatment-related toxicity. Specific detailed management guidelines have been created for diarrhea and/or colitis-related events (Appendix 4). However, for management of most other toxicities follow the guideline in Table 4.5.7-1.

Revised text:

No dose reduction is allowed. Dosing may be delayed up to + 3 days during the treatment phase to allow recovery from treatment-related toxicity. **Toxicity management guidelines for anti-CTLA-4 monoclonal antibodies have been developed and published in the past 5 years (Kaehler and Hauschild, 2011; Weber et al, 2012).** Specific detailed management guidelines have been created for diarrhea and/or colitis-related events (Appendix 4). However, for management of most other toxicities follow the guideline in Table 4.5.7-1.

Reason for change:

To provide additional reference for toxicity management and for consistency with text in Section 6.1.3

Change #10: Section 4.6.2 Excluded Concomitant Medications

Previous text:

The following medications are to be considered exclusionary by the investigator and are not permitted from signing of the ICF through 90 days post last dose during the study**.** The investigator and sponsor must be notified if a subject receives any of the following during the study:

1. Monoclonal antibodies against CTLA-4, PD1, PD-L1, or other agents (including prior use).
2. Immunosuppressive doses of steroids or other immunosuppressive medication. Note however, that inhaled and topical steroids when medically indicated as treatment for an acute illness or as pretreatment before CT scans (for contrast allergies) are allowed. The investigator is permitted to use corticosteroids as treatment for infusion reactions.
3. Live attenuated vaccinations during the study
4. Drugs with laxative properties and herbal or natural remedies for constipation should be avoided because of the potential for exacerbation of diarrhea

Revised text:

The following medications are to be considered exclusionary by the investigator and are not permitted from signing of the ICF through ~~90 days post last dose during the study~~ **the periods indicated.** The investigator and sponsor must be notified if a subject receives any of the following during the study:

1. Monoclonal antibodies against CTLA-4, PD1, **or** PD-L1 **through 90 days post last dose during the study**~~, or other agents (including prior use)~~
2. Immunosuppressive doses of steroids or other immunosuppressive medication **through 90 days post last dose during the study**. Note however, that inhaled and topical steroids when medically indicated as treatment for an acute illness or as pretreatment before CT scans (for contrast allergies) are allowed. The investigator is permitted to use corticosteroids as treatment for infusion reactions.
3. Live attenuated vaccinations during the study
4. Drugs with laxative properties and herbal or natural remedies for constipation should be avoided **through 90 days post last dose during the study** because of the potential for exacerbation of diarrhea
5. Live attenuated vaccinations during the study or up to 6 months post last dose of investigational product
6. Inactivated vaccinations ± 30 days around any dose of investigational product

Reason for change:

Item 1: other agents removed to correct typographical error and match the exclusion criteria;

Items 5 and 6: to further clarify the vaccination guidelines;

Additional changes to clarify the periods of exclusion for each of the medications

Change #11: Table 5.1.2 Schedule of Study Procedures for Every 12-Week Treatment, End of Treatment, and Follow-up Period, heading - W25 (± 3 Days) & Q12W (± 3 Days) Thereafter (W37, W49...)

Previous text:

Table 5.1-2 Schedule of Study Procedures for Every 12-Week Treatment, End of Treatment, and Follow-up Period

Study Period	Q12W Treatment Period		End of Treatment	Short Term Follow-up Visits			Long Term Follow-up Period	Protocol Section for Details
Visit Number	Dosing Visits V8, V10, V12...	Non-dosing Visits V9, V11, V13						
Procedure / Study Week	W25 (± 3 Days) and Q12W (± 14 Days) Thereafter (W37, W49...)	W31 (± 3 Days), W43, and W55		30 Days (± 3 Days) After Last Dose	60 Days (± 3 Days) After Last Dose	90 Days (± 3 Days) After Last Dose	Every 3 Months After 90 Day (± 14 Days) Follow-up Visit	

Revised text:

Table 5.1-2 Schedule of Study Procedures for Every 12-Week Treatment, End of Treatment, and Follow-up Period

Study Period	Q12W Treatment Period		End of Treatment	Short Term Follow-up Visits			Long Term Follow-up Period	Protocol Section for Details
Visit Number	Dosing Visits V8, V10, V12...	Non-dosing Visits V9, V11, V13						
Procedure / Study Week	W25 (± 3 Days) ~~and~~ & Q12W (~~± 14~~± 3 Days) Thereafter (W37, W49...)	W31 (± 3 Days), W43, and W55		30 Days (± 3 Days) After Last Dose	60 Days (± 3 Days) After Last Dose	90 Days (± 3 Days) After Last Dose	Every 3 Months After 90 Day (± 14 Days) Follow-up Visit	

Reason for change:

For consistency with treatment window for other assessments during the treatment period

Change #12: Section 5.1.3.1 Treatment Visits: Week 25 (+/- 3 days), Weeks 37, 49 (+/- 14 days)...; Visits 8, 10, 12, 14, 15 and 16

Previous text:

The first dose of 12-Week treatment (Week 25 ± 3 days) is 4 weeks after the last dose of the 4-Week treatment phase. All subsequent visits will be 12 weeks (± 14 days) later starting on Week 37.

Revised text:

The first dose of 12-Week treatment (Week 25 ± 3 days) is 4 weeks after the last dose of the 4-Week treatment phase. All subsequent visits will be 12 weeks (~~± 14~~ **± 3** days) later starting on Week 37.

Reason for change:

For consistency with schedule of procedures

Change #13: Section 5.1.5 Follow-up Periods

Previous text:

All subjects will be followed for safety every 30 days (± 3 days) through 90 days after the last dose of investigational product (± 14 days) or at the time of initiation of new systemic anticancer treatment. After 90 days, only subjects with investigational product-related SAEs will continue to be followed for safety. All subjects will be followed for survival every 3 months (± 14 days) until the end of the study (approximately 30 months from the date the last subject is randomized into the study or the sponsor stops the study).

Revised text:

All subjects will be followed for safety every 30 days (± 3 days) through 90 days after the last dose of investigational product ~~(± 14 days)~~ or at the time of initiation of new systemic anticancer treatment. After 90 days, only subjects with investigational product-related SAEs will continue to be followed for safety. All subjects will be followed for survival every 3 months (± 14 days) until the end of the study (approximately 30 months from the date the last subject is randomized into the study or the sponsor stops the study).

Reason for change:

Correct typographical error for consistency with schedule of procedures

Change #14: Section 5.2.1 Medical History and Physical Examination, Weight, Vital Signs, and ECG, paragraph 4

Previous text:

In order to evaluate the potential risk for QTc (the time between the start of the Q wave and the end of the T wave corrected for heart rate) prolongation with tremelimumab, subjects will have ECGs collected at specified time points noted in the schedule of events. All ECGs performed during the study will be 12-lead and will be obtained at baseline following the first dose on Week 1, Week 5, Week 13 and every 3 months thereafter during the first year of treatment (Visits 1, 2, 3, 5, 8, 10, and 12). Beginning with the second year of treatment (starting at Visit 14), ECGs will be performed every 6 months until discontinuation of treatment. All ECGs on dosing days must be performed between 2 and 6 hours after treatment administration. The first 100 subjects will have ECGs obtained in triplicate and within a 5-minute time period for all time points. The remaining subjects will have a single ECG performed for all time points.

Revised text:

In order to evaluate the potential risk for QTc (the time between the start of the Q wave and the end of the T wave corrected for heart rate) prolongation with tremelimumab, subjects will have ECGs collected at specified time points noted in the schedule of events. All ECGs performed during the study will be 12-lead and will be obtained at baseline following the first dose on Week 1, Week 5, Week 13 and every 3 months thereafter during the first year of treatment (Visits 1, 2, 3, 5, 8, 10, and 12). Beginning with the second year of treatment (starting at Visit 14), ECGs will be performed every 6 months until discontinuation of treatment. All ECGs on dosing days must be performed between 2 and 6 hours after treatment administration. The first 100 subjects will have ECGs obtained in triplicate and within a 5-minute time period for all time points. The remaining subjects will have a single ECG performed for all time points. **In case of clinically significant ECG abnormalities including an ECG that demonstrates a QTc value > 500 msec, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 min) to confirm prolongation.**

Reason for change:

To further clarify and be consistent with changes in Section 6.3.1.6

Change #15: Section 5.2.2 Clinical Laboratory Tests, serum chemistry table

Previous text:

- Calcium
- Chloride
- Magnesium
- Potassium
- Sodium
- Bicarbonate
- AST
- ALT
- Alkaline phosphatase (ALP)
- Total bilirubin
- Amylase [a]
- Thyroid stimulating hormone (TSH)
- Gamma glutamyl transferase (GGT)
- Lactic dehydrogenase (LDH)
- Uric acid
- Creatinine
- Blood urea nitrogen (BUN)
- Glucose
- Albumin
- Total protein
- Triglycerides
- Cholesterol
- Lipase [a]
- C-reactive protein (CRP) [a]

[b] To be analyzed at local and central lab.

Revised text:

- Calcium
- Chloride
- Magnesium
- Potassium
- Sodium
- Bicarbonate
- AST
- ALT
- Alkaline phosphatase (ALP)
- Total bilirubin
- Amylase [a]
- Thyroid stimulating hormone (TSH)
- Gamma glutamyl transferase (GGT)
- Lactic dehydrogenase (LDH)
- Uric acid
- Creatinine
- Blood urea nitrogen (BUN)
- Glucose
- Albumin
- Total protein
- Triglycerides
- Cholesterol
- Lipase [a]
- C-reactive protein (CRP) [a b]

[a] To be analyzed at local and central lab.

[b] To be analyzed at central lab only.

Reason for change:

C-reactive protein will be used for a subgroup analysis as described in Section 7.4, and is not a laboratory test routinely used in clinical practice for the oncologic treatment of cancer patients.

Change #16: Section 5.2.6.1 Response Assessments, paragraph 1

Previous text:

Imaging assessments will be performed at baseline (within 28 days before randomization with an exception discussed in Section 5.1.1) and every 3 months (± 14 days) after start of dosing until confirmed objective disease progression irrespective of whether the subject has discontinued investigational product.

Revised text:

Imaging assessments will be performed at baseline (within 28 days before randomization with an exception discussed in Section 5.1.1) and every 3 months ~~(± 14 days) after start of dosing~~ **during the 4-week treatment period, every 6 weeks during Weeks 25-61, and every 3 months thereafter** until confirmed objective disease progression irrespective of whether the subject has discontinued investigational product.

Reason for change:

The description of disease assessments was corrected to match the schedule of procedures

Added last sentence:

Additional scans can also be done at any time based on investigator discretion.

Reason for change:

Text added to clarify that the principal investigator can evaluate disease at any time based on clinical symptoms

Change #17: Section 6.1.3 Adverse Events of Special Interest

Previous text:

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the investigational product and requires close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing subject health care and analysis of these events in order to characterize and understand them in association with the use of this investigational product.

Revised text:

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the investigational product and requires close monitoring and ~~rapid~~ communication by the investigator to the sponsor. An AESI may be serious or nonserious. The ~~rapid~~ reporting of AESIs allows ongoing subject health care and analysis of these events in order to characterize and understand them in association with the use of this investigational product. **The mechanism of action of tremelimumab involves activation of the immune system and therefore the most common AEs associated with tremelimumab therapy are inflammatory in nature and can be seen in any organ. All events, regardless of their designation of special interest, will continue to be closely monitored and reviewed. A full list of possibly related AEs based on the totality of data evaluated to date is available in the Investigator's Brochure. Moreover, as per Section 4.5.7, toxicity management guidelines have been developed according to what has been published recently on the toxicity profile of the anti-CTLA-4 compounds (Kaehler and Hauschild, 2011; Weber et al, 2012).**

Reason for change:

Deleted description of rapid reporting, for consistency with reporting requirements described in Section 6.4.3;

Added text to provide information on potential AEs associated with the mechanism of action of tremelimumab, and to clarify that all AEs will be monitored regardless of whether they have been defined as an AESI in this protocol

Change #18: Section 6.1.3.6 Cardiovascular: QTc Prolongation, Resting 12-lead ECG

Previous text:

At screening, a 12-lead ECG must be performed to establish a baseline. Baseline QTc will be determined by the average of no less than 3 consecutive ECGs (within 5-10 minutes of one another) at the screening visit (prior to randomization). Additional 12-lead ECGs should also be performed in the event of QTc prolongation at any visit.

Electrocardiograms will be performed after the first dose and once Q12W thereafter for the first year of treatment. Electrocardiograms will be performed every 6 months after the first year of treatment or until discontinuation from treatment. Prior to discontinuation, all ECGs must be performed within 2 to 6 hours of the dosing. The final ECG will be performed at the short term follow-up visit.

For this study QTc prolongation is defined as:

- A single QTc value of ≥ 550 msec OR
- Two consecutive QTc measurements, within 48 hours of one another, where the QTc interval is ≥ 500 msec, but < 550 msec on both ECGs

Revised text:

At screening, a 12-lead ECG must be performed to establish a baseline. Baseline QTc will be determined by the average of no less than 3 consecutive ECGs (within 5-10 minutes of one another) at the screening visit (prior to randomization). ~~Additional 12-lead ECGs should also be performed i~~**I**n the event of QTc prolongation **(> 500 msec)** at any visit**, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 min) to confirm prolongation**.

Electrocardiograms will be performed after the first dose and once Q12W thereafter for the first year of treatment. Electrocardiograms will be performed every 6 months after the first year of treatment or until discontinuation from treatment. Prior to discontinuation, all ECGs must be performed within 2 to 6 hours of the dosing. The final ECG will be performed at the short term follow-up visit.

For this study QTc prolongation is defined as:

- A single QTc value of ≥ 550 msec OR

- ~~Two~~ **Three** consecutive QTc measurements, within 48 hours of one another, where the **average** QTc interval is ≥ > 500 msec, but < 550 msec on both ECGs

Reason for change:

To further clarify and be consistent with changes in Section 5.2.1

Change #19: Section 6.4.2.2 Notifying the Sponsor of Serious Adverse Events, paragraph 1

Previous text:

Within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational product, the investigator or qualified designee must complete the SAE Report Form and fax it to MedImmune Patient Safety or designee ( ).

MedImmune or designee) contact information:

Revised text:

Within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational product, the investigator or qualified designee must complete the SAE Report Form and fax it to MedImmune Patient Safety or designee (~~)~~.

MedImmune or designee contact information:

Reason for change:

The CRO was removed for SAE reporting

Change #20: Section 6.4.3.3 Other Events of Special Interest

Deleted

~~6.4.3.3 Other Events of Special Interest~~

~~Other events of special interest (as defined in Section 6.1.3) are required to be reported within 24 hours of knowledge of the event to MedImmune Patient Safety using the SAE Report Form, even if the event is considered to be nonserious (see Section 6.4.2.2 for contact information).~~

Reason for change:

This section, which describes the reporting requirements for other events of special interest, was removed because these events do not require immediate reporting.

Amendment 3

The main changes for this protocol amendment are:

- To increase the sample size from 180 subjects to 564 subjects;
- To add 2 interim analyses to the study;
- To add a secondary endpoint of OS at 18 months; and
- To clarify that the independent biostatistician will be from a third party.

Major changes made during this amendment include:

1. Cover page: The Asia/Pacific medical monitor was added.
2. Section (Study Abstract): The study abstract was updated to match the body of the protocol.
3. Section 1.2.3 (Summary of Clinical Experience): Updated safety and efficacy data were added.
4. Section 1.3 (Research Hypothesis): The statistical details were updated to match the revised statistical plan for the protocol.
5. Section 1.4 (Rationale for Study Conduct): The rationale section was updated to provide a rationale for the study expansion.
6. Section 1.5 (Benefit-risk and Ethical Assessment): Updated safety and efficacy data were added.

7. Section 2.2 (Secondary Objectives): The OS at 18 months analysis was added.
8. Section 4.2 (Subject Selection and Withdrawal): Several sections were clarified.
9. Section 4.4.2 (Unblinding for Interim Analyses): Section was added to describe the unblinding procedures for the interim analyses.
10. Section 4.5.2 (Other Study Medications): A sentence was added allowing the use of opioids under medical supervision.
11. Section 4.5.4.1 (Dose Calculation): Section was clarified that either baseline weight or weight on dosing days could be used to calculate the dosage required.
12. Table 4.5.7-2 (Guidelines for Skipping a Dose): Language around pre-medication was clarified.
13. Table 5.1-1 (Schedule of Study Procedures for Screening and Every 4-Week Treatment Period): PBMC collection was added at screening, Weeks 1, 5, and 13.
14. Table 5.1-2 (Schedule of Study Procedures for Every 12-Week Treatment, End of Treatment, and Follow-up Period): PBMC collection was added at the Q12W dosing visits and the end of study visit.
15. Section 5.1.1 (Screening [Visit 1]): Several procedures were clarified.
16. Section 5.1.2.1 (Week 1: First Infusion [Visit 2]): Wording was added to clarify the dosing procedures.
17. Section 5.2.1 (Medical History and Physical Examination, Weight, Vital Signs, and ECG): Pulse oximetry wording was added.
18. Section 5.2.2 (Clinical Laboratory Tests): Wording was added to allow serum pregnancy tests instead of urine pregnancy tests during the treatment phase.
19. Section 5.2.5 (Biomarker Evaluation and Methods): A description of PBMCs was added.
20. Section 5.2.6 (Tumor Biopsies): This section was added to describe procedure and requirements for standard of care biopsies.
21. Section 5.2.7 (Other Fluids/Tissues): This section was added to allow for standard of care drainage fluids to be collected.
22. Section 6.1.3.6 (Cardiovascular: QTc Prolongation): Clarification was given that triplicate ECGs are for the first 100 subjects and need to be 1 minute apart.
23. Section 6.4.2.2 (Notifying the Sponsor of Serious Adverse Events): The MedImmune drug safety email address was added.
24. Section 6.4.3 (Other Events Requiring Immediate Reporting): The definition of an immediately reportable event was added.
25. Section 7.2 (Analysis Populations): The Per-protocol population was removed.
26. Section 7.3.1 (Primary Endpoint): The primary endpoint was updated to match the expansion wording and describe the revised analysis.
27. Section 7.3.2.1 (Efficacy): An analysis of OS at 18 months was added, the hierarchical gate keeping strategy was added, and a description of the statistics for the PROs was added.
28. Section 7.5 (Interim Analysis): This section was revised to describe the 2 interim analyses planned.

29. Section 7.6 (Sample Size and Power Calculations): This section was revised to reflect the increase in the number of subjects planned and the revised power calculations for both interim and final analyses.
30. Section 7.7 (Independent Data Monitoring Committee): Language was added to describe the role of the IDMC for the interim analyses.
31. Appendix 1 (Sponsor Signature): The appendix was updated to follow the current protocol approval process.

Amendment 4

The main changes for this protocol amendment are:

- To provide the opportunity for placebo arm subjects who meet the required eligibility criteria to cross-in to receive tremelimumab, in the event of either the IDMC recommendation to unblind the study at the time of the second interim analysis, or after the final analysis.
- Updated p-values and hazard ratio values to align with Statistical Analysis Plan version 4.0.

Major changes made during this amendment include:

1. Cover page: The Senior Medical Director, Medical Monitor, and Medical Science Director were updated.
2. Study Abstract: The study abstract was updated to match the body of the protocol.
3. Sections 3.2, 4.4.2, and 5.1: Updated text to include the updated cross-in study design.
4. The header of Section 5.1.3.1 (Treatment Visits) was updated to correct the visit window for Weeks 37 and 49.
5. Section 5.1.4 (End of Treatment Visit) and Table 5.1-2 (Schedule of Study Procedures for Every 12-Week Treatment, End of Treatment, and Follow-up Period) were aligned for consistency, including addition of assessments for circulating soluble factors at end of treatment in Table 5.1-2 and addition of collection of cryopreserved PMBC in Section 5.1.4.
6. Section 5.1.6 (Cross-in Visits): Section was added to reflect the updated study design.
7. Section 7.3.2.1 (Efficacy): Removed the detail on the hierarchical gate keeping testing strategy for secondary endpoints since this information resides in the Statistical Analysis Plan.
8. Section 7.3.2.1 (Efficacy): Removed reference to confirmation of objective response in subheading Overall Response Rate to align with Statistical Analysis Plan.
9. Section 7.5, Interim Analysis (Table 7.5-1) and Study Abstract (Table 1-1): Clarified p-values and hazard ratio values to align with Statistical Analysis Plan version 4.0. This change supersedes the change made in Protocol Administrative change 2, dated 13 March 2014.
10. Synopsis and Section 7.6: Text was updated to align with changes made to Table 1-1 and Table 7.5-1, including changes to p-values and hazard ratio values to align with Statistical Analysis Plan version 4.0.

11. Section 7.5 (Interim Analysis): This section was updated to include a description of the cross-in to receive tremelimumab.
12. Appendix 1 (Sponsor Signature): The appendix was updated for the current Amendment 4 approval.
13. Appendix 8 was added to include the assessments for the new cross-in design and 'Changes to Protocol' section was changed to Appendix 9 (Note that per Amendment 5, this section was reverted back to Appendix 8).

Rationale for Protocol Amendment

The purpose of this protocol amendment is to:

- Provide the opportunity for placebo arm subjects who meet the required eligibility criteria to cross-in to receive tremelimumab, in the event of either the IDMC recommendation to unblind the study at the time of the second interim analysis, or after the final analysis.
- Reflect a change in Medical Monitors.
- Correct inconsistencies between sections for end of treatment study procedures.
- Correct inconsistencies regarding treatment window for Week 37 and all subsequent treatment visits.
- Clarify that the detail on the hierarchical gate keeping testing strategy resides in the Statistical Analysis Plan.
- Clarify that the statistical analysis of objective response rate will not require confirmation of response, as described in the Statistical Analysis Plan.
- Align the efficacy boundaries to the Lan and DeMets method to ensure the boundaries correspond with the principles described in the original protocol and ensure the criteria used at each interim analysis is maintained at any subsequent analysis (ie final analysis).

Amendment 5

The main changes for this protocol amendment are:

- To eliminate the cross-in option for placebo arm subjects, since the primary analysis of Study D4880C00003 demonstrated no statistically significant improvement in overall survival of tremelimumab compared with placebo.
- To outline procedures to be performed following the primary analysis of Study D4880C00003

Major changes made during this amendment include:

1. Study Abstract: The study abstract was updated to match the body of the protocol.

2. Sections 3.2, 4.4.2, 5.1, and 7.5: Updated text to remove the cross-in study option.
3. Added Table 5.1-3 "Schedule of Study Procedures for patients remaining on Tremelimumab treatment only post primary analysis of Study D4880C00003 and approval of Protocol Amendment 5"
4. Section 5.1.6: Modified assessments for patients who are continuing on trememlimumab to include only SAE reporting. All other listed assessments will be at the discretion of the investigator.
5. Sections 5, 6, and 10.1: Changed MedImmune Patient Safety to (also known as AZ DES) for SAE reporting. will be responsible for processing all SAEs onto the AZ global safety database.
6. Appendix 8 "Providing the Opportunity for Subjects in the Placebo Arm to Receive Tremelimumab" section was removed, since the primary analysis of Study D4880C00003 demonstrated no statistically significant improvement in overall survival of tremelimumab compared with placebo.

Rationale for Protocol Amendment

This amendment is being instigated after the primary analysis of this study has been conducted. The results demonstrated no statistically significant improvement in overall survival of tremelimumab compared with placebo in subjects with unresectable malignant mesothelioma. Due to the results of the primary analysis, the sponsor recommended that all patients remaining on study treatment were unblinded. Following unblinding, patients currently receiving tremelimumab who in the opinion of the investigator, are receiving clinical benefit will be given the option to continue to receive tremelimumab. Patients currently receiving placebo or those who have discontinued placebo are expected to withdraw from the study. For patients who continue to receive tremelimumab beyond this amendment, investigators will continue to report all SAEs to the sponsor until 90 days after receipt of their last dose of study treatment.