



Revised Clinical Study Protocol

Drug Substance MEDI4736 and
 Tremelimumab
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A Phase II Open-Label, Multi-Center Study of MEDI4736 Evaluated as Single Agent or in Combination with Tremelimumab in Patients with Metastatic Pancreatic Ductal Adenocarcinoma

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The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

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This clinical study protocol has been subject to a peer review according to AstraZeneca standard procedures.

The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

PROTOCOL SYNOPSIS

A Phase II Open-Label, Multi-Center Study of MEDI4736 Evaluated as Single Agent or in Combination with Tremelimumab in Patients with Metastatic Pancreatic Ductal Adenocarcinoma

International Coordinating Investigators

PPD



Number of patients planned

This study will consist of Part A, Lead-in, as well as a possible Part B, non-randomized expansion (Part B: Expansion) or a possible Part B, randomized controlled study (Part B: RCT). This study will initially enroll approximately 60 patients to receive MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy (Part A: Lead-in). Depending on the data in each arm from Part A, a non-randomized expansion phase may be initiated (Part B: Expansion approximately 140 additional patients, 70 patients per arm) and/or a randomized, controlled study (Part B: Randomized, controlled trial ([RCT]) may be initiated to compare MEDI4736 monotherapy and/or MEDI4736 + tremelimumab combination to Standard of Care (SoC; approximately 375 total additional patients, 125 patients per arm).

Study period		Phase of development
Estimated date of first patient enrolled	Q4 2015	II
Estimated date of last patient completed	Q3 2020	II

Study design

This is a Phase II, open-label, multi-center study to determine the efficacy and safety of MEDI4736 evaluated as single agent or in combination with tremelimumab in patients with metastatic pancreatic ductal adenocarcinoma (PDAC) whose disease has progressed on 5-FU-containing or gemcitabine-containing first-line chemotherapy. Initially, patients will be enrolled and randomized (1:1) to treatment with MEDI4736 monotherapy or MEDI4736 + tremelimumab, until 30 patients have been randomized to treatment in each arm (Part A: Lead-in). Patient recruitment and tumor assessment will be monitored on an ongoing basis.

The format of Part B will be determined based on the responses seen in the first 30 patients in each arm in Part A. A protocol amendment will be made if criteria are met to proceed to

Part B. The protocol amendment will include available data from Part A and any changes to study design and statistical plan, if needed.

- **Part B: Expansion.** If an ORR of >25% (ie, responses in ≥ 8 patients) is observed in the first 30 treated patients in either treatment arm in Part A (unless the totality of the data supports a different decision), after protocol amendment an additional 70 patients will be enrolled in that arm, for a total of 100 evaluable patients per arm.
- **Part B: Randomized, controlled trial (RCT).** If an ORR of >15% and <25% (ie, response in ≥ 5 patients and <8 patients) is observed in the first 30 treated patients in either treatment arm in Part A, a randomized, controlled substudy may be initiated after protocol amendment.

If Part B: RCT is initiated, this will be a randomized, controlled, open-label, multi-center, study to determine the efficacy and safety of MEDI4736 monotherapy and/or MEDI4736 + tremelimumab combination therapy versus SoC chemotherapy (1:1 or 1:1:1, depending on whether there are 2 or 3 treatment arms). Approximately 125 additional patients per treatment arm will be planned for enrollment. Treatment arms for MEDI4736 monotherapy and/or MEDI4736 + tremelimumab will only be included in the RCT if the corresponding treatment meets the appropriate criteria in Part A. Randomization in Part B: RCT will be stratified by best response to prior first-line chemotherapy (complete response [CR], partial response [PR], or stable disease [SD]) versus no response (progressive disease [PD]) and according to prior first-line chemotherapy, 5-FU-containing versus gemcitabine-containing.

Tumor assessments will be performed every 6 weeks ± 7 days for the first 48 weeks relative to the date of first infusion and then every 12 weeks ± 7 days thereafter until confirmed PD, with categorization of objective tumor response by Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1).

Objectives

Part A: Lead-in and Part B: Expansion

Primary objective:	Outcome measure:
To assess the efficacy of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy in terms of ORR	ORR in all patients using Investigator assessments according to RECIST 1.1

Secondary objectives:	Outcome measures:
To further assess the efficacy of the combination of MEDI4736 and tremelimumab and MEDI4736 alone in terms of DoR, DCR, PFS, PFS3, PFS6, OS, OS6, and OS12	DoR, DCR, PFS, PFS3, and PFS6 in all patients using Investigator assessments according to RECIST 1.1 OS, OS6, and OS12

Secondary objectives:	Outcome measures:
To assess the health-related QoL in metastatic PDAC patients treated with MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy as measured by EORTC QLQ-C30 global QoL scale (Part B only)	Adjusted mean change from baseline in global QoL score from the EORTC QLQ-C30 questionnaire
To assess the disease-related symptoms in metastatic PDAC patients treated with MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy as measured by EORTC QLQ-PAN26 pancreatic pain scale (Part B only)	Adjusted mean change from baseline in pancreatic pain score from the EORTC QLQ-PAN26 questionnaire
To investigate the immunogenicity of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy	Presence of ADAs for MEDI4736 and tremelimumab (confirmatory results: positive or negative; titers)
To assess the PK of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy	Concentration of MEDI4736/tremelimumab in blood and noncompartmental PK parameters (such as peak concentration and trough, as data allow; sparse sampling only)

Safety objective:	Outcome measures:
To assess the safety and tolerability profile of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy	AEs, physical examinations, laboratory findings (including clinical chemistry, hematology, and urinalysis), vital signs (including blood pressure and pulse), ECGs

Part B: Randomized, controlled trial

Primary objective:	Outcome measure:
To assess the efficacy of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy compared to SoC in terms of OS	OS

Secondary objectives:	Outcome measures:
To further assess the efficacy of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy compared to SoC in terms of ORR, DoR, DCR, PFS, PFS2, PFS3, and OS6, OS12	PFS, PFS2, PFS3, ORR, DoR, and DCR in all patients using Investigator assessments according to RECIST 1.1 OS6, OS12

Secondary objectives:	Outcome measures:
To investigate the relationship between PD-L1 expression by IHC and efficacy parameters	ORR, DoR, DCR, PFS3, and PFS6 across PD-L1 expression using Investigator assessments according to RECIST 1.1
To assess the health-related QoL in metastatic PDAC patients treated with MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy as measured by EORTC QLQ-C30 global QoL scale	Adjusted mean change from baseline in global QoL score from the EORTC QLQ-C30 questionnaire
To assess the disease-related symptoms in metastatic PDAC patients treated with MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy as measured by EORTC QLQ-PAN26 pancreatic pain scale	Adjusted mean change from baseline in pancreatic pain score from the EORTC QLQ-PAN26 questionnaire
To investigate the immunogenicity of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy	Presence of ADAs for MEDI4736 and tremelimumab (confirmatory results: positive or negative; titers)
To assess the PK of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy	Concentration of MEDI4736/tremelimumab in blood and noncompartmental PK parameters (such as peak concentration and trough, as data allow; sparse sampling only)

Safety objective:	Outcome measures:
To assess the safety and tolerability profile of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy compared to SoC	AEs, physical examinations, laboratory findings (including clinical chemistry, hematology, and urinalysis), vital signs (including blood pressure and pulse), ECGs

Target subject population

Patients (aged ≥ 18 years) with histologically or cytologically confirmed metastatic PDAC who have received no more than 1 prior chemotherapy regimen or any other systemic therapy for recurrent/metastatic PDAC and who had tumor progression following at least 2 months of prior standard first-line 5-FU-containing or gemcitabine-containing chemotherapy.

Duration of treatment

Patients in the Part A Lead-in or Part B will receive MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy for a 12- month period or until discontinuation criteria are met. Patients in the SoC arm of the Part B: Randomized, controlled trial will discontinue study drug at the first assessment of disease progression per RECIST 1.1.

Patients in the MEDI4736 monotherapy treatment arm who develop PD after completing 12 months of therapy may restart their assigned treatment with the same treatment guidelines followed previously. Patients in the MEDI4736 + tremelimumab arm may restart treatment if they complete the 4 dosing cycles with MEDI4736 + tremelimumab (with clinical benefit per Investigator judgement) but subsequently have confirmed progression of disease during or following treatment with MEDI4736 alone.

Patients who have discontinued all study treatment will enter follow-up.

Investigational product, dosage, and mode of administration

MEDI4736 monotherapy treatment arm

- 1.5 g MEDI4736 via IV infusion q4w, starting at Week 0, for up to a total of 12 months (up to 13 doses)

MEDI4736 + tremelimumab combination therapy treatment arm

- 1.5 g MEDI4736 by IV infusion q4w and 75 mg tremelimumab q4w by IV infusion starting at week 0 (up to 4 doses each), followed by 1.5 g MEDI4736 monotherapy by IV infusion q4w (starting on Week 16) to complete a total of 12 months of therapy (up to 9 additional doses)

Standard of Care (Part B: Randomized, controlled trial only)

- Gemcitabine-based or fluorouracil-based chemotherapy administered per local guidelines

Statistical methods

For each arm in Part A (Lead-in) of the study, once 15 patients have completed 2 post-baseline tumor assessments (at Weeks 6 and 12), predictive probability will be calculated to assess the chance of observing at least 5 out of 30 responses ($>15\%$ ORR [CR or PR], and/or at least 15/30 DCR at 12 weeks ($\geq 50\%$ DCR12) in that arm. If, predictive probability is below 10% for both endpoints, enrollment into the arm in which this happens will be stopped. A different decision outside of these criteria may be made, if the totality of the data supports it. Recruitment will continue while predictive probability is evaluated. If enrollment into an arm is to be stopped based on $<10\%$ predictive probability, no new patients will be recruited, but patients who are already on study will continue in accordance with study guidelines. If enrollment is fast enough so that, by the time 15 patients are evaluable (Weeks 6 and 12 tumor assessment data available), all 30 patients per arm have already been randomized, then the predictive probability calculations will not be carried out.

If the ORR in Part A is $>25\%$ (ie, ≥ 8 responses from 30 patients in an arm), then an additional 70 patients will be enrolled to that arm (Part B: Expansion) to evaluate ORR in 100 patients in total (unless the totality of the data supports a different decision). In the Part B: Expansion study, the primary endpoint, ORR, will be evaluated using a 2-sided, 95% Clopper-Pearson

confidence interval to the observed ORR in the expanded cohort of 100 patients. With 100 patients, there will be >90% power to reject the null hypothesis of a 10% response rate assuming a true response rate of 25% at 5% (2-sided) significance level (critical value ORR of 16.7%), while also providing adequate patients to reasonably characterize the safety profile of the expanded arm(s). A 10% response rate is considered a reasonable assumption for the average response rate achieved by current therapies in second-line advanced pancreatic cancer ([Rahma et al 2013](#)).

If the ORR in Part A is >15% (ie, ≥ 5 responses from 30 treated patients in an arm), then a randomized, controlled substudy may be initiated (Part B: RCT). If initiated, this substudy will be a randomized, open-label, multi-center, study to determine the efficacy and safety of MEDI4736 monotherapy and/or MEDI4736 + tremelimumab combination therapy versus SoC chemotherapy (randomized 1:1 or 1:1:1, depending on whether there are 2 or 3 treatment arms) with a primary endpoint of OS. If both arms move forward to part B, then the primary comparison will be conducted on MEDI4736 + tremelimumab combination therapy versus SoC chemotherapy. Approximately 125 additional patients per treatment arm will be planned for enrollment in this Part B: RCT. Treatment for MEDI4736 monotherapy and/or MEDI4736 + tremelimumab will only be included in the RCT if the corresponding treatment meets the appropriate criteria for Part A. A final decision to initiate the randomized portion of the study will be made after evaluation of all available efficacy and safety data from the lead-in phase, and may not be limited to the decision rules provided in the protocol. With 125 patients per arm for a 2-arm study, 196 events (78% maturity) would provide 90% power to detect a true average hazard ratio of 0.63 at a 2-sided 5% significance level (critical value for hazard ratio of 0.75). This assumes a median OS in the SoC arm of 5 months and a 2-month delay in survival curves separating. The data from Part B: RCT will be analyzed separately and will not be pooled with Part A for the purpose of statistical analysis.

For Part B: RCT, the randomization schedule will be stratified by best response to prior first-line chemotherapy (CR, PR, or SD) versus no response (PD), and by prior first-line chemotherapy, 5FU-containing versus gemcitabine-containing. The primary endpoint, OS, will be compared between treatments based on the hazard ratio, with 95% confidence intervals. The hazard ratio will be estimated using a stratified log rank test. If both arms are taken forward from Part A, then the primary comparison will be to compare MEDI4736 + tremelimumab combination therapy versus SoC. MEDI4736 monotherapy versus SoC will be compared hierarchically in order to strongly control the type I error. Full details of the multiple testing procedure will be provided in the SAP.

Secondary endpoints, including DoR, DCR, PFS, PFS2, PFS3 and PFS6, will be summarized based on Investigator assessments according to RECIST 1.1. PFS, PFS2, PFS3, PFS6, OS, OS6, OS12, and DoR rates and their medians will be calculated and plotted using Kaplan-Meier estimates, with 95% confidence intervals. Safety and tolerability will be evaluated through AEs, physical examinations, laboratory and vital sign measures, and electrocardiograms, using summary statistics. Disease-related symptoms and health-related quality of life will be assessed through an analysis of the EORTC QLQ-C30 global quality of life (QoL) and QLQ-PAN26 pancreatic pain scales. Adjusted mean change from baseline in

global QoL score will be analyzed using a mixed model for repeated measures (MMRM) analysis of all of the post-baseline scores for each visit and will be presented by treatment group. As a supportive analysis, global QoL improvement rate will be analyzed using a logistic regression model. An exploratory analysis will examine adjusted mean change from baseline on EORTC QLQ-C30 functioning domains (physical, role, cognitive, emotional, and social) and on EORTC QLQ-C30 and QLQ-PAN26 symptom scales/items (including pancreatic pain, fatigue, nausea, weight loss [difficulty gaining weight/loss of appetite], and jaundice). EORTC QLQ-C30 and QLQ-PAN26 compliance (overall compliance and by visit compliance) will be summarized for each treatment group.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study clinical study protocol.

Abbreviation or special term	Explanation
β-hCG	beta-Human chorionic gonadotropin
5-FU	Fluoropyrimidine
ADA	Antidrug antibody
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma drug concentration-time curve
AUC _{ss}	Area under the plasma drug concentration-time curve at steady state
BCRP	Breast cancer resistance protein
BICR	Blinded Independent Central Review
BoR	Best objective response
BP	Blood pressure
BSC	Best supportive care
CD	Cluster of differentiation
CI	Confidence interval
C _{max}	Maximum plasma concentration
C _{max,ss}	Maximum plasma concentration at steady state
CR	Complete response
CSA	Clinical Study Agreement
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTL	Cytotoxic T lymphocytes
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
C _{trough}	Trough plasma concentration
C _{trough,ss}	Trough plasma concentration at steady state

Abbreviation or special term	Explanation
DCR	Disease control rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDoR	Expected Duration of Response
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer quality of life core questionnaire
EORTC QLQ-PAN26	European Organisation for Research and Treatment of Cancer quality of life questionnaire pancreatic cancer module
EQ-5D-5L	EuroQol 5-dimension, 5-level health state utility index
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FOLFIRINOX	Multidrug combination of leucovorin, fluorouracil, irinotecan, and oxaliplatin
fT ₃	Free triiodothyronine
fT ₄	Free thyroxine
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IFN-γ	Interferon-gamma

Abbreviation or special term	Explanation
IgG	Immunoglobulin G
IHC	Immunohistochemical
IL	Interleukin
IMT	Immunomodulatory therapy
IP	Investigational Product
irAE	Immune-related adverse event
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LFT	Liver function test
LIMS	Laboratory Information Management System
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major histocompatibility complex
MHLW	Ministry of Health, Labor, and Welfare
miRNA	Micro-ribonucleic acid
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non-small-cell lung cancer
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
OS6	Proportion of patients alive at 6 months from randomization/enrollment
OS12	Proportion of patients alive at 12 months from randomization/enrollment
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-1	Programmed cell death 1

Abbreviation or special term	Explanation
PDAC	Pancreatic ductal adenocarcinoma
PD-L1	Programmed cell death ligand 1
PFS	Progression-free survival
PFS2	Progression-free survival ² ; time from the date of randomization to the earliest progression event(s) subsequent to that used for the PFS endpoint or death
PFS3	Proportion of patients with progression-free survival after 3 months
PFS6	Proportion of patients with progression-free survival after 6 months
P-gp	P-glycoprotein
PGx	Pharmacogenetic
PI	Principal Investigator
PK	Pharmacokinetics
PR	Partial response
PRO	Patient-reported outcomes
PRO-CTCAE	Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events
PS	Performance status
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks
q12w	Every 12 weeks
QoL	Quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
RCT	Randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RT-qPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SNP	Single nucleotide polymorphism

Abbreviation or special term	Explanation
SoC	Standard of care
sPD-L1	Soluble programmed cell death ligand 1
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WBDC	Web Based Data Capture
WT	Weight

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Pancreatic ductal adenocarcinoma (PDAC), which accounts for more than 90% of all pancreatic tumors, is a malignancy with an extremely poor prognosis, as shown by a 1-year survival rate of around 18% for all stages of the disease and an estimated 5-year survival rate of less than 5%. The low survival rates associated with PDAC primarily reflect the fact that tumors progress rapidly with few specific symptoms and are thus at an advanced stage at diagnosis in most patients (almost 80% of patients at diagnosis; [Hidalgo et al 2015](#)).

Metastatic PDAC is one of the most aggressive and highly lethal malignancies. Although it constitutes only about 3% of all cancers in the United States (US), it is the fourth leading cause of cancer deaths in both men and women and is responsible for 7% of all cancer-related deaths. The death rate from the disease rose from 5 per 100000 in 1930 to more than 10 per 100000 in 2003. The American Cancer Society estimates that in the US in 2014, about 39590 people (20170 men and 19420 women) will die of pancreatic cancer ([Dragovich et al 2014](#)). In the absence of predisposing conditions, such as familial pancreatic cancer and chronic pancreatitis, pancreatic cancer is unusual in persons younger than 45 years. After age 50 years, the frequency of pancreatic cancer increases linearly. The median age at diagnosis is 69 years in whites and 65 years in blacks; some single-institution data reported from large cancer centers suggest that the median age at diagnosis in both sexes has fallen to 63 years.

The poor prognosis reflects the limited treatment options available, highlighting the need for the development of newer therapeutic options. Very few patients with truly localized disease can be cured by surgery. Inoperable patients sometimes undergo surgery for symptom relief (eg, bypass or stent implantation, splanchnicectomy), but the main treatment is radiation and chemotherapy. Radiation therapy is used to control local symptoms like pain but has no proven effect on overall survival (OS; [Thota et al 2014](#)).

Despite recent advances in chemotherapeutics and in our understanding of the molecular biology of pancreatic cancer, there has been limited progress in therapeutic options for metastatic disease. Over the past 4 decades, studies of several combination therapies have demonstrated minimal or no survival benefit compared with gemcitabine alone as first-line therapy. Gemcitabine monotherapy had been the standard of care (SoC) for patients with metastatic pancreatic cancer for several years until combination therapy with gemcitabine plus erlotinib was shown to increase median survival by approximately 2 weeks. A Phase III trial of gemcitabine versus fluoropyrimidine (5-FU) as first-line therapy in patients with advanced or metastatic adenocarcinoma of the pancreas reported a significant improvement in survival among patients treated with gemcitabine (median survival durations were 5.65 and 4.41 months for gemcitabine-treated and 5-FU-treated patients, respectively [$p=0.0025$]). The survival rate at 12 months was 18% for gemcitabine patients and 2% for 5-FU patients ([Burris et al 1997](#)).

The National Cancer Institute of Canada performed a Phase III trial (CAN-NCIC-PA3 [NCT00026338]) that compared gemcitabine alone versus the combination of gemcitabine and erlotinib (100 mg/day) for first-line treatment in patients with advanced or metastatic pancreatic carcinomas. The corresponding median survival rate for patients receiving erlotinib was 6.2 months versus 5.9 months for patients receiving placebo. The 1-year survival rate for patients receiving erlotinib was 23% versus 17% for patients receiving placebo (Moore et al 2007). However, the modest survival benefit was tempered by a significant side effect profile and the high cost of treatment (Moore et al 2007). Later, the multidrug combination of leucovorin, fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) was noted to provide an increased median survival of 4.3 months versus gemcitabine; however, given its side effect profile, it is available only to a select group of patients with advanced pancreatic cancer. The patients were randomly assigned to receive FOLFIRINOX or gemcitabine. The median OS was 11.1 months in the FOLFIRINOX group compared with 6.8 months in the gemcitabine group (hazard ratio [HR] for death =0.57; 95% confidence interval [CI], 0.45 to 0.73; $p < 0.001$). Median progression-free survival (PFS) was 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group (HR for disease progression =0.47; 95% CI, 0.37 to 0.59; $p < 0.001$; Conroy et al 2011).

Recently, the gemcitabine plus nab-paclitaxel combination was shown to increase median survival by 1.8 months, with increased OS at 1 and 2 years; adverse effects were reasonable and included cytopenias and peripheral neuropathy. The multi-center, international Phase III trial (NCT00844649) included 861 patients with previously untreated metastatic pancreatic adenocarcinoma. The patients were randomly assigned to receive gemcitabine and nab-paclitaxel or gemcitabine monotherapy. The median OS was 8.5 months in the nab-paclitaxel/gemcitabine group compared with 6.7 months in the gemcitabine group (HR for death=0.72; 95% CI, 0.62 to 0.83; $p < 0.001$). Median PFS was 5.5 months in the nab-paclitaxel/gemcitabine group and 3.7 months in the gemcitabine group (HR for disease progression=0.69; 95% CI, 0.58 to 0.82, $p < 0.001$; Von Hoff et al 2013).

The current National Comprehensive Cancer Network recommendations suggest acceptable first-line chemotherapy combinations for patients with good performance status (ie, Eastern Cooperative Oncology Group [ECOG] performance status [PS] of 0 or 1), good pain management, patent biliary stent, and adequate nutritional intake; these combinations include FOLFIRINOX, nab-paclitaxel + gemcitabine, and gemcitabine plus erlotinib. The only recommended first-line chemotherapy option for patients with poor PS is gemcitabine monotherapy. The guidelines for choosing an appropriate treatment regimen for patients with metastatic pancreatic cancer thus remain ambiguous, and in the absence of a randomized trial comparing the combination regimens head to head, the dilemma remains regarding appropriate first-line therapy for these patients.

Invariably, regardless of choice of first-line therapy, patients with advanced/metastatic disease will progress, and at that point, the choice of treatment becomes considerably murkier. According to results from a US cooperative group trial (CALGB 80303), fewer than half of patients with advanced pancreatic cancer went on to receive any additional therapy after progressing on first-line study treatment. This reflects, in part, the fact that patients in this

setting frequently demonstrate significant clinical deterioration and a decline in PS and are no longer deemed appropriate candidates for further anticancer therapy.

Currently, there is no firmly established standard chemotherapy for patients after progression on first-line treatment. A variety of cytotoxic agents, either alone or in combination, have been evaluated, although primarily in the context of small single-arm or retrospective studies. Most regimens have been associated with median PFS in the range of 2 to 4 months, OS ranges between 4 and 8 months, and different response rates varying from 10% to 20%, highlighting the very poor prognosis of patients who are candidates for such treatment (Walker and Ko 2014). Targeted therapies studied in this chemotherapy-refractory setting, meanwhile, have produced even worse efficacy results (Li et al 2014, Walker and Ko 2014). The combination of 5-FU and oxaliplatin has been shown to confer a benefit in the second-line setting after first-line gemcitabine in a small clinical trial and can be considered as a treatment option in this setting. In patients treated with first-line FOLFIRINOX who can receive second-line chemotherapy after progression, gemcitabine can be considered as an option (NCCN Pancreatic Adenocarcinoma Guidelines). Despite some progress, enrollment of patients with pancreatic cancer in clinical trials for all lines of treatment should be encouraged to further improve the systemic treatment of this disease (Seufferlein et al 2012).

1.1.1 Immunotherapies

It is increasingly understood that cancers are recognized by the immune system, and under some circumstances, the immune system may control or even eliminate tumors (Dunn et al 2004). Studies in mouse models of transplantable tumors have demonstrated that manipulation of co-stimulatory or co-inhibitory signals can amplify T-cell responses against tumors (Peggs et al 2009). This amplification may be accomplished by blocking co-inhibitory molecules, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) or programmed cell death 1 (PD-1), from binding with their ligands, B7 or B7-homolog 1 (B7-H1) (programmed cell death ligand 1 [PD-L1]).

1.1.2 MEDI4736

MEDI4736 is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits the binding of PD-L1 and is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document). As MEDI4736 is an engineered mAb, it does not induce antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity. The proposed mechanism of action for MEDI4736 is interference of the interaction of PD-L1.

PD-L1 is frequently found to be expressed on many cancers with a high frequency, up to 88% in some cancer types. Tumors expressing PD-L1 can render cytotoxic T lymphocytes (CTLs) inactive or nonfunctional through engagement of the inhibitory receptor of PD-1. Pancreatic cancers that are PD-L1 positive have been found to have significantly poorer 1-year postoperative survival and OS compared to tumors that are PD-L1 negative (Nomi et al 2007). Results of several preclinical models have demonstrated that blockade of PD-1 or PD-L1, or

the use of PD-1-deficient T cells, can result in profound immune-mediated tumor control in many experimental systems ([Blank et al 2006](#), [Iwai et al 2002](#), [Iwai et al 2005](#)).

During the last decade, there has been a progressively increased interest in studying the therapeutic potential of immune therapy in PDAC. Several lines of evidence documenting the immune dysfunction associated with PDAC support the hypothesis that immunotherapy can alter the process of carcinogenesis ([Fokas et al 2015](#)).

In particular, preclinical and clinical studies in PDAC have indicated that blockades of immune checkpoints can have a positive effect on antitumor immunity. In fact, PD-L1-expression is directly related to a poorer prognosis and reduced number of tumor-infiltrating T lymphocytes, particularly cluster of differentiation (CD) 8(+) T cells. mAbs against PD-L1 or PD-1 induced a substantial antitumor effect on murine pancreatic cancer in vivo. PD-L1 blockades promoted CD8(+) T-cell infiltration into the tumor and induced local immune activation. Furthermore, the combination of anti-PD-L1 mAb and gemcitabine exhibited a significant synergistic effect on murine pancreatic cancer and resulted in complete response (CR) without overt toxicity ([Nomi et al 2007](#)). Available clinical data derived from a clinical trial evaluating a single agent showed a modest clinical activity together with a tolerable safety profile, suggesting the possibility to evaluate an alternative development strategy, such as combination with different compounds.

Treatment of 14 patients with PDAC with BMS-936559, a novel anti-PD-L1 antibody, showed no response in any of the treated patients ([Brahmer et al 2012](#)). Similarly, in a Phase II trial in 27 patients with locally advanced or metastatic PDAC receiving the anti-CTLA-4 agent ipilimumab, there were no responders by Response Evaluation Criteria in Solid Tumors (RECIST), but a patient experienced a delayed response after initial progressive disease (PD; [Pardoll 2012](#), [Royal et al 2010](#)). Preliminary data from Study CD ON-MEDI4736-1108 (referred to hereafter as Study 1108), a Phase I multi-arm expansion study of MEDI4736, showed 2 partial responses (PRs) in 29 evaluable patients ([Segal et al 2014](#)).

As an antibody that blocks the interaction between PD-L1 and its receptors, MEDI4736 may relieve PD-L1-dependent immunosuppressive effects and, therefore, enhance the cytotoxic activity of antitumor T cells. This hypothesis is supported by emerging clinical data from other mAbs targeting the PD-L1/PD-1 pathway, which provide early evidence of clinical activity and a manageable safety profile ([Brahmer et al 2012](#), [Topalian et al 2012](#)). To date, the responses tend to be more frequent in patients with tumors that express PD-L1 (PD-L1-positive), although, importantly, responses are also seen in patients with tumors that are non/low expressors of PD-L1.

MEDI4736 has been given to humans as part of ongoing studies as a single drug or in combination with other drugs. As of 14 July 2014, 509 patients have been enrolled and treated in 10 ongoing clinical studies on MEDI4736 (with 5 studies using MEDI4736 as monotherapy and 5 studies using MEDI4736 in combination therapy). Details on the safety profile of MEDI4736 are summarized in Section 1.3.2.1. Refer to the current MEDI4736

Investigator's Brochure (IB) for a complete summary of nonclinical and clinical information; see Section 6.7 for guidance on management of MEDI4736-related toxicities.

1.1.3 Tremelimumab

Tremelimumab, a CTLA-4 mAb of the IgG 2 kappa isotype, is an immunomodulatory therapy (IMT) that is being developed by AstraZeneca for use in the treatment of cancer. Tremelimumab is a human IgG 2 mAb directed against CTLA-4.

Binding of CTLA-4 to its target ligands (B7-1 and B7-2) provides a negative regulatory signal, which limits T-cell activation. Anti-CTLA-4 inhibitors antagonize the binding of CTLA-4 to B7 ligands and enhance human T-cell activation as demonstrated by increased cytokine (interleukin [IL]-2 and interferon-gamma [IFN- γ]) production in vitro in whole blood or peripheral blood mononuclear cell (PBMC) cultures (Tarhini and Kirkwood 2008). In addition, blockade of CTLA-4 binding to B7 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and antitumor activity in animal models, including killing of established murine solid tumors and induction of protective antitumor immunity. (Refer to the current tremelimumab IB for more information.) Therefore, it is expected that treatment with an anti-CTLA-4 antibody, such as tremelimumab, will lead to increased activation of the human immune system, increasing antitumor activity in patients with solid tumors. At the same time, it is unlikely that anti-CTLA-4 monotherapy will lead to long-term cures in the majority of patients as single agent. In this regard, a recently completed Phase II trial in patients with locally advanced or metastatic pancreatic cancer (NCT00836407) showed that anti-CTLA-4 monotherapy is ineffective in this patient population, only one patient experienced a delayed response after initial progressive disease (Royal et al 2010).

An extensive program of nonclinical and clinical studies has been conducted for tremelimumab both as monotherapy and combination therapy with conventional anticancer agents to support various cancer indications using different dose schedules. As of the data cutoff date of 12 November 2014 (for all studies except Study D4190C00006, which has a cutoff date of 4 December 2014), 1010 patients have received tremelimumab monotherapy (excluding 497 patients who have been treated in the blinded Phase IIb study, D4880C00003) and 197 patients have received tremelimumab in combination with other agents. More than 800 of these patients had melanoma and were treated at a dose of 15 mg/kg every 90 days. Details on the safety profile of tremelimumab monotherapy are summarized in Section 1.3.2.2. Refer to the current tremelimumab IB for a complete summary of nonclinical and clinical information; see Section 6.7 for guidance on management of tremelimumab-related toxicities.

Tremelimumab exhibited a biphasic pharmacokinetic (PK) profile with a long-terminal phase half-life of 22 days. Overall, a low incidence of antidrug antibodies (ADAs; <6%) was observed in treatment with tremelimumab.

1.1.4 MEDI4736 in combination with tremelimumab

Targeting both PD-1 and CTLA-4 pathways may have additive or synergistic activity (Pardoll 2012) because the mechanisms of action of CTLA-4 and PD-1 are nonredundant;

therefore, AstraZeneca is also investigating the use of MEDI4736 + tremelimumab combination therapy for the treatment of cancer.

Study D4190C00006 is a Phase Ib dose-escalation study to establish safety, PK/pharmacodynamics, and preliminary antitumor activity of MEDI4736 + tremelimumab combination therapy in patients with advanced non-small-cell lung cancer (NSCLC). The dosing schedule utilized is MEDI4736 every 2 or 4 weeks (q2w; q4w) up to Week 48 (12 months), combined with tremelimumab q4w up to Week 24 for 7 doses, then tremelimumab every 12 weeks (q12w) for 2 additional doses for up to 12 months. The study is ongoing and continues to accrue.

As of 27 January 2015, a total of 74 patients have been treated in the study, including 58 patients on the q4w dosing schedule and 16 patients on the q2w dosing schedule. Patients have received between 1 and 13 doses of MEDI4736 and between 1 and 9 doses of tremelimumab. Details on the safety profile of MEDI4736 + tremelimumab combination therapy are summarized in Sections 1.2.1 and 1.3.2.3. Refer to the current MEDI4736 IB and tremelimumab IB for a complete summary of nonclinical and clinical information; see Section 6.7 for guidance on management of MEDI4736 + tremelimumab-related toxicities.

As of 27 January 2015 in Study D4190C00006, an approximately dose-proportional increase in PK exposure (maximum plasma concentration [C_{\max}], trough plasma concentration [C_{trough}], and area under the plasma drug concentration-time curve from time zero to Day 28 post-dose [$AUC_{0-28\text{day}}$]) of both MEDI4736 and tremelimumab was observed over the dose range of 3 to 20 mg/kg MEDI4736 q4w or q2w and 1 to 10 mg/kg tremelimumab q4w. Four of 60 patients were ADA positive for either anti-MEDI4736 or anti-tremelimumab antibodies post-treatment; MEDI4736 PK was impacted in only 2 of these 4 patients. Complete soluble programmed cell death ligand 1 (sPD-L1) suppression (surrogate for PD-L1 targeting) was observed in almost all patients over the dose range of 3 to 20 mg/kg of MEDI4736 q4w or q2w.

1.1.5 Rationale for conducting this study

PDAC patients have poor outcomes, as a consequence of the very aggressive nature of the disease, and the limited activity of current treatment options, thus there is a significant unmet medical need for additional treatment options for use in this patient population. In addition, although clinical experience with MEDI4736 is limited, currently available data from the MEDI4736 first in human study (Study 1108) indicate encouraging response rates and duration of response (DoR) with a manageable safety profile in patients with a variety of solid malignancies, including a heterogeneous population of heavily pretreated patients with pancreatic cancer treated with MEDI4736 as monotherapy.

Combining multiple immunotherapy agents has been shown to result in improved response rates relative to monotherapy, for example, the concurrent administration of nivolumab and ipilimumab to patients with advanced melanoma induced higher objective response rates (ORRs) than those obtained with single-agent therapy. Importantly, responses appeared to be deep and durable (Wolchok et al 2013). The rationale for evaluating the combination of

MEDI4736 with tremelimumab is that the mechanisms of CTLA-4 and PD-1 are nonredundant, suggesting that targeting both may have additive or synergistic activity ([Pardoll 2012](#)). Similar results have been observed in an ongoing study of MEDI4736 + tremelimumab in NSCLC ([Antonia et al 2014a](#)), with further updated details presented in this clinical study protocol (CSP).

Chemotherapy, a mainstay intervention for cancer since the 1940s, has the potential to debulk the primary tumor mass and, therefore, can be used to alter the tumor microenvironment, thereby making it more receptive to an effective immune response.

Although chemotherapeutic drugs induce their primary damage in many different ways, most of them kill tumor cells by the induction of apoptosis. The massive apoptosis induced by chemotherapy could release pro-inflammatory mediators, such as heat-shock proteins, that act as danger signals and can activate dendritic cells through the toll-like receptor signaling pathways, thus engaging the innate immune response. It could also induce cytokine production patterns typical of the T-helper, type I phenotype, thereby promoting effective cytotoxic T-cell responses ([Zwierzina 2008](#)).

There is evidence that tumor-derived antigens induce tolerance during tumor progression. In mice, for example, persistent presentation of a tumor antigen causes cytotoxic T cells that were once active against the antigen to become tolerant, resulting in tumor outgrowth. Interestingly, functional capacities are regained when T cells are transferred to an antigen-free environment. The elimination of persistent tolerogenic tumor antigen environment via chemotherapy-induced debulking may play a role in generating an effective immune response ([Drake 2012](#)).

Another way in which cytotoxic drugs can make the tumor microenvironment more conducive to an effective immune response is by restoring the expression of tumor antigens or major histocompatibility complex (MHC) molecules that have been lost during tumor progression or upregulating the expression of costimulatory molecules (B7-1 and B7-2), thereby rendering the tumor cells themselves as more efficient antigen presenting cells. Others (5-fluorouracil and cisplatin) sensitize tumor cells to cytotoxic T lymphocytes (CTL)-mediated apoptosis through Fas- or perforin/granzyme-mediated pathways ([Emens and Jaffee 2005](#)).

Chemotherapy, even at conventional doses, can eliminate myeloid-derived suppressor cells (MDSC) and Tregs, thus removing some of the immune suppressive factors present in cancer patients. Cytotoxic drugs can modulate systemic mechanisms of active immune suppression or amplify expansion of antigen-specific T-cell expansion via cytoreduction by influencing the homeostasis of the hematopoietic compartment through transient lymphodepletion followed by rebound replenishment of immune cell pools ([Emens and Jaffee 2005](#)).

Moreover, cytoreductive chemotherapy generates a plethora of tumor-associated antigens, which are expressed in the context of MHC molecules on antigen-presenting cells and can potentially initiate antigen-specific T-cell activation. Furthermore, tumors carry many mutations, and there is clear evidence that most tumors express neo-antigens against which the host has a capacity to react. Conventional chemotherapy could unmask additional tumor

neo-antigens and thus increase the amount of material available for cross-priming (Emens and Jaffee 2005).

This immune response is driven by the accumulation of dendritic cells in the tumor, followed by their maturation, migration to lymph nodes, and priming of tumor-specific CD8+ CTL in a type I interferon-dependent manner. An antigen density within the tumor is an important determinant of the outcome of immune surveillance following chemotherapy (Kang et al 2013Kang et al 2013).

In this setting, immunotherapy has the potential to mount an ongoing and dynamic immune response that can kill tumor cells for an extended time after the conventional therapy has been administered. This long-lasting response is potentially able to completely eradicate tumor cells rather than producing only a temporary killing of cells, in contrast to standard chemotherapy. The most promising immune-based treatments are mAbs that act as checkpoint inhibitors (eg, MEDI4736 and tremelimumab), adoptive cell therapy (eg, T cells expressing chimeric antigen receptors), and vaccines (eg, sipuleucel-T).

Based on the preliminary clinical efficacy and safety data observed in the pancreatic cancer cohort of Study 1108 and the preliminary efficacy, safety, and tolerability data of MEDI4736 + tremelimumab combination therapy in Study D4190C00006 (a Phase Ib/II study of MEDI4736 + tremelimumab combination in NSCLC), this study is being conducted to determine the safety and efficacy of the combination of MEDI4736 with tremelimumab and MEDI4736 as monotherapy in a Phase II setting in PDAC.

1.2 Rationale for study design, doses and control groups

This study will utilize an open-label design due to the different treatment administration schedules and treatment durations.

1.2.1 MEDI4736 and tremelimumab dose and treatment regimen justification

1.2.1.1 MEDI4736 + tremelimumab combination therapy dose rationale

The MEDI4736 + tremelimumab combination therapy doses and regimen selected for this study are based on the goal of selecting an optimal combination dose of MEDI4736 and tremelimumab that would yield sustained target suppression (sPD-L1), demonstrate promising efficacy, and have an acceptable safety profile.

Pharmacokinetics/Pharmacodynamics data

In order to reduce the dosing frequency of MEDI4736 to align with the q4w dosing of tremelimumab, while ensuring an acceptable PK/pharmacodynamics, safety, and efficacy profile, cohorts in Study D4190C00006 were narrowed to 15 and 20 mg/kg MEDI4736 q4w. PK simulations from the MEDI4736 monotherapy data indicated that a similar area under the plasma drug concentration-time curve at steady state (AUC_{ss} ; 4 weeks) was expected following both 10 mg/kg q2w and 20 mg/kg q4w MEDI4736. The observed MEDI4736 PK data from the D4190C00006 study were well in line with the predicted monotherapy PK data developed preclinically. This demonstrates similar exposure of MEDI4736 20 mg/kg q4w and

10 mg/kg q2w, with no alterations in PK when MEDI4736 and tremelimumab (doses ranging from 1 to 3 mg/kg) are dosed together. While the median maximum plasma concentration at steady state ($C_{\max,ss}$) is expected to be higher with 20 mg/kg q4w (approximately 1.5 fold) and median trough concentration at steady state ($C_{\text{trough},ss}$) is expected to be higher with 10 mg/kg q2w (approximately 1.25 fold), this is not expected to impact the overall safety and efficacy profile, based on existing preclinical and clinical data.

Monotonic increases in pharmacodynamic activity were observed with increasing doses of tremelimumab relative to the activity observed in patients treated with MEDI4736 monotherapy. There was evidence of augmented pharmacodynamic activity relative to MEDI4736 monotherapy with combination doses containing 1 mg/kg tremelimumab, inclusive of both the 15 and 20 mg/kg MEDI4736 plus 1 mg/kg tremelimumab combinations.

Clinical data

As of 27 January 2015, a total of 74 patients with advanced NSCLC have been treated in Study D4190C00006. The 74 patients have received between 1 and 9 doses of tremelimumab and between 1 and 13 doses of MEDI4736. Various dose combinations were explored, with doses of tremelimumab ranging from 1 to 10 mg/kg and doses of MEDI4736 ranging from 3 to 20 mg/kg. Fifty-eight of these patients were in the q4w dosing schedule and 16 patients were in the q2w dosing schedule, with the goal of identifying the dose combination that best optimizes the risk:benefit profile in an acceptable range of PK and pharmacodynamic values.

Patients treated with doses of tremelimumab above 1 mg/kg had a higher rate of adverse events (AEs), including discontinuations due to AEs, serious AEs (SAEs), and severe AEs. Between the 10 mg/kg MEDI4736 + 1 mg/kg tremelimumab and 10 mg/kg MEDI4736 + 3 mg/kg tremelimumab cohorts treated at the q2w schedule, the number of patients reporting any AE, Grade 3 AEs, SAEs, and treatment-related AEs was higher in the 10 mg/kg MEDI4736 + 3 mg/kg tremelimumab cohort than the 10 mg/kg MEDI4736 + 1 mg/kg tremelimumab cohort. A similar pattern was noted in the q4w regimens, suggesting that, as the dose of tremelimumab increased above 1 mg/kg, a higher rate of treatment-related events may be anticipated. Further, the SAEs frequently attributed to immunotherapy, pneumonitis and colitis, were more commonly seen in cohorts using either 3 mg/kg or 10 mg/kg of tremelimumab compared to the 1-mg/kg dose cohorts. Together, these data suggest that a combination using a tremelimumab dose of 1 mg/kg appeared to minimize the rate of toxicity when combined with MEDI4736. As a result, all combination doses utilizing either the 3 or 10-mg/kg doses of tremelimumab were eliminated in the final dose selection.

In contrast, cohorts assessing higher doses of MEDI4736 with a constant dose of tremelimumab did not show an increase in the rate of AEs. The data suggested that increasing doses of MEDI4736 may not impact the safety of the combination as much as the tremelimumab dose. Further, safety data between the 10-mg/kg and 20-mg/kg cohorts were similar, with no change in safety events with increasing dose of MEDI4736.

In Study D4190C00006, of all treatment cohorts, the cohort of 11 patients treated in the 20 mg/kg MEDI4736 + 1 mg/kg tremelimumab group had the fewest AEs, Grade ≥ 3 AEs, SAEs, and treatment discontinuations due to AEs, but still showed strong evidence of clinical

activity. This cohort had a lower number of treatment-related Grade ≥ 3 AEs or treatment related SAEs. No dose-limiting toxicities (DLTs) were reported.

Preliminary clinical activity of the MEDI4736 and tremelimumab combination did not appear to change with increasing doses of tremelimumab. The 15- and 20-mg/kg MEDI4736 q4w cohorts demonstrated objective responses at all doses of tremelimumab, and increasing doses of tremelimumab did not provide deeper or more rapid responses.

Efficacy data suggested that the 20 mg/kg MEDI4736 + 1 mg/kg tremelimumab dose cohort may demonstrate equivalent clinical activity to other dose combinations. A total of 5 of 11 patients in the 20 mg/kg MEDI4736 + 1 mg/kg tremelimumab cohort were evaluable for efficacy with at least 8 weeks of follow-up. Of these, there were 2 patients (40%) with PR, 1 patient (20%) with SD, and 1 patient (20%) with PD. (The fifth patient had only a single scan, which was conducted outside the window for these evaluations.)

Additionally, of all cohorts, the 20 mg/kg MEDI4736 + 1 mg/kg tremelimumab dose cohort had the fewest AEs, Grade ≥ 3 AEs, SAEs, and treatment discontinuations due to AEs, but still showed some evidence of clinical activity. All together, the data suggested that a 20 mg/kg MEDI4736 + 1 mg/kg tremelimumab dose combination should be selected for further development.

1.2.1.2 Rationale for 4 cycles of combination therapy followed by MEDI4736 monotherapy

Long-term follow up on melanoma patients treated with ipilimumab, an anti-CTLA-4 targeting antibody (dosed every 3 weeks for 4 doses and then discontinued), shows that patients responding to ipilimumab derive long-term benefit, with a 3-year OS rate of approximately 22%. Furthermore, the survival curve in this population reached a plateau at 3 years and was maintained through 10 years of follow up ([Schadendorf et al 2013](#)).

Similar data have been presented for other anti-PD-1/PD-L1 targeting antibodies:

- Nivolumab (anti-PD-1) was dosed q2w for up to 96 weeks in a large Phase I dose-escalation and expansion study, and showed responses were maintained for a median of 22.94 months for melanoma (doses 0.1 mg/kg to 10 mg/kg), 17 months for NSCLC (doses 1, 3, and 10 mg/kg), and 12.9 months for renal cell carcinoma patients (doses 1 and 10 mg/kg) at the time of data analysis ([Brahmer et al 2014](#), [Drake et al 2013](#), [Hodi et al 2014](#)). Furthermore, responses were maintained beyond treatment discontinuation in the majority of patients who stopped nivolumab treatment (either due to protocol specified end of treatment, CR, or toxicity) for up to 56 weeks at the time of data analysis ([Topalian et al 2014](#)).
- MPDL3280a (anti-PD-L1) and the combination of nivolumab with ipilimumab, in which patients were dosed for a finite time period and responses maintained beyond treatment discontinuation have been reported ([Herbst et al 2013](#), [Wolchok et al 2013](#)).

Similar long term results may be expected with use of other immune-mediated cancer therapeutics including anti-CTLA-4 antibodies such as tremelimumab, anti PD-L1 antibodies such as MEDI4736, or the combination of the two.

The MEDI4736 + tremelimumab combination regimen will be administered for 4 doses followed by 1.5 g MEDI4736 monotherapy q4w.

1.2.1.3 MEDI4736 monotherapy dose rationale

A dose of MEDI4736 20 mg/kg q4w is supported by in-vitro data, non-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study 1108 in patients with advanced solid tumors (ongoing first-time-in-humans study) and from a Phase I trial performed in Japanese patients with solid tumor (NCT01938612).

PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg q2w or 15 mg/kg every 3 weeks (q3w), MEDI4736 exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥ 3 mg/kg q2w, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the MEDI4736 dosing frequency can be adapted to a particular regimen given the linearity seen at higher doses than 3 mg/kg. The expected half-life with doses ≥ 3 mg/kg q2w is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of MEDI4736 with PD-L1. Dose-related changes in a variety of peripheral biomarkers have been observed over the dose range of 0.1 to 15 mg/kg. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to MEDI4736. Of the 220 patients who received MEDI4736 monotherapy and for whom PK/ADA data were available as of 14 July 2014, 5 were ADA positive, with an impact on PK/pharmacodynamics reported in 1 patient at 3 mg/kg.

Data from Study 006 (Phase I trial in NSCLC patients using the combination of MEDI4736 and tremelimumab) also show an approximately dose-proportional increase in PK exposure for MEDI4736 over the dose range of 3 to 20 mg/kg MEDI4736 q4w or q2w. (For further information on PK observations in Study 006, please refer to Section 1.2.1).

The observed MEDI4736 PK data from the combination study were well in line with the predicted monotherapy PK data (5th median and 95th percentiles) for a q4w regimen. (For further information on PK observations in Study 006, please refer to Section 1.2.1).

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg q2w or 15 mg/kg q3w; Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg q2w and 20 mg/kg q4w regimens, as represented by AUC_{ss} (4 weeks). Median C_{max,ss} is expected to be higher with 20 mg/kg q4w (~1.5 fold) and median C_{trough,ss} is expected to be higher with 10 mg/kg q2w (~1.25 fold). Clinical activity with the 20 mg/kg q4w dosing regimen is anticipated to be consistent with 10 mg/kg q2w with the proposed similar dose of 20 mg/kg q4w expected to

(a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar area under the plasma drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg q4w and 10 mg/kg q2w regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg q4w.

Clinical data

As of 8 April 2015, there is initial safety data for 16 patients receiving the 20 mg/kg q4w dosing regimen (12 patients from Study 1108 and 4 patients from the Japan Phase I trial). The toxicities observed with 20 mg/kg q4w are consistent with the 10 mg/kg q2w regimen, and there were no DLTs observed. Of the 12 patients in Study 1108, 42% of patients have experienced any grade AE, with 2 being Grade 3 and above (17%). None of the Grade 3 and higher events was considered treatment-related. No patients on the Japan Phase I trial have experienced a Grade 3 or above AE. At present, the data do not suggest that the safety profile of MEDI4736 will be different in the 20 mg/kg q4w dosing regimen when compared to 10 mg/kg q2w regimen. In fact, as of 14 July 2014, 393 patients enrolled in Study 1108 have received MEDI4736, predominantly at 10 mg/kg q2w (either in the dose-escalation or dose-expansion phase of the study). Data presented at the European Society for Medical Oncology (ESMO) meeting 2014 with a later cutoff of 21 August 2014 showed that MEDI4736 was well tolerated at all doses in the NSCLC subset of patients enrolled into Study 1108, with drug-related Grade ≥ 3 AEs reported in 3% of patients and drug-related AEs leading to discontinuation reported in 1% of patients. No drug-related colitis or hyperglycemia of any grade, no Grade ≥ 3 pneumonitis reported, and no drug-related AEs leading to death were reported ([Antonia et al 2014b](#)). No DLTs were observed up to a dose of 10 mg/kg q2w or 15 mg/kg q3w.

Efficacy data on the NSCLC patients in Study 1108, presented at ESMO 2014 (cutoff date of 21 August 2014), showed a DCR at 12 weeks of 41% and ORR of 16% among 162 evaluable patients, with activity observed in both squamous and non-squamous histologies. The ORR was higher (25%; 12 CR/PR; n=48) in patients with PD-L1 positive tumors, defined as those with $\geq 25\%$ of tumor cells with membrane staining for PD-L1, compared to patients with PD-L1 negative tumors (10%; 7 CR/PR; n=74) ([Antonia et al 2014b](#)).

1.2.1.4 Rationale for fixed dosing

A population PK model was developed for MEDI4736 using monotherapy data from Study 1108 (Phase I study; N=292; doses=0.1 to 10 mg/kg q2w or 15 mg/kg q3w; solid tumors). Population PK analysis indicated only a minor impact of body weight (WT) on the PK of MEDI4736 (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg q2w) and fixed dosing (750 mg q2w) of MEDI4736 was evaluated by comparing predicted steady state PK concentrations (5th, median, and 95th percentiles) using the population PK model. A fixed

dose of 750 mg was selected to approximate 10 mg/kg (based on a median body WT of approximately 75 kg). A total of 1000 patients were simulated using a body WT distribution of 40 to 120 kg. Simulation results demonstrated that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with the fixed dosing regimen.

Similarly, a population PK model was developed for tremelimumab using data from Phase I through Phase III studies (N=654; doses=0.01 to 15 mg/kg q4w or every 90 days; metastatic melanoma; Wang et al 2014). A population PK model indicated minor impact of body WT on the PK of tremelimumab (coefficient of ≤ 0.5). The WT-based (1 mg/kg q4w) and fixed dosing (75 mg/kg q4w; based on a median body WT of approximately 75 kg) regimens were compared using predicted PK concentrations (5th, median, and 95th percentiles) using a population PK model in a simulated population of 1000 patients with a body WT distribution of 40 to 120 kg. Similar to MEDI4736, simulations indicated that both body WT-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less overall between-patient variability with the fixed dosing regimen.

Similar findings have been reported by others (Narwal et al 2013, Ng et al 2006, Wang et al 2009, Zhang et al 2012). Wang and colleagues investigated 12 mAbs and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/pharmacodynamics parameters (Zhang et al 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given the expectation of similar PK exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens. Based on an average body WT of 75 kg, a fixed dose of 1.5 g q4w MEDI4736 (equivalent to 20 mg/kg q4w) and 75 mg q4w tremelimumab (equivalent to 1 mg/kg q4w) is included in the current study.

1.3 Benefit/risk and ethical assessment

The following sections include summaries of the potential benefits and risks associated with MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy, respectively, prior to the overall benefit/risk assessment.

1.3.1 Potential benefits

1.3.1.1 MEDI4736

The majority of the safety and efficacy data currently available for MEDI4736 are based on the first time in-human, single-agent study (Study 1108) in patients with advanced solid tumors. Updated efficacy data from Study 1108 were presented at the European Society for Medical Oncology 2014 Congress. As of 21 August 2014, 373 patients with all tumor types were evaluable for response analysis, including 352 patients receiving 10 mg/kg MEDI4736 q2w. The DCR at 12 weeks in patients receiving 10 mg/kg MEDI4736 q2w was 33%, and the ORR was 10%. Greater DCR at 12 weeks (47% versus 28%) and ORR (22% versus 5%)

were observed in PD-L1-positive versus PD-L1-negative patients. Responses were ongoing in 92% of patients, with an objective response duration ranging from 0.1 to 32 weeks (Segal et al 2014). Of the 29 evaluable PDAC patients treated in Study 1108, 2 patients had PRs (Segal et al 2014). Other mAbs targeting the PD-L1/PD-1 pathway have shown clinical activity in this indication, as summarized in Section 1.1.4.

1.3.1.2 Tremelimumab

In a single-arm, Phase II study (Study A3671008) of tremelimumab administered at 15 mg/kg every 90 days to patients with refractory melanoma, an response rate of 7% and a median OS of 10 months in the second-line setting (as compared to approximately 6 months with best supportive care reported from a retrospective analysis; Korn et al 2008) were observed (Kirkwood et al 2010). In a randomized, open-label, first-line Phase III study of tremelimumab (administered at 15 mg/kg every 90 days) versus chemotherapy (dacarbazine or temozolomide) in advanced melanoma (Study A3671009), results of the final analysis showed a response rate of 11% and a median OS of 12.58 months in this first-line setting as compared to 10.71 months with standard chemotherapy; however, these results were not statistically significant (Ribas et al 2013). Additionally, in a Phase II maintenance study (Study A3671015) in patients with Stage IIIB or IV NSCLC that have responded or remained stable, PFS at 3 months was 22.7% in the tremelimumab arm (15 mg/kg) compared with 11.9% in the best supportive care arm (Study A3671015).

1.3.1.3 MEDI4736 + tremelimumab

The preclinical and clinical justification for this combination as noted in Section 1.2.1 also supports the synergy of this combination. Available data, such as those presented by Wolchok et al, suggest that the combination of agents targeting PD-1/PD-L1 and CTLA-4 may have profound and durable benefits in patients with melanoma (Wolchok et al 2013). Furthermore, preliminary efficacy data from Study D4190C00006 have demonstrated that this combination is clinically active and well tolerated. As of 27 January 2015, 53 patients were evaluable for response across various MEDI4736 + tremelimumab dose regimens. Of these, 12 (23%) patients had a best response of PR and 14 (26%) patients had a best response of SD. In the MEDI4736 20 mg/kg + tremelimumab 1 mg/kg q4w cohort, a total of 5 of 11 patients were evaluable for efficacy with at least 8 weeks of follow-up. Of these, there were 2 (40%) patients with PR, 1 (20%) patient with SD, and 1 (20%) patient with PD.

1.3.2 Potential risks

1.3.2.1 MEDI4736

Potential risks, based on the mechanism of action of MEDI4736 and related molecules, include immune-mediated reactions, such as enterocolitis, dermatitis, hepatitis/hepatotoxicity, endocrinopathy, pneumonitis, and neuropathy or neurologic events. Additional important potential risks include infusion-related reactions, hypersensitivity, anaphylaxis or serious allergic reactions, serious infections, and immune complex disease. Of the 393 patients with advanced solid tumors including PDAC treated with 10 mg/kg q2w in Study 1108 (as of the current IB, Edition 7.0, cutoff date of 14 July 2014), 331 (84.2%) patients had at least 1 AE regardless of causality. Treatment-related AEs were reported for 162 (41.2%) of 393 patients.

The most frequently reported ($\geq 2\%$ of patients) AEs assessed by the Investigator as treatment related (including all National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event [CTCAE] grades) were fatigue (13.5%); nausea (8.4%); diarrhea, decreased appetite, and rash (5.3% each); vomiting (4.8%); pruritus (4.1%); dyspnea (3.8%); pyrexia (3.1%); hypothyroidism, increased alanine aminotransferase [ALT], increased aspartate aminotransferase [AST], and cough (2.5% each); myalgia (2.3%); and abdominal pain and dizziness (2.0% each). Two patients discontinued treatment due to AEs assessed by the Investigator as treatment related (pneumonitis and increased transaminases). Grade 3 events assessed by the Investigator as treatment related that occurred in 2 or more patients were fatigue (4 patients); increased gamma-glutamyltransferase (3 patients); and vomiting, increased ALT, increased AST, and arthralgia (2 patients each). There were 2 patients with Grade 4 events (hypercalcemia and fatigue) assessed by the Investigator as treatment related and 1 patient with a Grade 5 event assessed by the Investigator as treatment related (angiopathy). For further details on the safety profile of MEDI4736 as monotherapy or combination therapy, please refer to the current IB.

Other mAbs targeting the PD-1/PD-L1 pathway are currently in clinical development. Among the most frequent AEs noted with treatment with these antibodies are fatigue, rash, diarrhea, and pruritus. Immune-mediated AEs of Grade ≥ 3 reported include pneumonitis, diarrhea, increased ALT, and increased AST. Other relevant risks include those associated with biological and immunotherapeutic agents, including infusion reactions and acute immunoglobulin E-mediated allergic reactions.

1.3.2.2 Tremelimumab

Potential risks, based on the mechanism of action of MEDI4736 and related molecules (ipilimumab) include potentially immune-mediated reactions that can result in an inflammatory response in any organ or tissue including the liver, gastrointestinal (GI) tract, thyroid glands, pancreas, skin, nervous system, respiratory tract, and adrenal glands. The profile of AEs and the spectrum of event severity have remained stable across the tremelimumab clinical program and are consistent with the pharmacology of the target. To date, no tumor type or stage appears to be associated with unique AEs (except for vitiligo that appears to be confined to patients with melanoma). Overall, 944 (97.0%) of the 973 patients treated with tremelimumab monotherapy as of the data cutoff date of 12 November 2014 experienced at least 1 AE. The events resulted in discontinuation of tremelimumab in 10.0% of patients, were serious in 36.5%, were Grade ≥ 3 in severity in 49.8%, were fatal in 67.7%, and were considered to be treatment related in 79.1% of patients. Among the overall fatal cases (67.7%) reported in the patients treated with tremelimumab monotherapy, the most frequent cause of death was ascribed to the patient's underlying malignant disease (61.8%), whereas the remaining causes included other or unknown/missing (7.1%), and due to investigational product (IP; 0.5%). The most frequent Grade ≥ 3 AEs (all causality) reported in $\geq 2\%$ of subjects (in decreasing order of frequency) were diarrhea, fatigue, colitis, disease progression, dyspnea, dehydration/nausea/vomiting, abdominal pain, decreased appetite, and asthenia. The events of diarrhea, abdominal pain, and colitis occurred at a higher rate in the 10 mg/kg group, whereas fatigue, disease progression, dyspnea, dehydration, nausea, vomiting, decreased appetite, and asthenia were reported more frequently in the 15 mg/kg group.

Treatment-related AEs were reported at similar rates in the 10 and 15 mg/kg groups (81.8% and 80.0%, respectively), and were mostly Grade 1 or 2 in severity (\geq Grade 3 treatment-related AEs reported in 26.1% of subjects). The most frequent treatment-related AEs (in $> 5\%$ of subjects) were diarrhea (41.2%), rash (27.2%), pruritus (25.1%), fatigue (23.8%), nausea (21.9%), vomiting (13.5%), decreased appetite (11.3%), headache (7.2%), pyrexia (7.0%), abdominal pain (6.7%), and colitis (5.5%).

1.3.2.3 MEDI4736 + tremelimumab

No safety studies in animals have been performed combining tremelimumab with MEDI4736. As both CTLA-4 and PD-L1 have mechanisms of actions that enhance activation of immune cells, their potential to induce cytokine release was tested in a whole-blood assay system. MEDI4736 and tremelimumab, either alone or in combination, did not induce cytokine release in blood from any donor.

Evaluation of the safety of MEDI4736 + tremelimumab in the ongoing Study D4190C00006, in patients with NSCLC, has so far shown a manageable safety and tolerability profile of the combination therapy.

Overall, 62 (83.8%) of the 74 patients reported an AE regardless of causality. The most frequently (10 or more patients) reported AEs were fatigue (37.8%; 28 patients); diarrhea (32.4%; 24 patients); amylase increased and pruritus (16.2%; 12 patients); decreased appetite, dyspnea, nausea, and rash (14.9%; 11 patients each), and headache and pyrexia (13.5%; 10 patients). Additional safety results from this study are presented in Section 1.2.1 and the MEDI4736 IB (Edition 7.0).

In the literature ([Wolchok et al 2013](#)), using the combination of the same class of drugs (eg, anti-PD-1 and anti-CTLA4 antibodies), specifically nivolumab + ipilimumab in a study involving patients with malignant melanoma, the safety profile of this combination had shown occurrences of AEs assessed by the Investigator as treatment-related in 93% of treated patients, with the most frequent events being rash (55% of patients), pruritus (47% of patients), fatigue (38% of patients), and diarrhea (34% of patients). Grade 3 or 4 AEs, regardless of causality, were noted in 72% of patients, with Grade 3 or 4 events assessed by the Investigator as treatment-related in 53%. The most frequent of these Grade 3 or 4 events assessed by the Investigator as treatment-related include increased lipase (13% of patients), AST (13% of patients), and ALT levels (11% of patients). Frequent Grade 3 or 4 selected AEs assessed by the Investigator as treatment-related in the combination therapy included hepatic events (15% of patients), GI events (9% of patients), and renal events (6% of patients). Isolated cases of pneumonitis and uveitis were also observed.

1.3.3 Overall benefit and risk assessment

There remains a significant unmet medical need for additional treatment options for patients with metastatic PDAC.

Treatment with agents targeting PD-1/PD-L1 (such as MEDI4736) or CTLA-4 (such as tremelimumab) has shown activity in several tumor types in a subset of patients deriving

meaningful and durable benefit. Efficacy data for patients treated with MEDI4736 monotherapy in the pancreatic cancer cohort have shown some clinical activity. Additionally, MEDI4736 + tremelimumab combination therapy has shown clinical activity in patients with recurrent or metastatic squamous cell cancer of the head and neck. Preliminary data generated from patients with NSCLC treated with MEDI4736 + tremelimumab combination therapy have also shown early signs of clinical activity, and data from competitors indicate that the combination may act synergistically ([Wolchok et al 2013](#)). Thus, these agents may potentially offer benefit to this patient population.

The study design aims to minimize potential risks, and intensive monitoring, including early safety assessment, is in place for those risks deemed to be most likely based on prior experience with the IPs (including MEDI4736, tremelimumab, and SoC).

The toxicity profile of the combination MEDI4736 + tremelimumab includes fatigue, colitis, diarrhea, AST or ALT increases, amylase and lipase increases, rash and pruritus, and other immune-mediated reactions, which were mostly reversible and manageable by the available protocol treatment guidelines.

In particular, based on the specific mechanism of action of MEDI4736 and tremelimumab leading to T-cell activation and proliferation, there is the possibility of observing immune-related AEs (irAEs) during the conduct of this study. Potential irAEs may be similar to those seen with the use of ipilimumab, BMS-936558, and BMS-936559 and may include immune-mediated enterocolitis, pneumonitis, dermatitis, hepatitis, and endocrinopathies ([Brahmer et al 2012](#), [Hodi et al 2010](#), [Topalian et al 2012](#)). Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (eg, infection or PD), an immune-related etiology should be considered for signs or symptoms of pneumonitis, enterocolitis, dermatitis, hepatitis, and endocrinopathy. It is recommended that management of irAEs follow the guidelines outlined in Section 6.7.

The rationale for this study is supported by the available nonclinical and clinical safety data, the limited survival benefit provided by the currently available treatment options to patients, the limited life expectancy due to malignant disease, the activity seen with MEDI4736 in this tumor type, and the strength of the scientific hypotheses evaluating the safety and tolerability of (1) MEDI4736 monotherapy and (2) MEDI4736 + tremelimumab combination therapy treatments in second-line therapy. Based on these considerations, the proposed treatments may have the potential to provide meaningful clinical benefit by generating durable clinical responses, thereby improving quality of life (QoL) and potentially extending survival. Furthermore, preclinical and clinical evidence indicate that the combination of PD-1/PD-L1 and CTLA-4 targeting agents may provide antitumor activity, with additional synergy from the combination ([Wolchok et al 2013](#)). Therefore, the investigation of the potential therapeutic efficacy of MEDI4736 monotherapy and the combination of MEDI4736 and tremelimumab in patients with PD-L1-positive and -negative tumors is acceptable, and the overall benefit/risk assessment supports the proposed study design.

1.4 Study design

This is a second-line Phase II study assessing MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy.

This is a Phase II, open-label, multi-center study to determine the efficacy and safety of MEDI4736 evaluated as single agent or in combination with tremelimumab in patients with metastatic PDAC whose disease has progressed on a 5-FU-containing or gemcitabine-containing first-line chemotherapy. A schematic diagram of the overall study design is shown in [Figure 1](#), and a detailed study flow chart is shown in [Figure 2](#). Patients will be enrolled globally.

Initially, patients will be enrolled in the study and randomized (1:1) to treatment with MEDI4736 monotherapy or MEDI4736 + tremelimumab, until 30 patients have been randomized to treatment in each arm (Part A: Lead-in). Randomization will be stratified according to best response to prior first-line chemotherapy (CR, PR, or SD) versus no response (PD) and according to prior first-line chemotherapy, 5-FU-containing versus gemcitabine-containing. Patient recruitment and tumor assessment will be monitored on an ongoing basis.

The format of Part B will be determined based on the responses seen in the first 30 patients in each arm in Part A. A protocol amendment will be made if criteria are met to proceed to Part B. The protocol amendment will include available data from Part A and any changes to study design and statistical plan, if needed.

1. **Part B: Expansion.** If an ORR of >25% (ie, responses in ≥ 8 patients) is observed in the first 30 treated patients in either treatment arm in Part A (unless the totality of the data support a different decision), after protocol amendment an additional 70 patients will be enrolled in that arm, for a total of 100 evaluable patients per arm.
2. **Part B: Randomized, controlled trial (RCT).** If an ORR of >15% and <25% (ie, response in ≥ 5 patients and <8 patients) is observed in the first 30 treated patients in either treatment arm in Part A, a randomized, controlled substudy may be initiated after protocol amendment.

If initiated, Part B: RCT will be an open-label, multi-center, study to determine the efficacy and safety of MEDI4736 monotherapy and/or MEDI4736 + tremelimumab combination therapy versus SoC chemotherapy in patients with metastatic PDAC who have failed 5-FU-containing or gemcitabine-containing first-line chemotherapy. Approximately 125 additional patients per treatment arm will be planned for enrollment. Treatment arms for MEDI4736 monotherapy and/or MEDI4736 + tremelimumab will only be included in the Part B: RCT if the corresponding treatment meets the appropriate ORR criteria in Part A. If initiated, the data from Part B: RCT will be analyzed separately and will not be pooled with Part A for the purpose of statistical analysis.

Patients will be randomized in Part B: RCT with a 1:1 or 1:1:1 ratio (depending on whether there are 2 or 3 treatment arms) in a stratified manner according to their best response to prior first-line chemotherapy (CR, PR, or SD) versus no response (PD) and according to prior first-line chemotherapy, 5-FU-containing versus gemcitabine-containing. Doses and treatment regimens are described in Section 7.2. Assessments will be conducted as indicated in Table 2, Table 3, and Table 4.

Figure 1 Phase II, MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy - study design

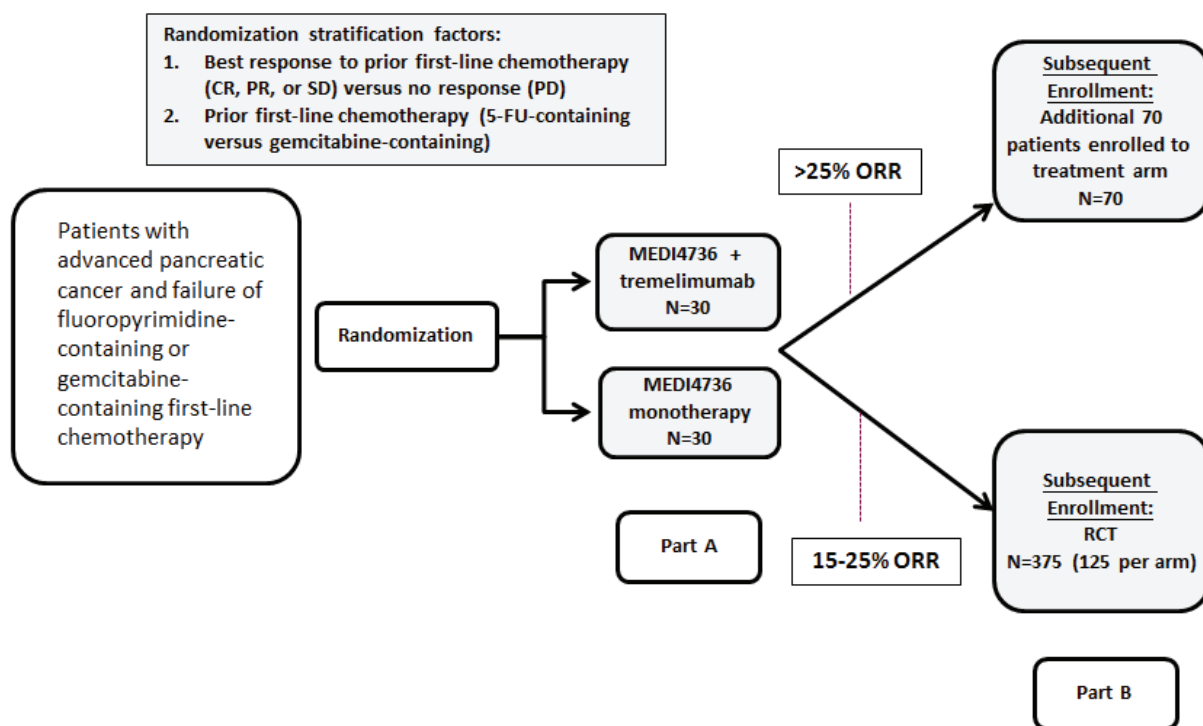
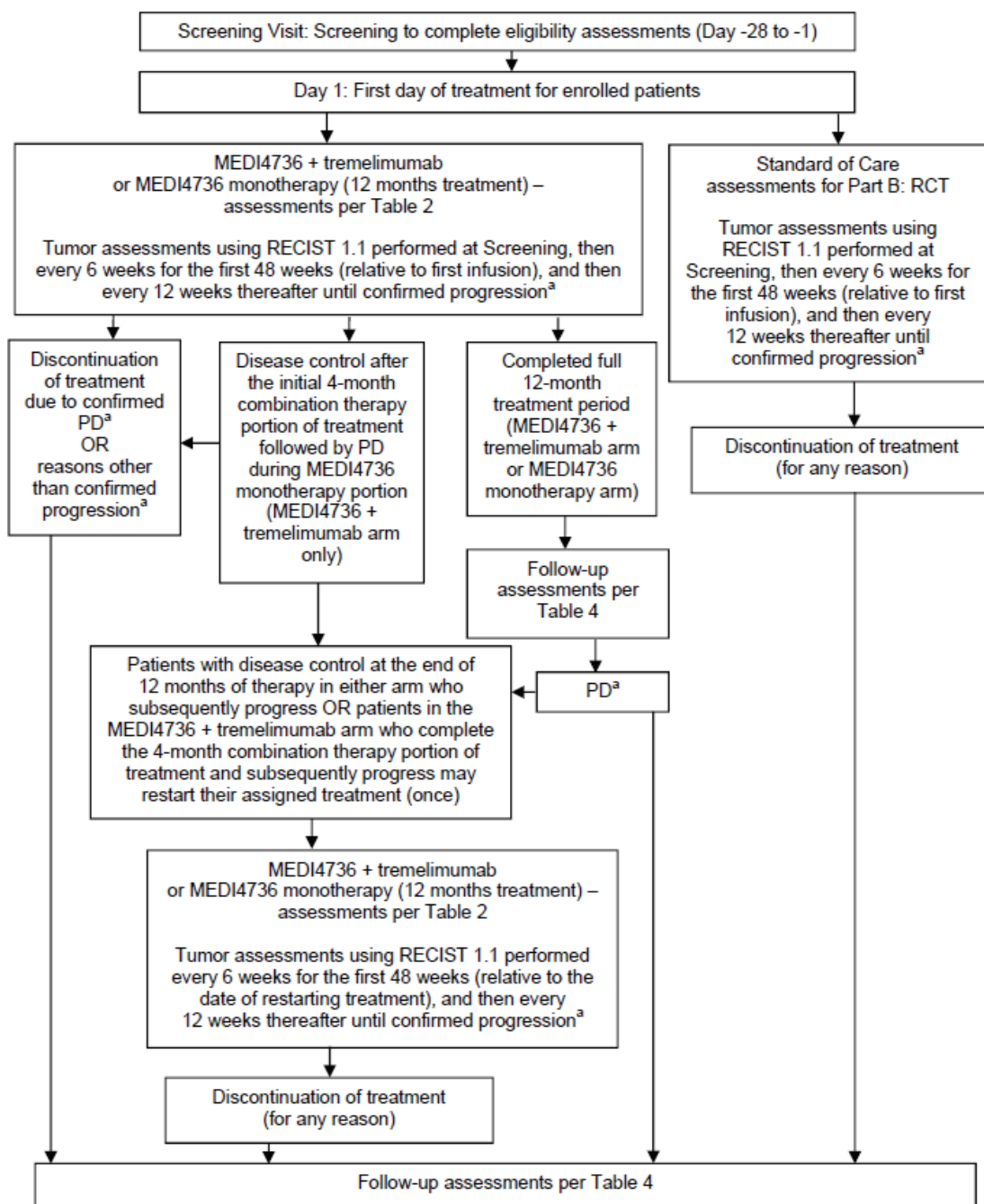


Figure 2 Phase II, MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy - study flow chart



^a Disease progression needs to be confirmed. The confirmatory scan should occur preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of PD in the absence of clinical deterioration. Administration of study treatment will continue between the initial assessment of progression and confirmation of progression. Patients treated through progression must meet the criteria described in Section 7.2.2. Patients with confirmed PD who continue to receive study treatment at the discretion of the Investigator (following consultation with the Sponsor) can receive study treatment for a maximum of

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Drug Substance MEDI4736 and Tremelimumab
Study Code D4198C00001
Edition Number 1
Date 17 August 2015

12 months. Patients in the SoC arm of Part B: RCT will discontinue study drug at the first assessment of disease progression per RECIST 1.1.

2. STUDY OBJECTIVES

2.1 Primary objective

Part A: Lead-in and Part B: Expansion

Primary objective:	Outcome measure:
To assess the efficacy of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy in terms of ORR	ORR in all patients using Investigator assessments according to RECIST 1.1 ^{a,b}

^a All images will be collected and stored for possible future central re-analysis.

^b Sensitivity analyses of ORR will be performed based on Investigator assessment according to RECIST 1.1 modified for confirmation of progression.

Part B: Randomized, controlled trial

Primary objective:	Outcome measure:
To assess the efficacy of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy compared to SoC in terms of OS	OS

2.2 Secondary objectives

Part A: Lead-in and Part B: Expansion

Secondary objectives:	Outcome measures:
To further assess the efficacy of the combination of MEDI4736 and tremelimumab and MEDI4736 alone in terms of DoR, DCR, PFS, PFS3, PFS6, OS, OS6, and OS12	DoR, DCR, PFS, PFS3, and PFS6 in all patients using Investigator assessments according to RECIST 1.1 ^a OS, OS6, and OS12
To assess the health-related QoL in metastatic PDAC patients treated with MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy as measured by EORTC QLQ-C30 global QoL scale (Part B only)	Adjusted mean change from baseline in global QoL score from the EORTC QLQ-C30 questionnaire
To assess the disease-related symptoms in metastatic PDAC patients treated with MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy as measured by EORTC QLQ-PAN26 pancreatic pain scale (Part B only)	Adjusted mean change from baseline in pancreatic pain score from the EORTC QLQ-PAN26 questionnaire

To investigate the immunogenicity of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy	Presence of ADAs for MEDI4736 and tremelimumab (confirmatory results: positive or negative; titers)
To assess the PK of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy	Concentration of MEDI4736/tremelimumab in blood and noncompartmental PK parameters (such as peak concentration and trough, as data allow; sparse sampling only)

^a All images will be collected and stored for possible future central re-analysis.

Part B: Randomized, controlled trial

Secondary objectives:	Outcome measures:
To further assess the efficacy of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy compared to SoC in terms of ORR, DoR, DCR, PFS, PFS2, PFS3, OS6, and OS12	PFS, PFS2, PFS3, ORR, DoR, and DCR in all patients using Investigator assessments according to RECIST 1.1 ^a OS6, OS12
To investigate the relationship between PD-L1 expression by IHC and efficacy parameters	ORR, DoR, DCR, PFS3, and PFS6 across PD-L1 expression using Investigator assessments according to RECIST 1.1
To assess the health-related QoL in metastatic PDAC patients treated with MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy as measured by EORTC QLQ-C30 global QoL scale	Adjusted mean change from baseline in global QoL score from the EORTC QLQ-C30 questionnaire
To assess the disease-related symptoms in metastatic PDAC patients treated with MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy as measured by EORTC QLQ-PAN26 pancreatic pain scale	Adjusted mean change from baseline in pancreatic pain score from the EORTC QLQ-PAN26 questionnaire
To investigate the immunogenicity of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy	Presence of ADAs for MEDI4736 and tremelimumab (confirmatory results: positive or negative; titers)
To assess the PK of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy	Concentration of MEDI4736/tremelimumab in blood and noncompartmental PK parameters (such as peak concentration and trough, as data allow; sparse sampling only)

^a All images will be collected and stored for possible future central re-analysis.

2.3 Safety objectives

Part A: Lead-in and Part B Expansion

Safety objective:	Outcome measures:
To assess the safety and tolerability profile of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy	AEs, physical examinations, laboratory findings (including clinical chemistry, hematology, and urinalysis), vital signs (including blood pressure and pulse), ECGs

Part B: Randomized, controlled trial

Safety objective:	Outcome measures:
To assess the safety and tolerability profile of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy compared to SoC	AEs, physical examinations, laboratory findings (including clinical chemistry, hematology, and urinalysis), vital signs (including blood pressure and pulse), ECGs

2.4 Exploratory objectives

Part A: Lead-in, Part B: Expansion, and Part B: Randomized, controlled trial

Exploratory objectives:	Outcome measures:
To assess the efficacy of MEDI4736 and tremelimumab and MEDI4736 alone according to irRECIST ^a	ORR, DoR, DCR, PFS, PFS3, and PFS6 using BICR assessments according to irRECIST ^a ORR, DoR, DCR, PFS3, and PFS6 in patients with PD-L1-positive tumors and patients with PD-L1-negative tumors using BICR assessments according to irRECIST (Part B: RCT only) ^a
To assess tolerability directly by patient self-reporting of specific PRO-CTCAE symptoms (Part B only)	Pre-selected PRO-CTCAE items (not more than 30) considered relevant to patients with metastatic PDAC treated with MEDI4736 or tremelimumab or SoC
To collect blood and tissue samples for defining biological responses to MEDI4736 or MEDI4736-tremelimumab and for identifying candidate markers that may correlate with likelihood of clinical benefit	Serum sPD-L1 Circulating soluble factors (eg, cytokines and autoantibodies) miRNA/mRNA T cell and MDSC phenotyping SNP genotyping

Exploratory objectives:	Outcome measures:
To collect and store DNA according to each country's local and ethical procedures for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy) to study treatments and/or susceptibility to disease (optional genetics component)	Correlation of polymorphisms with variation in PK, pharmacodynamics, safety, or response parameters observed in patients treated with MEDI4736 and the combination of MEDI4736 and tremelimumab, and/or susceptibility to disease
To assess change in performance status in metastatic PDAC patients treated with MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy as measured by the ECOG performance status scale	ECOG performance status
To describe and evaluate resource use associated with assigned treatments and underlying disease (Part B only)	Health resource utilization methods including HOSPAD, concomitant medications, and the AE module of the electronic case report form (eCRF)
To explore the impact of treatment and disease state on health state utility using the EuroQol 5-dimension, 5-level health state utility index (EQ-5D-5L) (Part B only)	The EQ-5D-5L will be used to derive health state utility based on patient-reported data.

Note: Exploratory objective analyses may be reported separately from the main clinical study report.

^a This analysis will be conducted only if central review data are generated at a future timepoint.

3. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

Patients must meet all of the following criteria:

1. Age ≥ 18 years at the time of screening.
2. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act [HIPAA] in the US, European Union [EU] Data Privacy Directive in the EU) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations. (For patients aged <20 years and enrolled in Japan, a written informed consent should be obtained from the patient and his or her legally acceptable representative.)

3. Histologically or cytologically confirmed PDAC that has metastasized. (Other pancreatic malignancies [eg, acinar cell carcinomas, adenosquamous carcinomas, and neuroendocrine islet cell neoplasms] are excluded from the study.)
4. No more than 1 prior chemotherapy regimen or any other systemic therapy for recurrent/metastatic PDAC. One other prior line of therapy administered either in a prior adjuvant, neoadjuvant, or definitive chemoradiation setting is permitted. In addition, patients must have tumor progression following prior standard first-line 5-FU-containing or gemcitabine-containing chemotherapy.
5. Life expectancy ≥ 12 weeks.
6. ECOG PS of 0 or 1.
7. At least 1 lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes, which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) scan and that is suitable for accurate repeated measurements.
8. No prior exposure to immune-mediated therapy, including, but not limited to, other anti-CTLA 4, anti-PD-1, anti PD-L1, or anti PD-L2 antibodies, therapeutic anticancer vaccines, and participation in previous MEDI4736 clinical trials.
9. Adequate organ and bone marrow function as defined below:
 - Hemoglobin ≥ 9 g/dL
 - Albumin ≥ 3 g/dL
 - Absolute neutrophil count $\geq 1500/\text{mm}^3$
 - Platelet count $\geq 100000/\text{mm}^3$
 - Serum bilirubin $\leq 1.5 \times$ the upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia [predominantly unconjugated bilirubin] in the absence of evidence of hemolysis or hepatic pathology), who will be allowed in consultation with their physician.
 - ALT and AST $\leq 2.5 \times$ ULN; for patients with hepatic metastases, ALT and AST $\leq 5 \times$ ULN
 - Serum creatinine ≤ 1.5 mg/dL or calculated creatinine clearance ≥ 50 mL/min as determined by the Cockcroft-Gault equation
10. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female premenopausal patients. Women will be considered post-menopausal if they

are amenorrheic for 12 months without an alternative medical cause. The following age specific requirements apply:

- Women <50 years old would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution
- Women \geq 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, radiation-induced oophorectomy with last menses >1 year ago, chemotherapy-induced menopause with >1 year interval since last menses, or surgical sterilization (bilateral oophorectomy or hysterectomy).

3.2 Exclusion criteria

Any of the following criteria would exclude the patient from participation in the study:

1. Any concurrent chemotherapy, investigational product (IP), biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for noncancer-related conditions (eg, hormone replacement therapy) is acceptable. Note: Local treatment of isolated lesions for palliative intent is acceptable (eg, local surgery or radiotherapy).
2. Receipt of any investigational anticancer therapy within 28 days or 5 half-lives, whichever is shorter, prior to the first dose of study treatment.
3. Concurrent enrollment in another clinical study, unless it is an observational (noninterventional) clinical study or during the follow-up period of an interventional study.
4. Receipt of last dose of an approved (marketed) anticancer therapy (chemotherapy, targeted therapy, biologic therapy, mAb, etc) within 21 days prior to the first dose of study treatment. If sufficient wash-out time has not occurred due to the schedule or PK properties of an agent, a longer wash-out period will be required, as agreed by AstraZeneca and the Investigator.
5. Major surgical procedure (as defined by the Investigator) within 21 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.
6. Patients weighing less than 30 kg.
7. History of leptomeningeal carcinomatosis.
8. Ascites requiring intervention (eg, need for paracentesis or Tenckhoff catheter)

9. Brain metastases or spinal cord compression. Patients with suspected brain metastases at screening should have a CT/MRI of the brain prior to study entry.
10. Any unresolved toxicity NCI CTCAE Grade ≥ 2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria. (Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with MEDI4736 or tremelimumab may be included after consultation with the Study Physician.)
11. Current or prior use of immunosuppressive medication within 14 days before the first dose of MEDI4736 or tremelimumab. The following are exceptions to this criterion:
 - Intranasal, inhaled, or topical steroids; or local steroid injections (eg, intra-articular injection)
 - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent
 - Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)
12. History of organ transplant that requires use of immunosuppressive agents.
13. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis, Crohn's disease], diverticulitis with the exception of diverticulosis, celiac disease, irritable bowel syndrome, or other serious gastrointestinal chronic conditions associated with diarrhea); systemic lupus erythematosus; Wegener syndrome (granulomatosis with polyangiitis; Graves' disease; rheumatoid arthritis, hypophysitis, uveitis, etc) within the past 3 years prior to the start of treatment. The following are exceptions to this criterion:
 - Patients with vitiligo or alopecia
 - Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement, or psoriasis not requiring systemic treatment
14. Uncontrolled intercurrent illness, including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs from MEDI4736 or tremelimumab, or compromise the ability of the patient to give written informed consent.

15. Other malignancy within 5 years except for noninvasive malignancies such as cervical carcinoma in situ, non-melanomatous carcinoma of the skin, or ductal carcinoma in situ of the breast that has/have been surgically cured.
16. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥ 470 ms calculated from 3 ECG reports (within 5 minutes at least 1 minute apart).
17. History of active primary immunodeficiency.
18. Active tuberculosis.
19. Active infection including hepatitis B, hepatitis C, or human immunodeficiency virus (HIV).
20. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live attenuated vaccine during the study and up to 30 days after the last dose of any IPs.
21. Female patients who are pregnant or breastfeeding, or male or female patients of reproductive potential who are not employing an effective method of birth control (see Section 3.8).
22. Known allergy or hypersensitivity to IP formulations or to other human monoclonal antibodies.
23. Any condition that, in the opinion of the Investigator, would interfere with evaluation of IP or interpretation of patient safety or study results.

Genetics research study (optional)

Exclusion criteria for participation in the optional (DNA) genetics research component of the study include previous allogeneic bone marrow transplant and non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection.

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrollment and randomization

Investigators should keep a record, the patient screening log, of patients who entered screening.

At screening/baseline (Days -28 to -1), the Investigators or suitably trained delegate will:

1. Obtain signed informed consent before any study specific procedures are performed, including optional consent for genetic research study.
2. Obtain a unique 7-digit enrollment number, beginning with 'E#' (ie, the "E-Code"). This is obtained through the Interactive Voice Response System (IVRS)/Interactive

Web Response System (IWRS). Enrollment numbers will start at 001 in each center, and go up sequentially. This number is the patient's unique identifier and is used to identify the patient on the eCRFs.

3. Determine patient eligibility (see Sections 3.1 and 3.2)

Note: Patients must be able to undergo a newly acquired tumor biopsy during screening (strongly encouraged) or to provide an available tumor sample taken <3 years prior to screening. The newly acquired or archival (<3 years) sample must be received by the central laboratory prior to dosing. Tumor lesions used for newly acquired biopsies should not be target lesions, unless there are no other lesions suitable for biopsy. Samples with limited tumor content and fine needle aspirate specimens are not acceptable. Specimens from metastatic bone lesions are typically unacceptable unless there is a significant soft tissue component. The tumor specimen should be of sufficient quantity to allow for PD-L1 IHC and other exploratory biomarker analyses and is preferred in formalin-fixed paraffin embedded blocks.

At randomization, once the patient is confirmed to be eligible, the Investigator or suitably trained delegate will complete a randomization call via the IVRS/IWRS. Randomization numbers will be assigned strictly sequentially by IVRS/IWRS as patients are eligible for entry into the study. The system will randomize the eligible patient to 1 of the 2 or 3 treatment groups (depending on the part of the study). Randomization will be stratified according to best response to prior first-line chemotherapy (CR, PR, or SD) versus no response (PD) and according to prior first-line chemotherapy, 5-FU-containing versus gemcitabine-containing.

If the patient is ineligible and not enrolled/randomized, the IVRS/IWRS should be contacted to terminate the patient in the system as a screen failure.

Patients will begin treatment on Day 1. Patients must not be treated unless all eligibility criteria have been met.

If a patient withdraws from participation in the study, then his or her enrollment code or randomization code cannot be reused. Withdrawn patients will not be replaced.

3.4 Procedures for handling incorrectly enrolled or randomized patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomized in error, incorrectly started on treatment, or subsequently fails to meet study criteria after initiation, the Investigator should inform the AstraZeneca Study Physician immediately, and a discussion should occur between the AstraZeneca Study Physician and the Investigator regarding

whether to continue or discontinue the patient from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

At baseline, patients who satisfy all the entry criteria will be centrally assigned to study drug by the IVRS/IWRS, according to the randomization scheme generated by the Biostatistics Group, AstraZeneca, or delegate. The randomization scheme will be produced by a computer software program that incorporates a standard procedure for generating randomization numbers. One randomization list will be produced for each of the randomization strata. A blocked randomization will be generated, and all centers will use the same list in order to minimize any imbalance in the number of patients assigned to each treatment group in Part A.

Patients will be identified to the IVRS/IWRS per country regulations. Randomization/enrollment codes will be assigned strictly sequentially, within each stratum, as patients become eligible for randomization. The IVRS/IWRS Centralized Randomization Center will inform the pharmacist of the kit identification number to be allocated to the patient at the randomization visit.

Every effort should be made to minimize the time between randomization/enrollment and starting study drug. It is recommended that patients commence study drug as soon as possible after randomization/enrollment (ie, on the same day after randomization in the IVRS/IWRS system).

The Investigator will call/log in to the IVRS/IWRS for each subsequent dispensing visit for assignment of a new kit identification number. The kit identification number dispensed at each visit will correspond to the treatment arm to which the patient was originally randomized/enrolled.

If a patient discontinues participation in the study, then their enrollment/randomization code cannot be reused.

3.6 Methods for ensuring blinding

This is an open-label study.

3.7 Methods for unblinding

This is an open-label study.

3.8 Restrictions

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

1. Female patients of childbearing potential who are sexually active with a nonsterilized male partner must use 2 methods of effective contraception from screening and must agree to continue using such precautions for 180 days after the

final dose of IP; cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

- 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).
 - Female patients must use 2 acceptable methods of effective contraception as described in [Table 1](#).
 - It is strongly recommended for the male partner of a female patient to also use male condom plus spermicide throughout this period.
 - Female patients must refrain from egg cell donation and breastfeeding while on study and for 180 days after your last dose of study drug.
2. Nonsterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from Day 1 and for 180 days after receipt of the final dose of IP. It is strongly recommended for the female partner of a male patient to also use an effective method of contraception throughout this period. In addition, male patients must refrain from sperm donation for 180 days after the final dose of study drug.
3. **All patients:** Patients should not donate blood while participating in this study and for 6 months following the last dose of study treatment.

Table 1 Effective methods of contraception (2 methods must be used)

Barrier Methods	Intrauterine Device Methods	Hormonal Methods
Male condom plus spermicide	Copper T	Implants
Cap plus spermicide	Progesterone T ^a	Hormone shot or injection
Diaphragm plus spermicide	Levonorgestrel-releasing intrauterine system (eg, Mirena [®]) ^a	Combined pill
		Minipill
		Patch

^a This is also considered a hormonal method.

3.9 Discontinuation of investigational product

An individual patient will not receive any further IP if any of the following occur in the patient in question:

1. Withdrawal of consent from further treatment with IP

2. Lost to follow-up
3. An AE that, in the opinion of the Investigator or the Sponsor, contraindicates further dosing
4. Any AE that meets criteria for discontinuation as defined in Section 6
5. Patient is determined to have met 1 or more of the exclusion criteria or failed to meet all of the inclusion criteria for study participation at study entry and continuing IP dosing might constitute a safety risk
6. Pregnancy or intent to become pregnant
7. Patient noncompliance that, in the opinion of the Investigator or Sponsor, warrants withdrawal from study medication (eg, refusal to adhere to scheduled visits)
8. Initiation of alternative anticancer therapy, including another investigational agent
9. Confirmed PD and Investigator determination that the patient is no longer benefiting from treatment with IP. Patients enrolled in the SOC arm will discontinue study drug at the first assessment of disease progression.

3.9.1 Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue the IP without prejudice to further treatment. A patient who decides to discontinue the IP will always be asked about the reason(s) for withdrawal and the presence of any AEs. If possible, they will be seen and assessed by an Investigator. AEs will be followed up (see Section 6). All study drugs provided to the patients should be returned by the patient. The AstraZeneca Study Physician should be notified of any ongoing AE that may delay treatment or necessitate permanent discontinuation of treatment.

Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment. Patients who are permanently discontinued will enter follow-up (see Table 3 and Table 4). All patients will be followed up for survival until the end of the study. Patients who decline to return to the site for follow-up evaluations (see Table 3 and Table 4) should be contacted by telephone every 2 months as an alternative.

If a patient is withdrawn from study, see Section 3.10.

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screen failures are patients who do not fulfill the eligibility criteria for the study, and therefore must not be enrolled and randomized. These patients should have the reason for study withdrawal recorded as “eligibility criteria not fulfilled” (ie, patient does not meet the required

inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (ie, not randomized patients). Patients can be rescreened a single time, but they cannot be re-randomized. Patients being rescreened should be assigned with a new enrollment code.

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (IP and assessments), without prejudice to further treatment.

Patients who withdraw consent for further participation in the study will not receive any further IP or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn his or her consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AE. The Investigator will follow up AEs outside of the clinical study until resolution. The patient will return electronic PRO devices, if applicable.

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed (see Section 3.11), such that there is insufficient information to determine the patient's status at that time. Patients who refuse continuing participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and any evaluations should resume according to the protocol.

Patients who decline to return to the site for follow-up evaluations (see Table 3 and Table 4) should be contacted by telephone every 2 months as an alternative. Withdrawn patients will not be replaced. When a patient is withdrawn from the study, study center personnel should call the IVRS/IWRS and register the patient withdrawal information.

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial patients are placed at undue risk because of clinically significant findings that meet any of the following criteria:

- Meet individual stopping criteria or are otherwise considered significant
- Are assessed as causally related to study drug,
- Are not considered to be consistent with continuation of the study

In addition, the study may be stopped if the criteria to proceed are not met (see Section 8.2). Regardless of the reason for termination, all data available for the patients at the time of discontinuation of follow-up must be recorded in the eCRFs. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests. If this study is discontinued, all other studies involving MEDI4736 or tremelimumab will remain open to enrollment and screening, if deemed appropriate by the Sponsor.

4. STUDY PLAN AND TIMING OF PROCEDURES

The procedures for the screening and 12-month treatment periods in this study are presented in [Table 2](#), and the procedures for the follow-up period are presented in [Table 3](#) and [Table 4](#).

Table 2 **Schedule of assessments for treatment and retreatment periods for MEDI4736 and MEDI4736 + tremelimumab (12 months)**

	Screening	C1		C2		C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	For details see Section	
		Window for each assessment: ±3 days, window for tumor assessment: ±7 days																
Day	-28 to -1	1	15	1	15	1	1	1	1	1	1	1	1	1	1	1		
Week (on Day 1 of the week)	-4 to -1	0	2	4	6	8	12	16	20	24	28	32	36	40	44	48		
Informed consent																		
Consent: genetic sample and analysis (optional)	X																4.1	
Written informed consent: study procedures/assignment of patient identification number	X																4.1	
Study procedures																		
Physical examination (full) ^a	X																5.2.2	
Targeted physical exam (based on symptoms) ^a		X		X		X	X	X	X	X	X	X	X	X	X	X	5.2.2	
Vital signs ^b	X	X		X		X	X	X	X	X	X	X	X	X	X	X	5.2.4	
Electrocardiogram ^c	X	As clinically indicated															5.2.3	
Concomitant medications	X	X	All visits															7.7
Demography	X																4.1	
Medical and surgical history	X																4.1	
History of tobacco and alcohol use	X																4.1	
Laboratory assessments																		
Serum or plasma chemistry (complete clinical chemistry panel including liver enzymes) ^d	X	X		X		X	X	X	X	X	X	X	X	X	X	X	5.2.1	
Hematology ^d	X	X		X		X	X	X	X	X	X	X	X	X	X	X	5.2.1	
Thyroid function tests (TSH, fT ₃ , and fT ₄) ^e	X	X		X		X	X	X	X	X	X	X	X	X	X	X	5.2.1	

	Screening	C1		C2		C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	For details see Section
		Window for each assessment: ±3 days, window for tumor assessment: ±7 days															
Day	-28 to -1	1	15	1	15	1	1	1	1	1	1	1	1	1	1	1	
Week (on Day 1 of the week)	-4 to -1	0	2	4	6	8	12	16	20	24	28	32	36	40	44	48	
Urinalysis ^f	X	X		X		X	X	X	X	X	X	X	X	X	X	X	5.2.1
Hepatitis B and C; HIV	X																5.2.1
Urine hCG or serum β-hCG ^g	X	X ^h	As clinically indicated														5.2.5
Coagulation parameters ⁱ	X	As clinically indicated															5.2.1
Monitoring																	
ECOG performance status	X	X		X		X	X	X	X	X	X	X	X	X	X	X	5.3.3
AE/SAE assessment	X	X	All visits														6.3
Pharmacokinetics																	
MEDI4736 PK sample (serum) ^{j,k}		X		X			X			X							5.4.2
Tremelimumab PK sample (serum) ^{j,k}		X		X			X										5.4.2
IP administration																	
Monotherapy arm																	
MEDI4736 (monotherapy) ^l		X		X		X	X	X	X	X	X	X	X	X	X	X	7.2.1
Combination therapy arm																	
MEDI4736 (combination therapy) ^l		X		X		X	X	X	X	X	X	X	X	X	X	X	7.2.1
Tremelimumab ^l		X		X		X	X										7.2.1
Quality of life assessments																	
EORTC QLQ-C30, EORTC QLQ-PAN26, and EQ-5D-5L ^m (Part B only)		X				X		X		X		X		X		X	5.3.1
PRO-CTCAE ⁿ (Part B only)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.3.1

	Screening	C1		C2		C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	For details see Section
		Window for each assessment: ±3 days, window for tumor assessment: ±7 days															
Day	-28 to -1	1	15	1	15	1	1	1	1	1	1	1	1	1	1	1	
Week (on Day 1 of the week)	-4 to -1	0	2	4	6	8	12	16	20	24	28	32	36	40	44	48	
Health economics measurements																	
Hospital resource use module (HOSPAD) (Part B only) ^o	To be completed at each hospitalization																5.3.4
Other laboratory assessments and assays																	
Immunogenicity assessment (ADA sampling [including ADA neutralizing antibodies] to identify ADA responses in patient circulation) ^k		X		X			X			X ^p							5.4.4
sPD-L1 concentration (to assess target engagement)		X		X			X			X							5.5.1.1
Circulating soluble factors		X		X			X										5.5.1.2
Mandatory tumor biopsy (newly acquired or archival <3 years old) ^q	X			X ^r													5.5.1.1
Archival tumor sample, if available, for patients who submit a newly acquired biopsy at screening	X																5.5.1.1
SNP genotyping and MDSC		X															5.5.1.2
miRNA/mRNA (to examine immune cell gene expression profiles in circulation) and PBMCs		X		X													5.5.1.2
Tumor assessment (CT or MRI) ^s	X	q6w for the first 48 weeks relative to first infusion, and q12w thereafter, until confirmed disease progression															5.1
PGx sample (optional [DNA element])		X															5.6

^a Body weight recorded at all physical examinations.

- ^b Blood pressure and pulse will be evaluated at the beginning of the infusion, every 30 minutes during treatment, and in the 1 hour post-infusion observation period: 30 and 60 minutes after the infusion (ie, 90 and 120 minutes from the start of the infusion) (± 5 minutes) – for the first infusion only and then for subsequent infusions as clinically indicated. These assessments should be followed for each of the component infusions. Body temperature and respiratory rate will be evaluated pre-dose (prior to each infusion).
- ^c Abnormal ECGs and the ECG obtained at screening will require triplicate results.
- ^d If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Results for safety bloods, serum or plasma chemistry and LFT enzymes must be available and reviewed before commencing an infusion. At any time per the Investigator's clinical judgment, more frequent LFT monitoring is allowed as clinically indicated. Gamma glutamyltransferase tested at screening, Day 1 and as clinically indicated.
- ^e fT_3 and fT_4 will only be measured if TSH is abnormal or if there is clinical suspicion of an adverse event related to the endocrine system.
- ^f Urinalysis performed at screening, Day 1, every 4 weeks, and as clinically indicated. If screening urinalysis is performed within 3 days prior to Day 1 it does not need to be repeated at Day 1.
- ^g Pre-menopausal female patients of childbearing potential only.
- ^h Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drug. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion.
- ⁱ Coagulation tests: activated partial thromboplastin time and international normalized ratio – only performed at screening and as clinically indicated.
- ^j On Day 1 and Week 12, PK samples will be collected pre-dose (within 60 minutes prior to treatment with any IP) and at the end of infusion (within 10 minutes of end of infusion of MEDI4736 and within 10 minutes of end of infusion of tremelimumab [for patients receiving MEDI4736 + tremelimumab]). On Week 4, PK samples will be collected pre-dose (within 60 minutes prior to treatment with any IP) only. On Week 24, PK samples will be collected pre-dose (within 60 minutes prior to treatment with any IP) and at the end-of-infusion for MEDI4736 (within 10 minutes of end of infusion), with no sample for tremelimumab.
- ^k The follow-up samples (3 and 6 months) for each molecule are relative to the respective last dose.
- ^l Patients in the MEDI4736 monotherapy arm will receive MEDI4736 every 4 weeks for up to 12 months (up to 13 doses). Patients in the MEDI4736 + tremelimumab combination therapy arm will receive MEDI4736 and tremelimumab every 4 weeks for the first 4 months (up to 4 doses) followed by MEDI4736 every 4 weeks for the subsequent 8 months (up to 9 doses). For the combination arm only – tremelimumab will be administered first; the MEDI4736 infusion will start approximately 1 hour after the end of the tremelimumab infusion. If there are no clinically significant concerns after the first cycle, and at the discretion of the physician, then for all other cycles MEDI4736 can be given immediately after the tremelimumab infusion has finished. Patients who achieve and maintain disease control (ie, CR, PR, or SD) through to the end of the assigned IP 12-month treatment period may restart treatment with the combination upon evidence of PD, with or without confirmation, during follow-up. Before restarting their assigned IP, the Investigator should ensure patients do not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient, and that the patient still fulfills the eligibility criteria for this study, including re-consenting to restart IP. To restart treatment, the patient must not have received an intervening systemic anticancer therapy after his or her assigned IP discontinuation. Patients should have a baseline tumor assessment within 28 days of restarting their assigned IP treatment; all further scans should occur q6w ± 7 days (relative to the date of restarting treatment) and q12w ± 7 days thereafter until study treatment is stopped (maximum of 12 months of further treatment). If a patient derives clinical benefit from the combination of MEDI4736 + tremelimumab, per judgment of the Investigator, and subsequently progresses while undergoing treatment with MEDI4736 alone, MEDI4736 q4w and tremelimumab induction may be reinstituted for 4 doses 1 time only (follow the same treatment guidelines as during the first 12 months).
- ^m PROs (EORTC QLQ-C30, QLQ-PAN26, and EQ-5D-5L) will be collected during Part B only. Patients will complete PROs using handheld electronic devices at study sites if assessment timepoint coincides with a study visit; otherwise patients will complete the PROs at home. PROs should be completed prior to any other visit procedures to ensure that any such clinical interactions do not bias the patient's response to the questionnaire items. Please note that the EORTC QLQ-C30 and EORTC QLQ-PAN26 are administered as a single questionnaire.
- ⁿ The PRO-CTCAE will be collected during Part B only. PRO-CTCAE will only be administered in those countries where a linguistically validated version exists.
- ^o HOSPAD module should be completed by site staff whenever the patient has attended or been admitted to the hospital. A reminder will be provided at each clinic visit.
- ^p ADAs for MEDI4736 only, not tremelimumab.
- ^q The newly acquired or archival (< 3 years) sample must be received by the central laboratory prior to dosing.
- ^r Newly acquired tumor sample to be collected at Week 4 (-1 week/+2 weeks)

^s RECIST assessments will be performed using CT/MRI assessments of the chest and abdomen, pelvis only when suspected or documented disease involvement. Additional anatomy may be imaged based on signs and symptoms of individual patients. Baseline assessments should be performed no more than 28 days before start of study treatment, and ideally should be performed as close as possible to the start of study treatment. Follow-up assessments will be performed q6w \pm 7 days for the first 48 weeks (relative to the date of the first infusion) and then q12w \pm 7 days until confirmed objective disease progression per RECIST 1.1. The confirmatory scans should preferably be performed at the next scheduled visit (relative to the date of the first infusion) and no less than 4 weeks after the initial assessment of complete response/partial response and disease progression (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits (relative to the date of the first infusion). All confirmatory scans should be recorded on the database. For all patients who are treated through progression, the Investigator should ensure patients do not have any significant, unacceptable or irreversible toxicities that indicate continuing treatment will not further benefit the patient, and that the patient still fulfils eligibility criteria for this study including re-consenting to continue treatment. For 're-treatment' patients who go on to have a subsequent 12 months of treatment, the same assessments should be done as in the first 12-month treatment period with the exception of the PK, ADA, sPD-L1, SNP, MDSC, and nAB assessments, which do not need to be collected a second time.

Note: Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient.

Note: All assessments to be performed pre-infusion unless stated otherwise.

β -hCG Beta-human chorionic gonadotropin; C Cycle; fT3 Free triiodothyronine; fT4 Free thyroxine; hCG Human chorionic gonadotropin; LFT Liver function test; TSH Thyroid-stimulating hormone; V Visit.

Table 3 **Schedule of assessments: follow-up for patients who have completed treatment and achieved disease control (until confirmed progression of disease)**

Evaluation	Time since last dose of IP							
	Day (±3)	Months (±1 week)						12 months and every 2 months (±2 weeks)
	30	2	3	4	6	8	10	
Physical examination ^a	X							
Vital signs (temperature, respiratory rate, blood pressure, and pulse)	X							
Weight	X							
AE/SAE assessment	X	X	X					
Concomitant medications	X	X	X					
Hospital resource use module (HOSPAD) (Part B only)	To be completed at each hospitalization							
ECOG performance status	At time points consistent with tumor assessments up to confirmed disease progression. Upon confirmation of progression, ECOG performance status should also be collected at other site visits that the patient attends, if appropriate site staff are available to collect such information. In addition, ECOG performance status should be provided when information on subsequent anticancer therapy is provided, where possible.							
Subsequent anticancer therapy	X	X	X	X	X	X	X	X
Survival status: for all patients, including phone contact with patients who refuse to return for evaluations and agree to be contacted		X		X	X	X	X	X
Urine hCG or serum β-hCG	X							
Hematology	X	X	X					
Serum or plasma chemistry	X	X	X					
Thyroid function tests (TSH, fT3, and fT4) ^b	X							
Pharmacokinetic assessment			X					
Immunogenicity assessment (ADA sampling [including ADA neutralizing antibodies] to identify ADA responses in patient circulation)			X		X			
sPD-L1 concentration (to assess target engagement)			X					
EORTC QLQ-C30, EORTC QLQ-PAN26, and EQ-5D-5L ^c (Part B only)	Every 8 weeks up to at least 6 months following disease progression							

Evaluation	Time since last dose of IP							
	Day (±3)	Months (±1 week)						12 months and every 2 months (±2 weeks)
	30	2	3	4	6	8	10	
PRO-CTCAE ^{c,d} (Part B only)	Every 4 weeks up to at least 6 months following disease progression							
Tumor assessment (CT or MRI)	For patients who achieve disease control following 12 months of treatment , tumor assessments should be performed q12w ±7 days relative to the date of first infusion until confirmed PD by RECIST 1.1 by investigational site review. Please refer to Table 2 for timings of confirmatory scans.							

^a Full physical exam

^b fT₃ and fT₄ will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an AE related to the endocrine system.

^c PROs (EORTC QLQ-C30, QLQ-PAN26, and EQ-5D-5L) will be collected during Part B only. PROs should be completed for least 6 months post-confirmed disease progression. Post-progression, patients should complete PROs at home if necessary to minimize noncompliance. PROs should be completed prior to any other visit procedures to ensure that any such clinical interactions do not bias the patient's response to the questionnaire items. Please note that the EORTC QLQ-C30 and EORTC QLQ-PAN26 are administered as a single questionnaire.

^d The PRO-CTCAE will be collected during Part B only. PRO-CTCAE will only be administered in those countries where a linguistically validated version exists.

β-hCG Beta-human chorionic gonadotropin; fT₃ Free triiodothyronine; fT₄ Free thyroxine; hCG Human chorionic gonadotropin; sPD-L1 Soluble PD-L1;
TSH Thyroid-stimulating hormone.

Table 4 **Schedule of assessments: follow-up for patients who have discontinued study treatment due to confirmed progression of disease and patients who have discontinued due to toxicity in the absence of confirmed progression of disease**

Evaluation	Time since last dose of IP							
	Day (±3)	Months (±1 week)						12 months and every 2 months (±2 weeks)
	30	2	3	4	6	8	10	
Physical examination ^a	X							
Vital signs (temperature, respiratory rate, blood pressure, and pulse)	X							
Weight	X							
AE/SAE assessment	X	X	X					
Concomitant medications	X	X	X					
Hospital resource use module (HOSPAD) (Part B only)	To be completed at each hospitalization							
ECOG performance status ^b	X	X	X	X ^b	X ^b	X ^b	X ^b	X ^b
Subsequent anticancer therapy	X	X	X	X	X	X	X	X
Survival status: for all patients, including phone contact with patients who refuse to return for evaluations and agree to be contacted ^c		X		X	X	X	X	X
Urine hCG or serum β-hCG	X							
Hematology	X	X	X					
Serum or plasma chemistry	X	X	X					
Thyroid function tests (TSH, fT ₃ , and fT ₄) ^d	X							
Pharmacokinetic assessment			X					
Immunogenicity assessment (ADA sampling [including ADA neutralizing antibodies] to identify ADA responses in patient circulation)			X		X			
sPD-L1 concentration (to assess target engagement)			X					
Circulating soluble factors (to assess cytokines, chemokines, growth factors, and antibodies against tumor and self antigens in circulation)	X							

Evaluation	Time since last dose of IP						
	Day (±3)	Months (±1 week)					
	30	2	3	4	6	8	10
miRNA/mRNA (to examine immune cell gene expression profiles in circulation)	X						
PBMCs	X						
EORTC QLQ-C30, EORTC QLQ-PAN26, and EQ-5D-5L ^e (Part B only)	Every 8 weeks up to at least 6 months following disease progression						
PRO-CTCAE ^{e,f} (Part B only)	Every 4 weeks up to at least 6 months following disease progression						
Tumor assessment (CT or MRI)	<p>An optional tumor biopsy upon evidence of PD should be performed according to institutional practice. It is accepted that any biopsy procedure should be technically feasible and not associated with unacceptable clinical risk.</p> <p>For patients who discontinue study treatment due to toxicity (or symptomatic deterioration), tumor assessments should be performed relative to the date of first infusion as follows: q6w ±7 days for the first 48 weeks and q12w ±7 days thereafter (per Table 2) until confirmed PD by RECIST 1.1. Please refer to Table 2 for timings of confirmatory scans.</p>						

^a Full physical exam.

^b ECOG performance status should also be collected at other site visits that the patient attends, if appropriate site staff are available to collect such information. In addition, ECOG performance status should be provided when information on subsequent anticancer therapy is provided, where possible.

^c Post-progression, patients will be followed for survival contact every 2 months (8 weeks) until death or until the end of the study.

^d fT₃ and fT₄ will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an AE related to the endocrine system.

^e The EORTC QLQ-C30 and QLQ-PAN26 will be collected during Part B only. PROs should be completed for least 6 months post-confirmed disease progression. Post-progression, patients should complete PROs at home if necessary to minimize noncompliance. PROs should be completed prior to any other visit procedures to ensure that any such clinical interactions do not bias the patient's response to the questionnaire items. Please note that the EORTC QLQ-C30 and EORTC QLQ-PAN26 are administered as a single questionnaire.

^f The PRO-CTCAE will be collected during Part B only. PRO-CTCAE will only be administered in those countries where a linguistically validated version exists.

β-hCG Beta-human chorionic gonadotropin; fT₃ Free triiodothyronine; fT₄ Free thyroxine; hCG Human chorionic gonadotropin; sPD-L1 Soluble PD-L1;

TSH Thyroid-stimulating hormone.

4.1 Enrollment/screening period

At screening, consenting patients are assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be enrolled in the study. All screening and enrollment procedures will be performed according to the assessment schedules in [Table 2](#).

Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations. All patients will be required to provide consent to supply a sample of their tumor (archival or newly acquired biopsy) for entry into this study. This consent is included in the main patient informed consent form (ICF).

Screening/baseline evaluations may be performed over more than 1 visit.

The timing of ECGs and vital sign assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the timepoints indicated in [Table 2](#) through [Table 4](#).

4.2 Treatment period

All procedures to be conducted during the 12-month treatment period will be performed according to the assessment schedules (see [Table 2](#)).

Whenever vital signs, ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: ECG, vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the timepoints indicated in [Table 2](#) through [Table 4](#).

4.3 Follow-up period

All procedures to be conducted during the follow-up period will be performed according to the assessment schedule (see [Table 3](#) and [Table 4](#)).

Whenever vital signs, ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: ECG, vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the exact nominal time.

5. STUDY ASSESSMENTS

A Web Based Data Capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

The Investigator will record data on the observations, tests, and assessments specified in the protocol on the eCRFs provided by AstraZeneca. The CRF will be accompanied with “Instructions for the Investigator,” which should be followed. These instructions provide guidance for the recording of study data in the eCRF, including how to change data incorrectly recorded.

5.1 Efficacy assessments

RECIST 1.1 criteria will be used to assess patient response to treatment by determining ORR, DoR, DCR, PFS, PFS2, PFS3, and PFS6. The RECIST 1.1 guidelines for measurable, nonmeasurable, target, and non-target lesions and the objective tumor response criteria (CR, PR, SD, or PD) are presented in [Appendix F](#). OS, OS6, and OS12 will also be evaluated.

The methods of assessment of tumor burden used at baseline are CT and/or MRI scans of the chest and abdomen; scans of the pelvis should only be done when there is suspected or documented disease involvement. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients.

The baseline assessments should be performed no more than 28 days before start of study treatment, and ideally should be performed as close as possible to the start of study treatment. Efficacy for all patients will be assessed by objective tumor assessments every 6 weeks (q6w \pm 7 days) for the first 48 weeks relative to the date of the first infusion, and q12w \pm 7 days thereafter until confirmed objective disease progression. If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at his or her scheduled visits.

A confirmatory scan is required following the initial demonstration of PD. The confirmatory scan should occur preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Treatment will continue between the initial assessment of progression and confirmation for progression.

If a patient discontinues treatment (and/or receives a subsequent anticancer therapy) prior to progression, then the patient should still continue to be followed until confirmed objective disease progression.

Categorization of objective tumor response assessment will be based on the RECIST 1.1 criteria of response: CR, PR, SD, and PD. Target lesion progression will be calculated in comparison to when the tumor burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of progression, tumor response (CR or PR) and SD will be calculated in comparison to the baseline tumor measurements obtained before starting treatment.

Objective tumor response (CR or PR) should be confirmed preferably at the next scheduled visit and not less than 4 weeks after the visit when the response was first observed.

Following confirmed progression, patients should continue to be followed up for survival every 2 months (8 weeks) as outlined in the follow-up schedule of assessments ([Table 4](#)). In addition, all patients will be contacted in the week following data cutoff to confirm survival status.

Patients randomized to the MEDI4736 monotherapy or MEDI4736 + tremelimumab arms who achieve and maintain disease control (ie, CR, PR, or SD) through to the end of the 12-month treatment period may restart treatment with their assigned IP upon evidence of PD, with or without confirmation, according to RECIST 1.1, during follow-up (patients receiving MEDI4736 + tremelimumab in combination may restart combination therapy following disease control lasting at least the first 4 cycles of combination therapy). To restart treatment, the patient must not have received an intervening systemic anticancer therapy post discontinuation. Patients who restart treatment must have a baseline tumor assessment within 28 days of restarting treatment with IP; all further scans should occur q6w \pm 7 days (relative to the date of restarting treatment) and then q12w \pm 7 days thereafter until confirmed disease progression. All assessments in [Table 2](#) will be followed for patients who continue to receive treatment.

It is important to follow the assessment schedule as closely as possible. Refer to the study plans ([Table 2](#) [screening and the treatment period], [Table 3](#) and [Table 4](#) [follow up]) and [Appendix F](#).

5.1.1 Central reading of scans

Investigator's assessment of all scans using RECIST 1.1 will be conducted (see [Section 8.5](#) for the analysis methods). All images will be collected and stored with the imaging provider for possible future central re-analysis at the discretion of the Sponsor. Guidelines for image collection, quality control, and storage will be provided in a separate document. The management of patients will be based solely upon the results of assessment conducted by the Investigator. When a Blinded Independent Central Review (BICR) is performed, three levels of review will be included in the radiology assessments: RECIST 1.1, RECIST 1.1 modified for confirmation of progression, and irRECIST 1.1.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated (see [Table 2](#) through [Table 4](#)).

Clinical laboratory safety tests, including serum pregnancy tests, will be performed in a licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. Urine pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The laboratory values to be measured are presented in [Table 5](#) (clinical chemistry) [Table 6](#) (hematology), and [Table 7](#) (urinalysis).

Table 5 Clinical chemistry (serum or plasma)

Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase
Alanine aminotransferase	Lipase
Amylase	Magnesium
Aspartate aminotransferase	Potassium
Bicarbonate	Sodium
Calcium	Total bilirubin ^a
Chloride	Total protein
Creatinine	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyltransferase ^b	Uric acid

^a If total bilirubin is $\geq 2 \times$ ULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin

^b At baseline and as clinically indicated

Table 6 Hematology

Basophils	Mean corpuscular volume
Eosinophils	Monocytes
Hematocrit	Neutrophils
Hemoglobin	Platelet count
Lymphocytes	Red blood cell count
Mean corpuscular hemoglobin	Total white cell count
Mean corpuscular hemoglobin concentration	

Note: Coagulation parameters: activated partial thromboplastin time and international normalized ratio to be assessed at baseline and as clinically indicated

Table 7 **Urinalysis**

Bilirubin	pH
Blood	Protein
Glucose	Specific gravity
Ketones	Color and appearance

Note: Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells

If a patient shows an AST or ALT $\geq 3 \times$ ULN together with total bilirubin $\geq 2 \times$ ULN, refer to [Appendix E](#) for further instructions. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's Law case or if any of the individual liver test parameters fulfill any of the SAE criteria. All patients with an elevated AST, ALT, or bilirubin value (the latter at $\geq 1.5 \times$ ULN) at the time of the last dose of study treatment should have a further liver chemistry profile (AST, ALT, bilirubin, and alkaline phosphatase) performed 30 days (± 3 days) after permanent discontinuation of study treatment. Results for safety blood assessments must be available and reviewed before commencing an infusion.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section [6.3.8](#).

All patients with Grade 3 or 4 laboratory values at the time of completion or discontinuation from study treatment must have further tests performed until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

5.2.2 Physical examination

Physical examinations will be performed according to the assessment schedules (see [Table 2](#) through [Table 4](#)). Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. All physical examinations will include body weight measurement. Situations in which physical examination results should be reported as AEs are described in Section [6.3.7](#).

5.2.3 ECG

Resting 12-lead ECGs will be recorded according to the assessment schedules (see [Table 2](#)). ECGs should be obtained after the patient has been in a supine position for 5 minutes and should be recorded while the patient remains in that position.

ECGs will be recorded at screening and as clinically indicated.

Abnormal ECGs and the ECG obtained at screening will require triplicate results. In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional

12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm prolongation.

Situations in which ECG results should be reported as AEs are described in Section 6.3.7.

5.2.4 Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules (see Table 2 through Table 4).

On infusion days, patients will be monitored during and after infusion of IP as presented in the bulleted list below.

Supine BP will be measured after the patient has rested for at least 5 minutes.

BP and pulse will be evaluated at the beginning of the infusion, every 30 minutes during treatment, and in the 1-hour post-infusion observation period: 30 and 60 minutes after the infusion (ie, 90 and 120 minutes from the start of the infusion) (± 5 minutes) – for the first infusion only and then for subsequent infusions as clinically indicated. These assessments should be followed for each of the component infusions.

Body temperature and respiratory rate will be evaluated pre-dose (prior to each infusion).

Two or more BP readings should be taken at 2-minute intervals and averaged. If the first 2 diastolic readings differ by more than 5 mmHg, an additional reading should be obtained and the measurements should be averaged. The date and time of collection and measurement will be recorded on the appropriate eCRF. Additional monitoring with assessment of vital signs is at the discretion of the Investigator per standard clinical practice or as clinically indicated.

Situations in which vital signs results should be reported as AEs are described in Section 6.3.7.

5.2.5 Other safety assessments

Pregnancy tests on either urine (human chorionic gonadotropin [hCG]) or blood (serum beta-human chorionic gonadotropin [β -hCG]) samples will be performed for premenopausal women of childbearing potential at the times specified in the assessment schedule (see Table 2 through Table 4). Tests will be performed by the hospital's local laboratory. If results are positive, the patient is ineligible and must be discontinued from treatment. In the event of a suspected pregnancy during the study, the test should be repeated.

Other safety tests to be performed at screening include assessment for hepatitis B surface antigen, hepatitis C antibodies, HIV antibodies, thyroid-stimulating hormone, free triiodothyronine, and free thyroxine.

5.3 Other assessments

5.3.1 Patient reported outcomes (PRO)

“PRO” is an umbrella term referring to all outcomes and symptoms that are directly reported by the patient. PROs have become a significant endpoint when evaluating effectiveness of treatments in clinical studies. The following PROs will be administered in this study: EORTC QLQ-C30, EORTC QLQ-PAN26, the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), and the EQ-5D-5L; see [Appendix G](#)).

The PRO instruments will be self-administered by the patients as ePROs using handheld devices at study sites or at home. All assessments should be completed without assistance from site staff according to the assessment schedules (see [Table 2](#), [Table 3](#), and [Table 4](#)), before any other study procedures are conducted at a given visit. Study coordinators should ensure that patients have completed the PRO assessment for that visit before the patient is seen by a study nurse or physician (unless these are the same person). It takes approximately 15 to 30 minutes for patients to complete the questionnaires; therefore, the burden to the patient is moderate. If patients have had scans at an outside facility or missed a scheduled data collection site visit, PRO questionnaires should still be completed by the patient at home on that scheduled visit date.

5.3.1.1 EORTC QLQ-C30

The EORTC QLQ-C30, Version 3 questionnaire is included for the purpose of assessing HRQoL and is a well-established measure of HRQoL/health status, and commonly used as an endpoint in cancer clinical trials. It assesses HRQoL/health status through 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), and a global health and QoL scale. Six single-item symptom measures are also included: dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties (see [Appendix G](#)). For each of the 15 domains, final scores are transformed such that they range from 0 to 100, where higher scores indicate greater functioning, greater HRQoL, or greater level of symptoms ([Aronson et al 1993](#)).

5.3.1.2 EORTC QLQ-PAN26

For patients with pancreatic cancer, a disease-specific self-administered questionnaire for pancreatic cancer was developed (EORTC QLQ-PAN26; [Appendix G](#)) to be used in conjunction with the EORTC QLQ-C30 ([Fitzsimmons and Johnson 1998](#), [Fitzsimmons et al 2005](#)). The EORTC QLQ-PAN26 consists of 26 items that comprise 7 multi-item scales (pancreatic pain [4 items], eating related [2 items], hepatic [2 items], altered bowel habit [2 items], body image [2 items], health care satisfaction [2 items], and sexuality [2 items]) and 10 single-item scales (swollen abdomen, taste changes, indigestion, flatulence, weight loss, loss of muscle strength, dry mouth, burden of treatment, fear of future health, and ability to plan future). When items are grouped into domains rather than reporting specific items, it is important that the correct scoring algorithm is followed. Higher scores represent more symptoms, except for health care satisfaction scale and sexuality scale where

higher scores represent greater satisfaction and sexuality. For change scores, a score of +5 is considered deterioration (except for the 2 scales mentioned above) and a score of -5 is considered as improvement. Thus, final scores are transformed such that they range from 0 to 100, where higher scores indicate greater functioning or greater level of symptoms ([Aaronson et al 1993](#)).

5.3.1.3 PRO-CTCAE

The PRO-CTCAE is included to address tolerability from the patients' perspective. It was developed by the NCI. The PRO-CTCAE will only be administered in those countries where a linguistically validated version exists. It was developed in recognition that collecting symptom data directly from patients using PRO tools can improve the accuracy and efficiency of symptomatic AE data collection. This was based on findings from multiple studies demonstrating that physicians and nurses underestimate symptom onset, frequency, and severity in comparison with patient ratings ([Basch et al 2009](#), [Litwin et al 1998](#), [Sprangers and Aaronson 1992](#)). These symptoms have been converted to patient terms (eg, CTCAE term "myalgia" converted to "aching muscles"). For several symptoms, like fatigue and pain, additional questions are asked about symptom frequency, severity, and interference with usual activities. The items included in the PRO CTCAE have undergone extensive qualitative review among experts and patients. These items have been extensively evaluated by patients with cancer to be clear, comprehensible, and measuring the symptom of interest. In this study, only items that are considered relevant for the trial, site of cancer, and cancer treatment are selected (see [Appendix G](#)).

5.3.1.4 EQ-5D-5L

The EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal ([EuroQol Group 1990](#)). Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys. The questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty ([EuroQol Group 2013](#)).

Since 2009, the EuroQol group has been developing a more sensitive version of the EQ-5D (the EQ-5D-5L) which expands the range of responses to each dimension from 3 to 5 levels of increasing severity ([Herdman et al 2011](#)). Preliminary studies indicate that the 5L version improves upon the properties of the 3L measure in terms of reduced ceiling effect, increased reliability and an improved ability to differentiate between different levels of health ([Janssen et al 2008a](#), [Janssen et al 2008b](#), [Pickard et al 2007](#)).

The patient will be asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analogue scale, where the patient will be asked to rate current health status on a scale of 0 to 100, with 0 being the worst imaginable health state (see [Appendix G](#)).

5.3.2 Administration of the patient-reported outcome questionnaires

Patients will complete the PRO assessments by using a handheld electronic device (ePRO).

Each center must allocate the responsibility for the administration of the PRO instruments to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a back-up person to cover if that individual is absent. The PRO questionnaires must be administered and completed at the clinic as per the schedule of assessments if the assessment timepoint coincides with a study visit; otherwise patients will complete the PROs at home. The PRO questionnaires will be administered on the days specified in the schedules of assessments (see [Table 2](#), [Table 3](#), and [Table 4](#)). Post-progression, patients should complete PROs at home if necessary to minimize noncompliance.

The following best practice guidelines should be followed when collecting PRO data via an electronic device:

- PRO questionnaires must be completed prior to any other study procedures (following informed consent) and before discussion of disease progression to avoid bias in the patient's responses to the questions.
- PRO questionnaires must be completed by the patient in private.
- The research nurse or appointed site staff must explain to patients the value and relevance of study participation and inform them that these questions are being asked to find out, directly from them, how they feel. The research nurse or appointed site staff should also stress that the information is confidential. Therefore, if the patients have any medical problems, they should discuss them with the doctor or research nurse separately from the ePRO assessment.
- The research nurse or appointed site staff must train the patient on how to use the ePRO device, using the materials and training provided by the ePRO vendor, and provide guidance on whom to call if there are problems with the device.
- The research nurse or appointed site staff must remind patients that there are no right or wrong answers and avoid introducing bias by not clarifying items.
- The patient should not receive help from relatives, friends, or clinic staff to answer the PRO questionnaires. If a patient uses visual aids (eg, spectacles or contact lenses) for reading and does not have them when he or she attends the clinic, the patient will be exempted from completing the PROs.
- Site staff must not read or complete the PRO questionnaires on behalf of the patient. If the patient is unable to read the questionnaire (eg, is blind or illiterate), that patient should be exempted from completing PRO questionnaires but may still participate in the study. Patients exempted in this regard should be flagged appropriately by the site staff.

- The patient should be given sufficient time to complete the PRO questionnaires at his or her own speed.
- The research nurse or appointed site staff or family member must monitor compliance; minimizing missing data is a key aspect of study success. Compliance must be checked at each study visit and should be checked more frequently to identify problems early. If compliance drops below 85%, a check-in call from the site to ask the patient if he or she has any difficulties is highly recommended.

5.3.3 ECOG performance status

ECOG performance status will be assessed at the times specified in the assessment schedules (see [Table 2](#) through [Table 4](#)) based on the following:

0=Fully active, able to carry on all pre-disease performance without restriction

1=Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work

2=Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours

3=Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours

4=Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

5=Dead

Any significant changes from baseline or screening must be reported as an AE.

5.3.4 Health resource use

For the purposes of economic evaluation for payer submissions, it is necessary to capture healthcare resource use related to the treatment and the underlying disease. Within the study, the following will be captured:

- Hospital episodes captured by hospital resource use module (HOSPAD). HOSPAD is an eCRF module completed by sites capturing information from patient's medical records regarding the type of contact (hospitalizations, outpatient, day case), reason, and length of stay by ward type (including intensive care unit).
- Treatment related to AEs (including the method of delivery of the treatment) captured in AE/SAE assessment module
- Treatment not related to the study captured in concomitant medications eCRF

5.4 Pharmacokinetics

5.4.1 Collection of samples

Blood samples for determination of MEDI4736 and tremelimumab concentration in serum will be obtained according to the assessment schedules (see [Table 2](#) through [Table 4](#)).

Details on sample processing, handling, shipment, and storage are provided in the Laboratory Manual.

5.4.2 Determination of drug concentration of MEDI4736 and tremelimumab

Samples for determination of MEDI4736 and tremelimumab concentration in serum will be analyzed by a designated third party laboratory on behalf of AstraZeneca. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual. Full details of the analytical method used will be described in a separate Bioanalytical Validation Report.

5.4.3 Storage and destruction of pharmacokinetic samples for MEDI4736 and tremelimumab

PK samples will be disposed 5 to 10 years after the IPs are approved for marketing or formal discontinuation of clinical development of the IP.

PK samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR, but will be reported separately in a bioanalytical validation report.

Any residual back up PK samples may be used for future exploratory biomarker research (in this case, residual back-up PK samples will be shipped to AstraZeneca Biobank; see details in the Laboratory Manual).

5.4.4 Collection of samples to measure the presence of ADAs

The presence of ADAs will be assessed in serum samples taken according to the assessment schedules (see [Table 2](#) through [Table 4](#)).

Samples will be measured for the presence of ADAs and ADA-neutralizing antibodies for MEDI4736 and tremelimumab using validated assays. Tiered analysis will be performed to include screening, confirmatory, and titer assay components, and positive-negative cut points previously statistically determined from drug-naïve validation samples will be used.

5.4.5 Storage and destruction of ADA samples

ADA samples will be disposed 5 to 10 years after the IPs are approved for marketing or formal discontinuation of clinical development of the IP.

ADA samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled samples to further evaluate and validate the analytical method. Results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but will be reported separately in a bioanalytical validation report.

Any residual back-up ADA samples may be used for future exploratory biomarker research (in this case, residual back-up PK samples will be shipped to AstraZeneca Biobank; see details in the Laboratory Manual).

5.5 Biomarker analysis

The patient's consent to the use of donated biological samples is mandatory.

Mandatory tumor and blood biomarkers to be evaluated for the purpose of evaluation of patient selection and for exploratory analyses are described in Section 5.5.1. Exploratory biomarkers may be evaluated as determined by additional data (see Section 5.5.1.2). Samples will be taken according to the assessment schedules (see Table 2 through Table 4).

Biomarkers that have demonstrated the potential to identify patients who are likely to respond to treatment with IP (from other MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy studies) may be investigated to determine a patient's biomarker status and for possible correlation with efficacy endpoints in an exploratory analysis outside the scope of the CSR.

Exploratory biomarker research will not form part of the CSR. The results may be pooled with biomarker data from other MEDI4736 monotherapy or MEDI4736 combination therapy studies to test existing hypotheses or to generate hypotheses to be tested in future studies.

5.5.1 Collection of samples

5.5.1.1 Collection of biomarker samples for evaluation of patient selection

Provisions of tissue are as follows:

- **MANDATORY:** Provision of a tumor biopsy, formalin-fixed and embedded in paraffin, for the purpose of PD-L1 expression analyses and for enabling exploratory analyses as described in the proceeding section. A newly acquired tumor biopsy is strongly preferred; however, if not feasible with an acceptable clinical risk, an archival sample taken <3 years prior to screening can be submitted. This sample must be received by the central laboratory prior to dosing.

Samples should be collected via an image-guided core needle (at least 18 gauge) or an excisional archival tumor biopsy sample. Where institutional practice in this

setting uses a smaller gauge needle, samples should be submitted in sufficient number to ensure that a valid result can be achieved.

When tissue is acquired for this study, effort should be made to maximize material for downstream analyses. Two cores, using an 18-gauge or larger needle, are required for determining PD-L1 expression levels. These should be placed in formalin and processed to a single paraffin embedded block, as described in the Pathology Manual. When a smaller gauge needle is used, the number of cores rises to 3 or 4. That written, and as a guidance, it is anticipated that 4 passes of a core needle will provide sufficient tissue. Whenever feasible, additional cores should be obtained and immediately frozen as described in the Laboratory Manual.

Tumor lesions planned for biopsy should not be used as index lesions for assessment of disease.

- **MANDATORY:** If clinically feasible, on-treatment collection of tumor biopsies at the timepoints indicated in [Table 2](#). The Investigator must consult with the Study Physician if such sampling is not feasible.
- **OPTIONAL:** If a newly acquired tumor sample is submitted during screening, an additional archived tumor tissue block (formalin-fixed, paraffin-embedded) is strongly encouraged, where such samples exist in a quantity sufficient to allow for analysis.
- The collection of tumor biopsies at the time of progression and prior to retreatment is strongly encouraged. The biopsy procedure at retreatment should be omitted only if there is unacceptable clinical risk or the procedure is otherwise considered not feasible. The Investigator must consult with the Study Physician prior to making the decision not to biopsy at retreatment.

Additional tumor biopsies collected as part of clinical care (eg, for mixed responses or upon PD) can be submitted for further analysis.

See the Laboratory Manual for further details of requirements.

Tumor biopsies will be stored at AstraZeneca Research and Development or an appropriate vendor selected by AstraZeneca. Core biopsies may be used for correlative studies such as IHC assay, tumor mutation analysis, ribonucleic acid (RNA) analysis, proteomic analysis, immunophenotyping, and assessment of immunodiversity. A brief outline of such analyses is provided in the exploratory biomarker data description in Section [5.5.1.2](#). Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

5.5.1.2 Exploratory biomarker data

Blood and tumor samples for exploratory biomarker analyses will be obtained according to the assessment schedules presented in [Table 2](#) through [Table 4](#). Details for collection, volumes, storage, and shipment of biologic samples are presented in a separate Laboratory Manual.

Pharmacodynamic changes in biomarker measures will be monitored, when applicable. Baseline measures (and early, on-treatment changes) will be correlated with outcomes. Note that samples will be obtained from patients enrolled to each treatment arm. Data will be compared across treatment arms to determine if changes are specific to one treatment arm versus the other. Similar comparisons will be made with baseline measures to determine if biomarkers (or combination of markers) are prognostic or may be candidate, predictive markers of outcomes associated with MEDI4736 monotherapy and MEDI4736 combination therapy.

All samples collected for such exploratory analyses will be stored at the site, a reference laboratory, or at Sponsor's facilities and may be used for subsequent research relevant to evaluating response to immunotherapy.

The exploratory biomarker plan is described by sample type below.

Tumor markers (in formalin-fixed paraffin-embedded tissue)

Tissue obtained as part of screening procedures and for establishing PD-L1 expression will be analyzed for additional markers by IHC assay. At a minimum, CD8 and CD4/FoxP3 measures will be completed in an effort to enumerate cytotoxic versus regulatory T cells. Based on availability of tissue, a panel of additional, immune-relevant markers expressed on tumor-infiltrating lymphocytes or on tumor cells may be assessed. Markers of special interest include, but are not limited to, Ox40, GITR, PD-L2, Tim-3, CD137, Lag-3, and markers that may identify MDSCs, which may change on treatment ([Highfill et al 2014](#)).

Tissues obtained at screening may be assessed also for somatic mutations and/or for an interferon-gamma (IFN- γ) gene expression signature (eg, IFN- γ) by reverse transcription quantitative polymerase chain reaction (RT-qPCR), in situ hybridization, NanoString[®], and/or similar methodologies.

Whole blood for DNA/single nucleotide polymorphism genotyping

Genomic DNA will be extracted from whole blood obtained pretreatment from all patients. Genotyping of immunomodulatory genes such as PD-1, PD-L1, CTLA-4, and human leukocyte antigen loci may be completed to determine whether natural variation within such genes is associated with likelihood of clinical benefit and/or with likelihood of drug-related AEs. Genes associated with solid tumor development, disease progression, or likelihood of tumor response to chemotherapy may, likewise, be investigated. Genotyping will occur retrospectively, data will not be shared with patients, and results will not impact treatment decisions.

Genotypes may also be correlated with biomarker measures (eg, gene and/or protein expression) obtained from other sample types described in this exploratory biomarker section. A primary hypothesis is that different genotypes will be associated with different expression levels of factors within the PD-1 and CTLA-4 signaling pathways. Such variations in expression may affect the ability of a patient to mount an appropriate immune reaction to a tumor and/or affect the likelihood of response to therapeutics targeting these pathways.

Therefore, genotyping may provide easy-to-measure baseline information regarding a patient's immune system. One goal of this research is to understand how such genetic information may be used to predict pharmacodynamic responses to therapy.

Whole blood gene expression (PaxGene-RNA)

Whole blood samples will be obtained before or after treatment as outlined in [Table 2](#) through [Table 4](#) from all patients. Total RNA will be prepared for quantification of RNA and/or miRNA expression using RT-qPCR, microarray, sequencing, or similar methodology.

Focus is likely to be given to the expression of immunomodulatory genes previously found to be up-regulated in response to MEDI4736 and/or tremelimumab. Pretreatment expression of such genes may indicate active immune responses that may be augmented by checkpoint inhibitor immunotherapies; correlations with outcome data will be completed on select candidate predictive markers with the aim of characterizing useful expression thresholds for identifying patients likely to receive benefit. Similar procedures may be completed using select peripheral blood mononuclear cell (PBMC) samples described below.

Myeloid-derived suppressor cells

Flow cytometry will be completed on all patients to quantify pretreatment circulating MDSC subtypes. Different MDSC count thresholds will be analyzed for their ability to predict clinical benefit from therapy.

Peripheral blood mononuclear cells

Whole blood samples will be collected for preparation of PBMCs and storage for potential downstream analyses. A variety of assays may be pursued, including immune cell composition/activation status analyses by flow cytometry, MDSC assessments in banked specimens, T-cell functional assays (eg, ELISPOT), receptor occupancy analyses to measure target engagement, tetramer analyses to monitor antigen-specific T cells, RNA/miRNA expression, and/or the assessment of the diversity and clonality of T-cell receptor gene rearrangements using DNA.

Soluble factors (plasma)

Plasma will be obtained before or after treatment as outlined in [Table 2](#) through [Table 4](#). The concentrations of a panel of cytokines and chemokines will be assessed. Focus is likely to be given to factors involved in Th1-driven immune responses, including IFN- γ and interleukin (IL)-18. High pretreatment expressions (concentrations) of such factors may indicate active immune responses that may be augmented by checkpoint inhibitor immunotherapies; correlations with outcome data will be completed on select candidate predictive markers, with an aim of characterizing useful expression thresholds for identifying patients likely to receive benefit or, alternatively, for identifying patients likely to suffer drug-related AEs.

Similarly, the concentrations of a battery of immune cell ligands or receptors may be assessed. Proteins of special interest include CTLA4, PD-1, PD-L1, B7-1, B7-2, and IL6R.

Plasma may also be used for the detection/quantification of autoantibodies (against tumor-associated antigens) on ProtoArray[®] or a similar assay platform containing antigens preselected based on documented expression in study indications. Seroconversion following treatment will be used as an indicator of overcoming tolerance. Pretreatment seropositivity against specific antigens may provide predictive value, particularly when combined with data regarding the presence of antigen-specific T cells (Yuan et al 2011). Therefore, select candidate autoantibody measures may be evaluated for associations with clinical benefit and for directing PBMC-based, antigen-directed measures as described for PBMCs above.

5.5.2 Management of biomarker data

The biomarker data will have unknown clinical significance. AstraZeneca will not provide biomarker research results to patients, their family members, any insurance company, any employer, clinical study Investigator, general physician, or any other third party, unless required to do so by law. The patient's samples will not be used for any purpose other than those described in the study protocol.

Individual patients will not be identified in any report or publication resulting from this work. The data and results of this research may be reviewed with collaborators and published, but neither the patient's name nor any other personal identifiers will appear in any publication or report.

5.5.3 Storage, re-use, and destruction of biological samples

Samples will be stored for a maximum of 15 years from the end of study, after which they will be destroyed. Summaries and analyses for exploratory biomarkers will be documented in a separate analysis plan and will be reported outside the CSR in a separate report. The results of this biomarker research may be pooled with biomarker data from other studies involving MEDI4736 or tremelimumab to generate hypotheses to be tested in future research.

5.5.4 Labeling and shipment of biological samples

The Principal Investigator (PI) will ensure that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B, Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria); see [Appendix C](#).

Any samples identified as infectious materials in Category A will not be shipped, and no further samples will be taken from the involved patients unless agreed upon with AstraZeneca and appropriate labeling, shipment, and containment provisions are approved.

5.5.5 Chain of custody of biological samples

A full chain of custody will be maintained for all samples throughout their life cycle.

The PI at each site will keep full traceability of collected biological samples from the patients, while in storage at the site until shipment or disposal (where appropriate), and will keep documentation of receipt of arrival.

The sample receiver will keep full traceability of the samples, while in storage and during use until used or disposed of or until further shipment, and will keep documentation of receipt of arrival.

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, and auditing of external laboratory providers.

Samples retained for further use will be registered in the AstraZeneca Biobank during the entire life cycle.

5.5.6 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of or destroyed, and the action will be documented. If samples have already been analyzed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological samples is an integral part of the study, then the patient is withdrawn from further study participation.

The PI will:

- Ensure that AstraZeneca is immediately notified of the patient's withdrawal of informed consent to the use of donated samples
- Ensure that biological samples from that patient, if stored at the study site, are immediately identified, disposed of, or destroyed and that the action is documented
- Ensure that the laboratory(ies) holding the samples is/are immediately informed about the withdrawn consent and that samples are disposed of or destroyed, the action is documented, and the signed document is returned to the study site
- Ensure that the patient and AstraZeneca are informed about the sample disposal

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

5.6 Pharmacogenetics

Refer to [Appendix D](#) for details of the genetic research (optional DNA component).

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The PI is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and nonserious AEs.

6.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, and washout, follow-up), that fulfills 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see [Appendix B](#).

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

AEs and SAEs will be collected from the time the informed consent is signed through 90 days after the last dose of the last study treatment.

6.3.2 Follow-up of unresolved adverse events

During the course of the study, all AEs and SAEs should be proactively followed up for each patient. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation or study completion.

Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional

information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged to be necessary.

6.3.3 Variables

- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- Changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IPs (yes or no)
- Action taken with regard to IPs
- Administration of treatment for the AE
- Whether the AE caused the patient's withdrawal from the study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Seriousness criteria fulfilled
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to Other Medication
- Description of the AE

The grading scales found in the revised NCI CTCAE, Version 4.03, will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of CTCAE, Version 4.03 can be downloaded from the Cancer Therapy Evaluation Program website (<http://ctep.cancer.gov>).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

The Investigator will assess causal relationship between the IP and each AE and answer “yes” or “no” to the question, “Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?”

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as “yes.”

A guide to the interpretation of the causality question is found in [Appendix B](#).

6.3.5 Relationship to protocol procedures

The Investigator is also required to provide an assessment of the relationship of SAEs to protocol procedures on the SAE report form. This includes both non-treatment-emergent (ie, SAEs that occur prior to the administration of IP) and treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection). 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 or intervention that was described in the protocol for which there is no alternative etiology present in the patient’s medical record.
- Not protocol related: The event is related to an etiology other than the procedure or intervention that was described in the protocol. The alternative etiology must be documented in the study patient’s medical record.

6.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: “Have you had any health problems since the previous visit/you were last asked?” or revealed by observation will be collected and recorded in the eCRF.

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.7 Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital signs will be summarized in the CSR. Deterioration, as compared to baseline, in protocol-mandated laboratory values and vital signs should, therefore, only be reported as AEs if they fulfill any of the SAE criteria or if they are considered the reason for discontinuation of treatment with the IPs.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE, and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in nonmandated parameters should be reported as AE(s).

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination, as compared with the baseline assessment, will be reported as an AE.

6.3.8 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq 3 \times$ ULN together with total bilirubin $\geq 2 \times$ ULN may need to be reported as SAEs. Please refer to [Appendix E](#) for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.3.9 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of, existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression should not be reported as an AE during the study.

6.3.10 New cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study.

6.3.11 Deaths

All deaths that occur during the study, or within the protocol-defined follow-up period after the administration of the last dose of study treatment, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Physician at the next monitoring visit and should be documented in the eCRF. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the Study Physician as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. A post-mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Drug Safety or its representative within the usual timeframes.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IPs or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 day, that is, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel should inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, that is, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site personnel reports an SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

The reference documents for definition of expectedness/listedness are the IBs for MEDI4736 and tremelimumab.

The PI is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such.**

6.5 Overdose

Use of IP in doses in excess of that specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of overdose of IP, and possible symptoms of overdose are not established.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigators or other site personnel should inform appropriate AstraZeneca representatives immediately or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply (see Section 6.4). For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

6.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day, that is, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy, and the PREGOUT is used to report the outcome of the pregnancy.

6.6.2 Paternal exposure

Male patients must refrain from fathering a child or donating sperm during the study and for 180 days following the last dose.

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

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

6.7 Management of IP-related toxicities

The following general guidance should be followed for management of toxicities.

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned IP along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted (see the Dosing Modification and Toxicity Management Guidelines).
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

In addition, there are certain circumstances in which MEDI4736 and tremelimumab should be permanently discontinued (see Section 3.9 and the Dosing Modification and Toxicity Management Guidelines).

Following the first dose of IP, subsequent administration of MEDI4736 and tremelimumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines. All toxicities will be graded according to NCI CTCAE, Version 4.03. Dose reductions are not permitted. In case of doubt, the Investigator should consult with the Study Physician.

6.7.1 MEDI4736 and MEDI4736 + tremelimumab

Adverse events of special interest (AESIs) are events of scientific and medical interest specific to the further understanding of the MEDI4736 and tremelimumab safety profile and require close monitoring and rapid communication by the Investigator to AstraZeneca. MEDI4736 and tremelimumab AESIs may be serious or non-serious. The rapid reporting of these AESIs allows ongoing analysis of these events in order to characterize and understand them in association with the use of these IPs.

Information on MEDI4736 and MEDI4736 + tremelimumab AESIs and guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for MEDI4736 and MEDI4736 + tremelimumab are provided in the Dosing Modification and Toxicity Management Guidelines.

6.7.2 Standard of care

Toxicities related to SoC treatment in the RCT: Part B should be managed as per local guidelines and the relevant approved labelling.

6.8 Study governance and oversight

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

AstraZeneca will supply MEDI4736 and tremelimumab. The SoC products (for Part B: RCT) will be sourced locally.

Investigational product	Dosage form and strength
MEDI4736	50 mg/mL solution for infusion
Tremelimumab	20 mg/mL solution for infusion
SoC (for Part B: RCT only)	Treatment-dependent ^a

^a Under certain circumstances when local sourcing is not feasible, standard of care treatment may be supplied centrally through AstraZeneca.

7.1.1 MEDI4736

MEDI4736 will be supplied by AstraZeneca as a 500-mg vial for solution for infusion. The solution contains 50 mg/mL MEDI4736, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume) polysorbate 80; it has a pH of 6.0. Total in-use storage time from needle puncture of MEDI4736 vial to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). If the in-use storage time exceeds these limits, a new dose must be prepared from new vials. MEDI4736 does not contain preservatives, and any unused portion must be discarded. MEDI4736 vials should be stored at refrigerated temperatures (2°C to 8°C), and should not be frozen.

Preparation of MEDI4736 doses for administration with an IV bag

The dose of MEDI4736 for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Doses of 1.5 g will be administered using a bag containing 250 mL 0.9% (weight/volume) saline and delivered through an IV administration set with a 0.2-µm in-line filter. A volume of 0.9% (weight/volume) saline equal to the volume of MEDI4736 to be added to the IV bag must be removed from the bag prior to the addition of MEDI4736. The calculated volume of MEDI4736 is then added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

Preparations are to be in accordance with the study-specific drug handling instructions.

No incompatibilities between MEDI4736 and polyethylene, polypropylene, polyvinylchloride, or polyolefin copolymers have been observed.

7.1.2 Tremelimumab

Tremelimumab is supplied as a sterile solution for IV infusion, 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 isotonic solution at pH 5.5. Tremelimumab vials should be stored at refrigerated temperatures (2°C to 8°C), and should not be frozen.

Product preparation and reconstitution of tremelimumab

The dose of tremelimumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total in-use storage time from needle puncture of the product vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Tremelimumab does not contain preservatives, and any unused portion must be discarded.

Preparation of tremelimumab doses for administration with an IV bag

Doses of 75 mg will be administered using a bag containing 250 mL 0.9% (weight/volume) saline and delivered through an IV administration set with a 0.2-µm in-line filter. A volume of 0.9% (weight/volume) saline equal to the volume of tremelimumab to be added to the IV

bag must be removed from the bag prior to the addition of tremelimumab. The calculated volume of tremelimumab is then added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

Preparations are to be in accordance with the study-specific drug handling instructions.

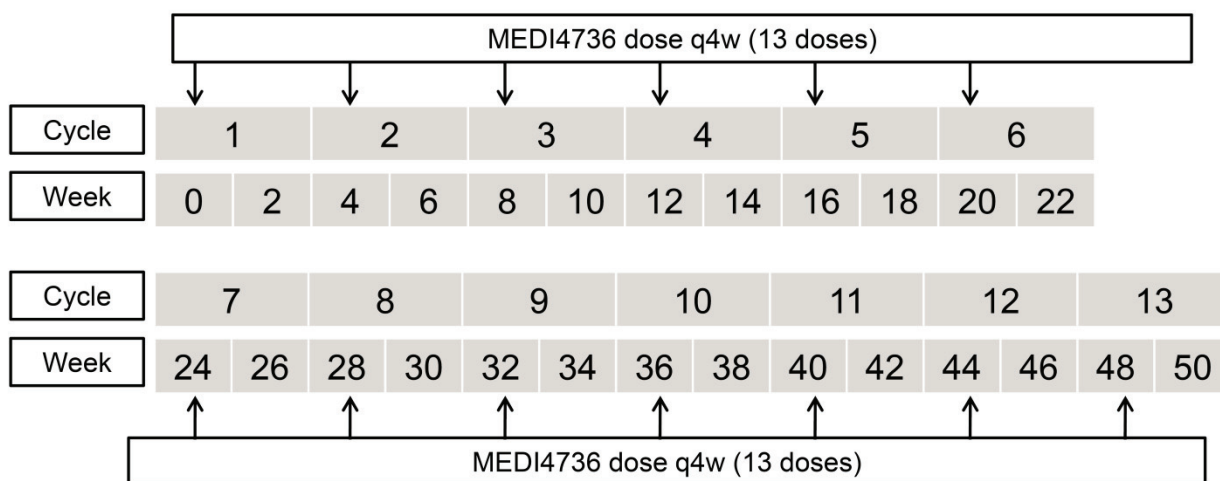
7.2 Dose and treatment regimens

7.2.1 Treatment regimens

MEDI4736 monotherapy

Patients in the MEDI4736 monotherapy treatment arm will receive 1.5 g MEDI4736 via IV infusion q4w for up to 12 months (up to 13 doses). See [Figure 3](#).

Figure 3 MEDI4736 monotherapy dosing schedule

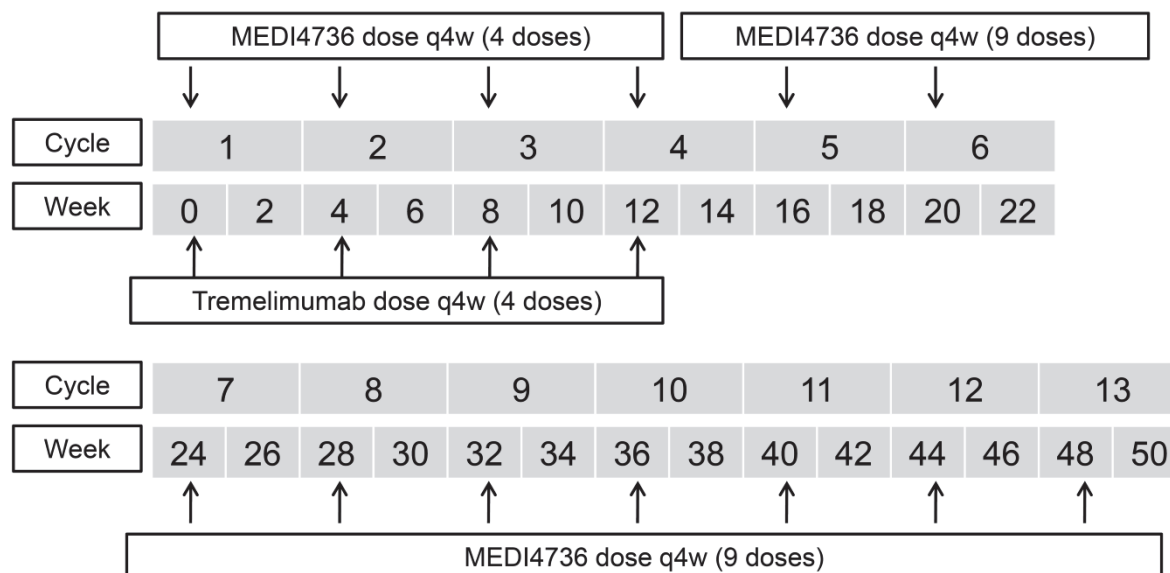


MEDI4736 + tremelimumab

Patients in the MEDI4736 + tremelimumab arm will receive 1.5 g MEDI4736 via IV infusion q4w for 4 months with 75 mg tremelimumab via IV infusion q4w for 4 doses (4 doses each). Patients will then continue with MEDI4736 monotherapy at 1.5 g q4w, beginning at Week 16, 4 weeks after the last dose of combination therapy, up to a total of 9 additional doses, with the final dose at Week 48. See [Figure 4](#).

Tremelimumab will be administered first. MEDI4736 infusion will start approximately 1 hour after the end of tremelimumab infusion. The duration will be approximately 1 hour for each infusion. A 1-hour observation period is recommended after the first infusion of MEDI4736 and tremelimumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each MEDI4736 and tremelimumab infusion).

Figure 4 **MEDI4736 + tremelimumab combination therapy dosing schedule**



Standard of care

Patients randomized to the SoC treatment arm of Part B: RCT will receive SoC treatment with a gemcitabine-based chemotherapy (for patients whose first-line chemotherapy was fluorouracil-based) or fluorouracil-based chemotherapy (for patients whose first-line chemotherapy was gemcitabine-based). Treatment will be as per local guidelines.

7.2.2 Duration of treatment

Treatment will be administered beginning on Day 1.

Patients in Part A or Part B will receive MEDI4736 monotherapy or MEDI4736 + tremelimumab combination for 12 months or until confirmed PD, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met, or unless the criterion for initiating retreatment on MEDI4736 + tremelimumab combination therapy is met as described below. Patients enrolled in the SoC arm of Part B: RCT will discontinue study drug at the first assessment of disease progression per RECIST 1.1.

Patients randomized to the MEDI4736 monotherapy or MEDI4736 + tremelimumab arms who meet the retreatment criteria below for their respective treatment arm will follow the same treatment guidelines followed during the initial 12-month treatment period, including the same dose and frequency of treatments and the same schedule of assessments, with the exception of the PK, ADA, sPD-L1, SNP, MDSC, and nAB assessments, which do not need to be collected a second time. Retreatment will not be permitted for patients randomized to SoC treatment in Part B: RCT. Crossover within the study will not be permitted. Patients who meet the criteria for retreatment for their respective treatment arm may only receive retreatment once. Patients randomized to monotherapy MEDI4736 may undergo retreatment in 1 clinical scenario, described below:

1. Patients who achieve or maintain disease control (ie, CR, PR, or SD) through to the end of the 12-month treatment period may restart their assigned treatment with MEDI4736 upon evidence of PD, with or without confirmation and according to RECIST 1.1, during follow-up.

Patients randomized to the combination of MEDI4736 and tremelimumab arm may undergo retreatment in 2 clinical scenarios, described below:

1. Patients who achieve and maintain disease control (ie, CR, PR, or SD) through to the end of the 12-month treatment period may restart treatment with the combination upon evidence of PD, with or without confirmation and according to RECIST 1.1, during follow-up.
2. Patients who complete the 4 dosing cycles of the combination of MEDI4736 and tremelimumab portion of the regimen (with clinical benefit per Investigator judgment), but subsequently have evidence of PD during the MEDI4736 monotherapy portion of the combination regimen, with or without confirmation according to RECIST 1.1, may restart treatment with the combination.

For both treatment arms, before restarting their assigned treatment, the Investigator should ensure that the patient:

1. Does not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient
2. Still fulfills the eligibility criteria for this study, including re-consenting to restart IP
3. Has not have received an intervening systemic anticancer therapy after their assigned treatment discontinuation
4. Has had a baseline tumor assessment within 28 days of restarting their assigned treatment; all further scans should occur with the same frequency as during the initial 12 months of treatment (relative to the date of restarting treatment) until study treatment is stopped (maximum of 12 months of further treatment).

During the retreatment period, patients in the MEDI4736 + tremelimumab arm will resume MEDI4736 dosing at 1.5 g q4w with 75 mg of tremelimumab q4w for 4 doses each. Patients will then continue with MEDI4736 monotherapy at 1.5 g q4w, beginning at Week 16, 4 weeks after the last dose of combination therapy, up to a total of 9 additional doses, with the final dose at Week 48.

Patients in the MEDI4736 monotherapy treatment arm will resume MEDI4736 dosing at 1.5 g q4w for up to 12 months (up to 13 doses).

Patients who the Sponsor and Investigator determine may not continue treatment after confirmed PD during the 12-month initial treatment period or in the 12-month retreatment

period will enter follow-up. Patients who have discontinued treatment due to toxicity or symptomatic deterioration, or who have commenced subsequent anticancer therapy, will be followed up until confirmed disease progression or death (whichever occurs first).

Treatment through progression and retreatment in the MEDI4736 monotherapy or MEDI4736 + tremelimumab arms is at the Investigator's discretion, and the Investigator should ensure that patients do not have any significant, unacceptable, or irreversible toxicities that indicate that continuing treatment will not further benefit the patient. The Investigator should ensure that patients still meet all of the inclusion criteria and none of the exclusion criteria for this study and that these patients meet the following specific criteria for treatment in the setting of PD:

- Written informed consent to continue treatment or retreatment in the setting of PD. This consent document will specify that treatment beyond initial evidence of PD is not the standard-of-care and that alternative treatment options, either locally licensed treatments or other clinical trials, are available for this patient population.
- Absence of clinical symptoms or signs indicating clinically significant disease progression and no decline in ECOG performance status to >1
- Absence of rapid disease progression or threat to vital organs or critical anatomical sites (eg, central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) requiring urgent alternative medical intervention

A patient with confirmed progression randomized to the MEDI4736 arm cannot continue therapy with MEDI4736 or obtain retreatment with MEDI4736 if dosing is ongoing and the progression occurs in a target lesion that has previously shown a confirmed response. A patient with a confirmed progression randomized to the MEDI4736 + tremelimumab arm cannot continue therapy or obtain retreatment if dosing is ongoing in the combination portion of therapy and progression occurs in a target lesion that has previously shown a confirmed response.

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labelling. Label text will be translated into local language.

Labels will be provided as either a single panel label or as multi-language booklet labels.

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The IP label on the pack/bottle/carton specifies the appropriate storage. Storage is also described in the IB.

7.5 Compliance

The administration of all study drugs (including IPs) should be recorded in the appropriate sections of the eCRF.

Patients should return all unused medication and empty containers to the Investigator.

Treatment compliance will be assured by site reconciliation of medication dispensed and returned.

7.6 Accountability

The study drug provided for this study will be used only as directed in the study protocol. The study personnel will account for all study drugs.

Drug accountability should be performed until the patient stops study treatment completely. Study site personnel will account for all study drugs received at the site, for all unused study drugs, and for appropriate destruction of study drugs. Certificates of delivery, destruction, and return should be signed.

Study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The IP Storage Manager is responsible for managing the study drug from receipt by the study site until the return of all unused study drug to AstraZeneca. AstraZeneca will provide the study documents “Procedures for drug accountability” and “Procedures for drug storage,” which describe the specific requirements. The Investigator(s) is responsible for ensuring that the patient has returned all unused study drug.

7.7 Concomitant and other treatments

The Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF.

Patients must be instructed not to take any medications, including over-the-counter products, without first consulting with the Investigator.

Restricted, prohibited, and permitted concomitant medications are described in the following tables. Refer to Section 6.7 for guidance on management of IP-related toxicities.

Prohibited medication/class of drug:	Usage:
Any investigational anticancer therapy concurrent with those under investigation in this study	Should not be given during the study
mAbs against CTLA-4, PD-1, or PD-L1 through 90 days after the last dose of IP	Should not be given during the study

Prohibited medication/class of drug:	Usage:
Any concurrent chemotherapy, radiotherapy (except for local treatment of isolated lesions, excluding target lesions, for palliative intent [eg, by local surgery or radiotherapy]), immunotherapy, biologic therapy, or hormonal therapy for cancer treatment.	Should not be given during the study. (Concurrent use of hormones for noncancer related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable.)
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, azathioprine, and tumor necrosis factor alpha (TNF- α) blockers.	Should not be given during the study. (Use of immunosuppressive medications for the management of IP-related AEs or in patients with contrast allergies is acceptable. In addition, use of inhaled, topical, or intranasal corticosteroids is permitted. Temporary uses of corticosteroids for concurrent illnesses [eg, food allergies or CT scan contrast hypersensitivity,] are acceptable upon discussion with the Study Physician.)
Live attenuated vaccines	Should not be given within 30 days of dosing of IP
Herbal and natural remedies	Should be avoided during the study (with the exception of homeopathic remedies, which could be used following discussion with the Investigator)
Drugs with laxative properties and herbal or natural remedies for constipation	Should be avoided through 90 days post-last dose of tremelimumab
Sunitinib	Should not be given through 90 days after the last dose of tremelimumab

Rescue/supportive medication/class of drug:	Usage:
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as “prohibited” as listed above.	To be administered as prescribed by the Investigator
BSC (including antibiotics, nutritional support, growth factor support, anti-emetic, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy, etc])	Should be used when necessary for all patients
Opioids	Can be used but with caution and under medical control after discussion with the Study Physician

7.7.1 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

7.8 Post study access to study treatment

After the final analysis, AstraZeneca will continue to supply open-label drug to patients receiving MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy up to completion of a patient's treatment period (initial or repeat) (see Section 7.2).

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

A comprehensive statistical analysis plan (SAP) within 3 months of the first enrolled patient and any subsequent amendments will be documented, with final amendments completed prior to reporting of the data.

8.2 Sample size estimate

Part A: Lead-in and Part B: Expansion

Once 15 efficacy outcomes are observed in the first 15 patients in each arm (ie, a minimum follow-up of 2 post-baseline tumor assessments at Week 6 and Week 12), predictive probability will be used to calculate the chance of observing at least 5 out of 30 responses ($\geq 15\%$ CR/PR) in each arm, and at least 15 out of 30 patients achieving DCR at 12 weeks ($\geq 50\%$ DCR12). This will make use of a Beta – Binomial posterior predictive distribution, where at the outset a non-informative prior is assumed for the ORR or DCR12 (Beta[1,1]), and a Beta-Binomial distribution can then be used to calculate the probability of achieving the required ORR or DCR from 30 evaluable patients given the data observed (see Table 8). If predictive probability is $<10\%$ for both ORR and DCR12, recruitment into the arm in which this happens will be stopped. A different decision outside of these criteria may be made, if the totality of the data supports it. Recruitment will continue while predictive probability is calculated. If an arm is to be stopped following the predictive probability calculation, no new patients will be recruited to that arm, but patients who are already on study will continue in accordance with study guidelines outlined in Section 7.2. If enrollment is fast enough so that, by the time 15 patients are evaluable (Weeks 6 and 12 tumor assessment data available), all 30 patients per arm have already been randomized, then the predictive probability calculations will not be carried out.

Table 8 **Illustrative stopping boundaries for ORR and DCR12 based on 15 evaluable patients (both criteria to be met to stop an arm)**

Endpoint	Stopping boundary (predictive probability)
ORR	0/15 (1.8%)
DCR12	<5/15 (5.3%)

If an ORR >25% (ie, ≥ 8 CR/PR) is recorded among the first 30 treated patients in either of the treatment arms in Part A (unless the totality of the data supports a different decision), an additional 70 patients will be enrolled in that arm, for a total of 100 evaluable patients per arm in the Part B: Expansion study.

In Part B, 100 patients (30 from Part A plus an additional 70 from Part B) will provide >90% power for an exact test of a single proportion, assuming a null hypothesis (H_0) of ORR=10%, and an alternative hypothesis (H_A) of ORR=25%, at the 2-sided 0.05 alpha level. (Critical value, ORR = 16.7%), while also providing adequate patients to reasonably characterize the safety profile of the expanded arm(s). A 10% response rate is considered a reasonable assumption for the average response rate achieved by current therapies in second-line advanced pancreatic cancer ([Rahma et al 2013](#)).

Part B: Randomized, controlled trial

Should the ORR in Part A in at least 1 arm be >15% ($\geq 5/30$ responses) then a randomized controlled trial may be initiated.

If initiated, this will be a separate randomized, open- label, multi-center, study to determine the efficacy and safety of MEDI4736 monotherapy and/or MEDI4736 + tremelimumab combination therapy versus SoC chemotherapy (1:1:1 or 1:1) with primary endpoint of OS. If both arms are taken forward from Part A, then the primary comparison will be to compare MEDI4736 + tremelimumab combination therapy versus SoC. Approximately 125 additional patients per treatment arm will be randomized in this Part B: RCT. Treatment for MEDI4736 monotherapy and/or MEDI4736 + tremelimumab will only be included in this RCT if the corresponding treatment meets the appropriate criteria in Part A. A final decision to initiate Part B (RCT) will be made after evaluation of all available efficacy and safety data from the lead in phase (Part A), and may not be limited to the decision rules provided in the protocol. The data from Part B: RCT will be analyzed separately and will not be pooled with Part A for the purpose of statistical analysis.

It is assumed that median OS on SoC chemotherapy will be 5 months. With an assumed 2-month delay in the treatment effect of the experimental therapy emerging relative to SoC (ie, an HR of 1 for the first 2 months) followed by an HR of 0.51 thereafter and a minimum follow-up time of 11.5 months from the end of patient recruitment, this yields an anticipated overall average HR of 0.63. Under these assumptions, analysis would occur after 196 events in a 250-patient, 2-arm study (78% maturity, 196/250) and would be expected around

20.5 months after the first patient is randomized. If the true average HR is 0.63, then with 196 events the study will have 90% power to demonstrate a statistically significant difference at a 2-sided 5% significance level (critical value for HR of 0.75).

Non-uniform accrual of patients (with $k=1.5$) over 9 months is assumed when estimating the analysis times. The total proportion of patients randomized at time t [$t \leq 9$ months] following the start of the study is therefore assumed to be $(t/9)^{1.5}$.

8.3 Definitions of analysis sets

Definitions of the analysis sets for each outcome variable are provided in [Table 9](#).

Table 9 Summary of outcome variables and analysis populations

Outcome variable	Population
Efficacy data	
ORR	Full analysis set
DoR, DCR, PFS, PFS2, PFS3, PFS6, OS, OS6, OS12, PROs, and symptom endpoints	Full analysis set
Demography	Full analysis set
PK data	PK analysis set
Safety Data	
Exposure	Safety analysis set
AEs	Safety analysis set
Laboratory measurements	Safety analysis set
ECOG performance status	Safety analysis set
Vital signs	Safety analysis set

8.3.1 Full analysis set

The full analysis set will include all randomized patients (ie, the intent-to-treat [ITT] population) and will classify them on the basis of randomized or allocated treatment, regardless of the treatment actually received. Patients who were randomized but who did not subsequently go on to receive study treatment are included in the ITT population. For the purposes of evaluating the data in Part A to expand into Part B, only patients who actually received at least 1 dose of study treatment will be included in the Full Analysis Set.

8.3.2 Safety analysis set

All patients who received at least 1 dose of IP and for whom any post-dose data are available will be included in the Safety Analysis Set. When assessing safety and tolerability, summaries will be produced based on the Safety Analysis Set.

8.3.3 PK analysis set

All patients who received at least 1 dose of IP per protocol for whom any post-dose data are available and who do not violate or deviate from the protocol in ways that would significantly affect the PK analyses will be included in the PK Analysis Set. The population will be defined by the Study Physician, Pharmacokineticist, and Statistician prior to any analyses being performed.

8.4 Outcome measures for analyses

8.4.1 Calculation or derivation of efficacy variables

The analysis of the primary endpoint for Part A: Lead-in) and Part B: Expansion, ORR, will be based on Investigator assessments according to RECIST 1.1. Sensitivity analyses for this ORR in Part A: Lead-in and Part B: Expansion will be conducted based on Investigator assessment according to RECIST 1.1 modified for confirmation of progression. OS will be evaluated as the primary endpoint in Part B: RCT.

The analyses of the secondary endpoints of ORR, DoR, DCR, PFS, PFS2, PFS3, and PFS6 will be based on Investigator assessments according to RECIST 1.1. OS, OS6, and OS12 will also be evaluated as secondary endpoints.

8.4.1.1 RECIST 1.1-based endpoints

Investigator RECIST 1.1-based assessments

All RECIST assessments, whether scheduled or unscheduled, will be included in the calculations. This is also regardless of whether a patient discontinues study treatment or receives another anticancer therapy.

At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, or PD depending on the status of their disease compared with baseline and previous assessments. Baseline will be assessed within the 28 days prior to the treatment start date. If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE; unless there is evidence of progression, in which case the response will be assigned as PD). Endpoints (of ORR, DoR, DCR, PFS, PFS2, PFS3, and PFS6) will be derived from the overall visit response date and the scan dates.

Please refer to [Appendix F](#) for the definitions of CR, PR, SD, NE, and PD.

Storage of data for possible BICR of RECIST 1.1-based assessments

All radiological scans for all patients (including those at unscheduled visits or outside visit windows) will be stored for possible assessment by BICR.

8.4.1.2 Primary endpoints

Objective response rate

The primary endpoint for Part A: lead-in and Part B: Expansion is ORR, which will be assessed according to Investigator assessment. ORR (per RECIST 1.1) is defined as the number (%) of patients with a confirmed overall response of CR or PR and will be based on the Full Analysis Set. A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging, preferably at the next regularly scheduled imaging visit and not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. Therefore, data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Any patient who discontinues treatment without progression, receives a subsequent therapy, and then responds will not be included as responders in the ORR.

For sensitivity analysis, ORR will be assessed using the RECIST Investigator assessed tumor data following a modification where any objective progression requires confirmation. Therefore, data obtained up until confirmed progression, or the last evaluable assessment in the absence of a confirmed progression, will be included in the assessment of ORR. Note that the response may be after an unconfirmed progression.

Overall survival

The primary endpoint for Part B: RCT is OS. OS is defined as the time from the date of randomization until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

Note: Survival calls will be made in the week following the date of data cut-off for the analysis, and if patients are confirmed to be alive or if the death date is post the data cut-off date, these patients will be censored at the date of data cut-off. Death dates may be found by checking publicly available death registries.

8.4.1.3 Secondary endpoints

Duration of response

DoR (per RECIST 1.1 as assessed by Investigator assessment) will be defined as the time from the date of first documented response until the first date of documented progression or death in the absence of disease progression. The end of response should coincide with the date of progression or death from any cause used for the RECIST 1.1 PFS endpoint, based on Investigator assessment.

The time of the initial response will be defined as the latest of the dates contributing toward the first visit response of CR or PR. If a patient does not progress following a response, then their DoR will be censored at the PFS censoring time. DoR will not be defined for those patients who do not have documented response.

Additionally, DoR will be obtained using the algorithm described, but following a modification where any objective progression requires confirmation. Therefore, the end of response should coincide with the date of progression or death from any cause. The time of the initial response will be defined as the latest of the dates contributing toward the first visit response of PR or CR. Note that the time of initial response may be after an unconfirmed progression.

Disease control rate

DCR at 3 or 12 months is defined as the percentage of patients who have a best objective response (BoR) of CR or PR in the first 3 or 12 months, respectively, or who have demonstrated SD for a minimum interval of 12 or 52 weeks, respectively (-7 days, ie, 105 or 357 days, respectively), following the start of study treatment.

DCR will be determined programmatically based on RECIST 1.1 using Investigator assessments and all data up until the first progression event. This will use all data up until the progression event that is used for the analysis (ie, unconfirmed progressions are not considered progression events, which means that the BoR that contributes to the DCR may be after an unconfirmed progression for some patients).

Progression-free survival (PFS)

PFS (per RECIST 1.1 using Investigator assessments) will be defined as the time from the date of first dose/randomization until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from allocated/randomized therapy or receives another anticancer therapy prior to progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment. If the patient has no evaluable visits or does not have baseline data, they will be censored at 0 days unless they die within 2 visits of baseline.

The PFS time will always be derived based on scan/assessment dates not visit dates.

RECIST 1.1 assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- For investigational assessments, the date of progression will be determined based on the earliest of the RECIST assessment/scan dates of the component that indicates progression.
- When censoring a patient for PFS, the patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

Note: For target lesions, only the latest scan date is recorded out of all scans performed at that assessment for the target lesions, and similarly for non-target lesions, only the latest scan date is recorded out of all scans performed at that assessment for the non-target lesions.

PFS based on RECIST 1.1 modified for confirmation of progression will be performed for exploratory purposes using the algorithm described above for the RECIST 1.1 Investigator assessments, but following a modification whereby any objective disease progression must be confirmed by the next scheduled scan. The confirmatory scan is preferably at the next regularly scheduled imaging visit and must be no sooner than 4 weeks after the initial suspected progression. If disease progression is confirmed (or disease progression occurs and no further scans are recorded) then the date of progression will be when it was originally observed. Patients with a single disease progression and no further tumor assessment scans will be treated as PD in the analysis. In the absence of significant clinical deterioration, the investigational site is advised to continue the patient on study therapy until progression has been confirmed. If progression is not confirmed, the patient should continue study therapy and on-treatment assessments. For Part B: RCT, patients enrolled in the SoC arm will discontinue study drug at the first assessment of disease progression.

Progression-free survival₂ (second progression) (PFS₂)

Time from randomization to second progression (PFS₂) is defined as the time from the date of randomization to the earliest of the progression event(s) subsequent to that used for the PFS endpoint or death. Patients alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without a second disease progression, that is, censored at the latest of the PFS or PFS₂ assessment date if the patient has not had a second progression or death.

Proportion of patients alive and progression-free after 3 months

The PFS rate at 3 months (PFS₃) will be calculated using Kaplan-Meier estimates. Tumor progression will be determined based on Investigator assessment and RECIST 1.1.

Proportion of patients alive and progression-free after 6 months

The PFS rate at 6 months (PFS₆) will be calculated using Kaplan-Meier estimates. Tumor progression will be determined based on Investigator assessment and RECIST 1.1.

Proportion of patients alive at 6 months from randomization/enrollment

The OS₆ will be defined as the Kaplan-Meier estimate of OS at 6 months.

Proportion of patients alive at 12 months from randomization/enrollment

The OS₁₂ will be defined as the Kaplan-Meier estimate of OS at 12 months.

Best objective response

BoR is calculated based on the overall visit responses from each RECIST assessment, described in [Appendix F](#). It is the best response a patient has had during their time in the

study up until RECIST progression (or confirmed progression where applicable) or the last evaluable assessment in the absence of RECIST progression.

Categorization of BoR will be based on RECIST ([Appendix F](#)) using the following response categories: CR, PR, SD, PD, and NE.

BoR will be determined programmatically based on RECIST using all Investigator assessment data up until the first progression event. Furthermore, it will be determined programmatically based on RECIST modified for confirmation of progression. This will use all data up until the progression event that is used for the analysis (ie, unconfirmed progressions are not considered progression events, which means that the BoR may be after an unconfirmed progression for some patients).

For patients whose progression event is death, BoR will be calculated based upon all evaluable RECIST assessments prior to death.

For patients who die with no evaluable RECIST assessments, if the death occurs 13 weeks (ie, 12 weeks \pm 7 days) after enrollment, then BoR will be assigned to the PD category. For patients who die with no evaluable RECIST assessments, if the death occurs >13 weeks (ie, 12 weeks \pm 7 days) after the date of enrollment, then BoR will be assigned to the NE category.

Progression events that have been censored due to them being >13 weeks after the last evaluable assessment will not contribute to the BoR derivation.

8.4.2 Calculation or derivation of safety variables

8.4.2.1 Adverse events

Data from all cycles of treatment will be combined in the presentation of safety data. AEs (both in terms of Medical Dictionary for Regulatory Activities [MedDRA] preferred terms and CTCAE grade) will be listed individually by patient.

Any AE occurring before treatment with IP will be included in the data listings but will not be included in the summary tables of AEs. Any AE occurring within 90 days of discontinuation of IP (ie, the last dose of a given IP therapy) may be included in the AE summaries, but the majority of those summaries will omit the AEs observed after a patient has received further therapy for cancer. Further details will be provided in the SAP. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of IP) will be flagged in the data listings.

A separate data listing of AEs occurring more than 90 days after discontinuation of IP will be produced. These events will not be included in AE summaries.

8.4.2.2 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation. Based on

the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs. Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious) or significant additional treatment.

8.4.2.3 Safety assessments

For the change from baseline summaries for vital signs, laboratory data, ECGs, and physical examination, the baseline value will be the latest result obtained prior to the start of study treatment.

The QTcF will be derived during creation of the reporting database using the reported ECG values (RR and QT).

$QTcF = QT/RR^{(1/3)}$ where RR is in seconds

Corrected calcium will be derived during creation of the reporting database using the following formulas:

$\text{Corrected calcium (mmol/L)} = \text{Total calcium (mmol/L)} + ([40 - \text{albumin (G/L)}] \times 0.02)$

The denominator used in laboratory summaries will only include evaluable patients, in other words, those who had sufficient data to have the possibility of an abnormality.

For example:

- If a CTCAE criterion involves a change from Baseline, evaluable patients would have both 1 pre-dose and at least 1 post-dose value recorded
- If a CTCAE criterion does not consider changes from baseline, to be evaluable the patient need only have 1 post-dose-value recorded.

The denominator in vital signs data should include only those patients with recorded data.

8.4.3 Calculation or derivation of patient-reported outcome variables

PRO questionnaires will be assessed using the EORTC QLQ-C30 questionnaire, EORTC QLQ-PAN26 questionnaire, and PRO-CTCAE. All items/questionnaires will be scored according to published scoring guidelines or the developer's guidelines, if published guidelines are not available. All PRO analyses will be based on the Full Analysis Set (FAS; ITT population), unless stated otherwise.

8.4.3.1 EORTC QLQ-C30

The EORTC QLQ-C30 consists of 30 questions that can be combined to produce 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and

nausea/vomiting), 6 individual items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global measure of health status (overall health and overall quality of life). The EORTC QLQ-C30 will be scored according to the EORTC QLQ-C30 scoring manual (Fayers et al 2001). An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales/symptom items, each of the functional scales, and the global health status scale in the EORTC QLQ-C30 according to the EORTC QLQ-C30 Scoring Manual. Higher scores on the global health status and functioning scales indicate better health status/function, but higher scores on symptom scales/items represent greater symptom severity.

The change from baseline in HRQoL will be assessed using the EORTC QLQ-C30 global QoL scale, which includes 2 items from the EORTC QLQ-C30: “How would you rate your overall health during the past week?” (Item 29) and “How would you rate your overall QoL during the past week?” (Item 30).

Definition of clinically meaningful changes

Changes in score compared with baseline will be evaluated. A minimum clinically meaningful change is defined as an absolute change in the score from baseline of ≥ 10 for scales/items from the EORTC QLQ-C30 (Osoba et al 1998). For example, a clinically meaningful improvement in physical function (as assessed by EORTC QLQ-C30) is defined as an increase in the score from baseline of ≥ 10 , whereas a clinically meaningful deterioration is defined as a decrease in the score from baseline of ≥ 10 . At each post-baseline assessment, the change in symptoms/functioning from baseline will be categorized as improvement, no change or deterioration as shown in Table 10.

Table 10 Mean change and visit response in health related quality of life

Score	Change from baseline	Visit response
EORTC QLQ-C30 Global quality of life score	$\geq +10$	Improvement
	≤ -10	Deterioration
	Otherwise	No change
EORTC QLQ-C30 symptom scales/items	$\geq +10$	Deterioration
	≤ -10	Improvement
	Otherwise	No change
EORTC QLQ-C30 functional scales	$\geq +10$	Improvement
	≤ -10	Deterioration
	Otherwise	No change

For each subscale, if $< 50\%$ of the subscale items are missing, then the subscale score will be divided by the number of nonmissing items and multiplied by the total number of items on the subscales (Fayers et al 2001). If at least 50% of the items are missing, then that subscale will

be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded. If there is evidence that the missing data are systematic, missing values will be handled to ensure that any possible bias is minimized.

Exploratory PRO endpoints

Time to symptom deterioration

For each of the symptoms scales in the EORTC QLQ-C30, time to symptom deterioration will be defined as the time from randomization until the date of the first clinically meaningful symptom deterioration (an increase in the score from baseline of ≥ 10) or death (by any cause) in the absence of a clinically meaningful symptom deterioration, regardless of whether the patient withdraws from study treatment or receives another anticancer therapy prior to symptom deterioration. Death will be included as an event only if the death occurs within 2 visits of the last PRO assessment where the symptom change could be evaluated.

Patients whose symptoms (as measured by EORTC QLQ-C30) have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the symptom could be evaluated. Also, if symptoms deteriorate after 2 or more missed PRO assessment visits or the patient dies after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where the symptom could be evaluated. If a patient has no evaluable visits or does not have baseline data he or she will be censored at 0 days.

Time to HRQoL/function deterioration

For HRQoL (as measured by EORTC QLQ-C30), time to deterioration will be defined as the time from the date of randomization until the date of the first clinically meaningful deterioration (a decrease in the function scales or the global health status/HRQoL from baseline of ≥ 10) or death (by any cause) in the absence of a clinically meaningful deterioration, regardless of whether the patient withdraws from study treatment or receives another anticancer therapy prior to HRQoL/function deterioration. Death will be included as an event only if the death occurs within 2 visits of the last PRO assessment where the HRQoL/function change could be evaluated.

Patients whose HRQoL (as measured by EORTC QLQ-C30) have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the HRQoL/function could be evaluated. Also, if HRQoL deteriorates after 2 or more missed PRO assessment visits or the patient dies after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where HRQoL/function could be evaluated. If a patient has no evaluable visits or does not have baseline data he or she will be censored at 0 days.

Symptom improvement rate

The symptom improvement rate will be defined as the number (%) of patients with 2 consecutive assessments at least 14 days apart that show a clinically meaningful improvement (a decrease from baseline score ≥ 10 for EORTC QLQ-C30 symptom scales) in

that symptom from baseline. The denominator will consist of a subset of the ITT population who has a baseline symptom score ≥ 10 .

HRQoL/function improvement rate

The HRQoL/function improvement rate will be defined as the number (%) of patients with 2 consecutive assessments at least 14 days apart that show a clinically meaningful improvement (an increase from baseline score ≥ 10 for EORTC QLQ-C30 functional scales and global health status/HRQoL) in that scale from baseline.

8.4.3.2 EORTC QLQ-PAN26

For EORTC QLQ-PAN26, 7 multi-item subscales scores (pancreatic pain [4 items], eating related [2 items], hepatic [2 items], altered bowel habit [2 items], body image [2 items], health care satisfaction [2 items], sexuality [2 items]) and 10 single-item scales (swollen abdomen, taste changes, indigestion, flatulence, weight loss, loss of muscle strength, dry mouth, burden of treatment, fear of future health, and ability to plan future) will be derived as specified in the scoring manual.

8.4.3.3 Calculation or derivation of healthy state utility (EQ-5D-5L)

The EQ-5D-5L index comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For each dimension, respondents select which statement best describes their health on that day from a possible 5 options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems, and extreme problems). A unique EQ-5D health state is referred to by a 5-digit code allowing for a total of 3125 health states. For example, state 11111 indicates no problems on any of the 5 dimensions. These data will be converted into a weighted health state index by applying scores from EQ-5D value sets elicited from general population samples (the base case will be the United Kingdom valuation set, with other country value sets applied in scenario analyses). Where values sets are not available, the EQ-5D-5L to EQ-5D-3L crosswalk will be applied. In addition to the descriptive system, respondents also assess their health on the day of assessment on a visual analogue scale, ranging from 0 (worst imaginable health) to 100 (best imaginable health). This score is reported separately. The evaluable population will comprise the FAS (ITT population).

8.4.4 Calculation or derivation of pharmacokinetic variables

8.4.4.1 Population pharmacokinetics and exposure-response/safety analysis

A population PK model analysis might be performed using a nonlinear mixed-effects modelling approach. The impact of physiologically-relevant patient characteristics (covariates) and disease on PK will be evaluated. The relationship between the PK exposure and the effect on safety and efficacy endpoints will be evaluated. The results of such an analysis will be reported in a separate report. The PK, pharmacodynamics, demographic, safety, and efficacy data collected in this study may also be combined with similar data from other studies and explored using population PK and/or PK-pharmacodynamic methods.

8.4.4.2 Pharmacokinetic noncompartmental analysis

The actual sampling times will be used in the PK calculations. PK concentration data and summary statistics will be tabulated. Individual and mean blood concentration-time profiles will be generated. PK parameters will be determined using standard noncompartmental methods. The following PK parameters will be determined after the first and steady-state doses: peak and trough concentration (as data allow). Samples below the lower limit of quantification will be treated as missing in the analyses.

8.4.4.3 Immunogenicity analysis

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable ADAs against MEDI4736 monotherapy or MEDI4736 in combination with tremelimumab. The immunogenicity titer and presence of neutralizing ADAs will be reported for samples confirmed positive for the presence of ADAs. The effect of immunogenicity on PK, pharmacodynamics, efficacy, and safety will be evaluated, if the data allow.

8.4.5 Calculation or derivation of biomarker variables

Biomarker status, as defined in the exploratory objectives, will be assessed for evaluable patients in each cohort according to prespecified criteria that will be detailed in the SAP.

8.4.6 Calculation or derivation of pharmacogenetic variables

In the case of genetic data, only the date that the patient gave consent to participation in the genetic research and the date the blood sample was taken from the patient will be recorded in the eCRF and database. The genetic data generated from the study will be stored in the AstraZeneca Laboratory Information Management System (LIMS) database or other appropriate system. This database is a secure database, which is separate from the database used for the main study. Some or all of the dataset from the main study may be duplicated within the AstraZeneca LIMS database for exploratory genetic analysis. Data will be reported outside the CSR (please see [Appendix D](#)).

8.5 Methods for statistical analyses

The primary hypothesis being tested is that treatment with MEDI4736 in combination with tremelimumab or as MEDI4736 monotherapy, will deliver improved ORR compared to SoC in the treatment of patients with metastatic PDAC who have failed 5-FU-containing or gemcitabine-containing first-line chemotherapy.

Descriptive statistics will be used for all variables, as appropriate, and will be presented by treatment group. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment arm.

Baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of IP, except for efficacy variables. For efficacy variables, baseline is defined as the last visit prior to treatment start date.

All data collected will be listed. Efficacy and PRO data will be summarized and analyzed based on the FAS. PK data will be summarized and analyzed based on the PK Analysis Set. Safety data will be summarized on the Safety Analysis Set.

All outputs will be summarized by treatment arm for all enrolled patients (ITT).

Results of all statistical analysis will be presented using a 95% CI and 2-sided p-value, unless otherwise stated.

Table 11 details which endpoints are to be analyzed, together with preplanned sensitivity analyses indicating which analysis is regarded as primary for that endpoint. Formal statistical analysis will be done only for ORR. Nominal p-values will be provided for all other endpoint and sensitivity analyses.

Unless otherwise stated, data and endpoints derived from RECIST tumor assessments will refer Investigator assessed data.

Table 11 Preplanned statistical and sensitivity analyses to be conducted

Endpoints analyzed	Notes
Objective response rate	Summarized by treatment arm with lower 95% Clopper-Pearson confidence limits (Part A) Part B: Expansion - Formal analysis using exact test for a binomial proportion, with 2-sided 95% Clopper-Pearson CI
Duration of response	Kaplan Meier plots and summaries
DCR	Summarized by treatment arm n (%) Parts A and B.
Best objective response	Summary statistics, N (%)
Progression free survival, PFS3, PFS6	Kaplan Meier plots, estimates and summaries as appropriate Part B: RCT - Stratified log rank test
Overall survival, OS6, OS12	Kaplan Meier plots and summaries. Part B: RCT - Stratified log rank test

Multiple testing strategy

For Part B: RCT, if both arms are taken forward from Part A, then the primary comparison will be to compare MEDI4736 + tremelimumab combination therapy versus SoC. MEDI4736 monotherapy versus SoC will be compared hierarchically in order to strongly control the type I error. Full details of the multiple testing procedure will be provided in the SAP.

8.5.1 Analysis of the primary variables

Objective response rate

The primary endpoint (ORR) for Part A and Part B: Expansion (if initiated) will be estimated for each treatment arm with 95% exact CIs. The primary analysis will be based on the programmatically derived ORR based on Investigator assessments, and using all scans regardless of whether they were scheduled or not. An additional sensitivity analysis will be performed on programmatically derived ORR using Investigator data (RECIST modified for confirmation of progression) to determine if there is any difference when using progression confirmation rules.

The primary analysis population for ORR will be the FAS.

Summaries will be produced that present the number and percentage of patients with a tumor response (CR/PR). The number (%) of patients with a confirmed response and the number (%) of patients with a single visit response (ie, an unconfirmed response) will also be presented.

Overall survival

Kaplan-Meier plots of OS will be presented for each treatment arm of the study. Summaries of the number and percentage of patients who have died, are still in survival follow-up, are lost to follow-up and have withdrawn consent will be provided along with median OS for each cohort/treatment arm (if calculable).

The OS6 will be summarized (using the Kaplan-Meier curve) and presented for each treatment arm.

For Part B: RCT, the primary OS analysis will be performed in the ITT population using a stratified log-rank test adjusting for response to prior chemotherapy and type of prior chemotherapy. The effect of each experimental arm versus SoC treatment will be estimated by the HR together with its corresponding 95% CI and p-value.

The HR and its CI can be estimated from the stratified log-rank as follows ([Berry et al 1991](#), [Collett 2003](#), [Selke and Siegmund 1983](#)):

$$HR = \exp\left(\frac{U}{V}\right)$$

$$95\% \text{ CI for HR} = \left(\exp\left\{\frac{U}{V} - \frac{1.96}{\sqrt{V}}\right\}, \exp\left\{\frac{U}{V} + \frac{1.96}{\sqrt{V}}\right\} \right)$$

Where $U = \sum_k U_k = \sum_k \sum_i (d_{1ki} - e_{1ki})$ is the stratified log-rank test statistic obtained from the SAS LIFETEST procedure, $\sqrt{V} = \sqrt{\sum_k V_k}$ is its standard deviation, k denotes the stratum, and d_{1ki} and e_{1ki} are the observed and expected events in Group 1, stratum k.

The assumption of proportionality will be assessed. Proportional hazards will be tested firstly by examining plots of complementary log-log (event times) versus log (time) and, if these raise concerns, by fitting a time-dependent covariate to assess the extent to which this represents random variation. If a lack of proportionality is evident, the variation in treatment effect will be described by presenting piecewise HR calculated over distinct time-periods. In such circumstances, the HR can still be meaningfully interpreted as an average HR over time unless there is extensive crossing of the survival curves. If lack of proportionality is found, this may be is a result of treatment-by-covariate interactions, which will be investigated.

A sensitivity analysis for OS will examine the censoring patterns to rule out attrition bias, achieved by a Kaplan-Meier plot of time to censoring where the censoring indicator of OS is reversed.

Subgroup analyses will be conducted comparing OS between treatments in the following subgroups of the FAS:

- Response to previous chemotherapy (CR/PR/SD vs PD)
- Type of previous chemotherapy (5-FU-containing or gemcitabine-containing chemotherapy)

The HR (MEDI4736 or MEDI4736 + tremelimumab: SoC) and 95% CI in each subgroup will be calculated from a single Cox model. These will be presented on a forest plot including the HR and 95% CI from the overall population.

Other baseline variables may also be assessed if there is clinical justification or an imbalance is observed between the treatment arms. The purpose of the subgroup analyses is to assess the consistency of treatment effect across expected prognostic factors.

The presence of quantitative interactions will be assessed by means of an overall global interaction test. This will be performed in the overall population by comparing the fit of a Cox proportional hazards model including treatment, all covariates, and all covariate-by-treatment interaction terms, with one that excludes the interaction terms and will be assessed at the 2-sided 10% significance level. If the fit of the model is not significantly improved then it will be concluded that overall the treatment effect is consistent across the subgroups.

If the global interaction test is found to be statistically significant, an attempt to determine the cause and type of interaction will be made. Stepwise backwards selection will be performed on the saturated model, whereby (using a 10% level throughout) the least significant interaction terms are removed one-by-one and any newly significant interactions re-included

until a final model is reached where all included interactions are significant and all excluded interactions are nonsignificant. Throughout this process all main effects will be included in the model regardless of whether the corresponding interaction term is still present. This approach will identify the factors that independently alter the treatment effect and prevent identification of multiple correlated interactions.

Any quantitative interactions identified using this procedure will then be tested to rule out any qualitative interaction using the approach of [Gail and Simon 1985](#).

If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 20 events in a subgroup), the relationship between that subgroup and OS will not be formally analyzed. In this case, only descriptive summaries will be provided.

8.5.2 Analysis of the secondary variables

8.5.2.1 Duration of response

In order to analyze the DoR between treatment arms (only relevant for Part B randomized, controlled study), the Expected Duration of Response (EDoR) will be derived for each treatment arm ([Ellis et al 2008](#)). The EDoR is the product of the proportion of patients responding to treatment and the mean DoR in responding patients and provides an estimate based on all randomized patients. Treatments will be compared by calculating the ratio of EDoRs, using an appropriate probability distribution (to be specified in the SAP) for DoR in responding patients. Additionally, descriptive data will be provided for the DoR in responding patients, including the associated Kaplan-Meier curves (without any formal comparison of treatment arms or p-value attached).

8.5.2.2 Disease control rate

The DCR will be summarized (ie, number of patients).

8.5.2.3 Progression-free survival

Kaplan-Meier plots of PFS will be presented for each treatment arm. Summaries of the number and percentage of patients who have died, are still in survival follow-up, are lost to follow-up and have withdrawn consent will be provided along with median OS for each cohort (if calculable).

Additionally, for Part B: RCT, formal comparative analysis of PFS will be carried out in the same way as for OS.

8.5.2.4 Progression-free survival2 (second progression)

For Part B: RCT, PFS2 will be summarized and analyzed in the same way as PFS.

8.5.2.5 Proportion of patients with progression-free survival after 3 months and 6 months

The PFS and PFS6 will be calculated using Kaplan-Meier estimates, as the cumulative probability of progression-free survival to each of those two time periods. Estimates of PFS3 and PFS6 will each be presented with 95% CIs. Median progression-free survival and plots of PFS rates over time will also be presented, based on the Kaplan-Meier estimates.

8.5.3 Proportion of patients alive at 6 and 12 months

The OS6, and OS12, will be calculated using Kaplan-Meier estimates of the cumulative probability of survival at each of those time periods. The survival estimates of OS6 and OS12 will be presented with 95% CIs. Median survival and survival plots over time will also be produced and presented, based on Kaplan-Meier estimates.

8.5.4 Patient-reported outcomes

The analysis population for PRO data will be the PRO analysis set including patients with evaluable baseline EORTC QLQ-C30 and QLQ-PAN26 forms. The HRQoL and pancreatic pain will be assessed through an analysis of the EORTC-QLQ-C30 global QoL and PAN-26 pancreatic pain scales.

8.5.4.1 EORTC QLQ-C30

Adjusted mean change from baseline in global QoL score will be analyzed using a mixed model for repeated measures (MMRM) analysis of all of the post-baseline scores for each visit and will be presented by treatment group. The study discontinuation visit and the safety follow-up visit will be excluded from this analysis. Restricted maximum likelihood (REML) estimation will be used. The model will include treatment, visit and treatment by visit interaction as explanatory variables and the baseline QoL score as a covariate. Treatment, visit and treatment by visit interaction will be fixed effects in the model. The treatment by visit interaction will remain in the model regardless of significance.

An unstructured covariance matrix will be used to model the within-subject error and the Kenward-Roger approximation will be used to estimate the degrees of freedom.

If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be tried in order until convergence is reached: toeplitz with heterogeneity, autoregressive with heterogeneity, toeplitz, and autoregressive.

The adjusted mean change from baseline estimates and corresponding 95% CIs will be presented by visit for each treatment group and corresponding plots over time will be presented.

As a supportive analysis, EORTC QLQ-C30 global QoL score improvement rate will be analyzed using a logistic regression model. If the overall response rate is <5%, no analysis will be performed (note that if the response rate in only one of the treatment groups is <5% but ≥5% in the other treatment group then the analysis will still be performed). If the overall expected response rate is low (<20%) a Fisher's exact test will be considered and mid p-values used. The results of the analysis will be presented in terms of an odds ratio together with its associated profile likelihood CIs and p-values (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model).

EORTC QLQ-C30 compliance (overall compliance and by visit compliance) will be summarized for each treatment group.

Descriptive statistics and graphs will be reported for the global QoL score by visits as well as unadjusted change in these scores from baseline. Summary tables of EORTC QLQ-C30 best overall QoL response as defined in [Table 10](#) will be provided (improvement, deterioration, no change).

8.5.4.2 EORTC QLQ-PAN26

Patient-reported outcomes as measured by EORTC QLQ-PAN26 will be summarized descriptively; the change from baseline for domain, subscale scores, and individual items by treatment group at each time point and change from baseline will be explored. EORTC QLQ-PAN26 compliance (overall compliance and by visit compliance) will be summarized for each treatment group.

Exploratory analyses

Exploratory analyses examining adjusted mean change from baseline will be performed for EORTC QLQ-C30 functioning domains (physical, role, cognitive, emotional, and social) and for the individual EORTC QLQ-C30 and QLQ-PAN26 symptom scales/items (with a particular focus on pancreatic pain, fatigue, nausea, weight loss [difficulty gaining weight/loss of appetite], and jaundice), using the same MMRM model described for the global QoL score.

Descriptive statistics and graphs will be reported for the EORTC QLQ-C30 functioning domains and EORTC QLQ-C30 and QLQ-PAN26 symptom scales/items (specifically pancreatic pain, fatigue, nausea, weight loss [difficulty gaining weight/loss of appetite], and jaundice).

EORTC QLQ-C30: Time to symptom deterioration will be analyzed for each of the 3 symptom scales (fatigue, pain, and nausea/vomiting) and the 5 individual symptom items (dyspnea, insomnia, appetite loss, constipation, and diarrhea). Time to QoL/function deterioration will be analyzed for the 5 function scales (physical, role, emotional, cognitive, and social) and global health status/QoL. This will be achieved by comparing treatment arms using a stratified log-rank test as described for the primary analysis of OS. The sensitivity analysis to ascertain attrition bias will be performed as described for the primary analysis of OS. However, subgroup analyses and treatment interaction testing will not be performed. The HR and 95% CI for each scale/item will be presented graphically on a forest plot.

A summary of the symptom improvement rate for each of the 3 symptom scales and the 5 individual symptom items will be produced. Similarly, a summary of QoL/function improvement rate for each of the 5 function scales (physical, role, emotional, cognitive, and social) and global health status/QoL will be produced. Symptom improvement rate and QoL/function improvement rate will be analyzed by comparing between treatment arms using a logistic regression model as described for the analysis of ORR. The odds ratio and 95% CI for each scale/item will be presented graphically on a forest plot.

Time to deterioration will be presented using a Kaplan-Meier plot for each of the 3 symptom scales (fatigue, pain, and nausea/vomiting), 5 individual symptom items (dyspnea, insomnia, appetite loss, constipation, and diarrhea), 5 functional scales (physical, role, emotional, cognitive, and social), and global health status/QoL. Summaries of the number and percentage of patients experiencing a clinically meaningful deterioration or death and the median time to deterioration will also be provided for each treatment arm.

Summaries of original and change from baseline values of each symptom scale/item, the global HRQoL score, and each functional domain will be reported by visit for each treatment arm. Graphical presentations may also be produced as appropriate. Summaries of the number and percentage of patients in each response category at each visit for each ordinal item (in terms of the proportion of patients in the categories of improvement, no change, and deterioration as defined in Section 8.4.3.1) will also be produced for each treatment arm.

8.5.4.3 PRO-CTCAE

PRO-CTCAE data will be presented using summaries and descriptive statistics based on the FAS. Further details will be provided in the SAP.

8.5.5 Safety data

Safety and tolerability data will be presented by treatment arm using the safety population.

Data from all cycles of treatment will be combined in the presentation of safety data. AEs (both in terms of MedDRA preferred terms and CTCAE grade) will be listed individually by patient. The number of patients experiencing each AE will be summarized by treatment arm and CTCAE grade. Additionally, data presentations of the rate of AEs per person-years at risk may be produced. Any safety summaries examining retreatment with MEDI4736

monotherapy and MEDI4736 + tremelimumab combination therapy will be produced separately.

Other safety data will be assessed in terms of physical examination, clinical chemistry, hematology, vital signs, and ECGs. Exposure to MEDI4736 monotherapy, MEDI4736 + tremelimumab combination therapy, and SoC will be summarized. Time on study and MEDI4736 monotherapy, MEDI4736 + tremelimumab combination therapy, and SoC combination therapy dose delays/interruptions will also be summarized. At the end of the study, appropriate summaries of all safety data will be produced, as defined in the SAP.

8.5.6 Pharmacokinetic data

PK concentration data will be listed for each patient and each dosing day, and a summary provided for all evaluable patients.

8.5.6.1 Immunogenicity analysis

Immunogenicity results will be listed by patient and a summary will be provided of the number and percentage of patients who develop detectable anti-MEDI4736 or anti-tremelimumab antibodies. The immunogenicity titer and neutralizing ADA data will be listed for samples confirmed positive for the presence of anti-MEDI4736 or anti-tremelimumab antibodies.

The effect of immunogenicity on PK, pharmacodynamics, efficacy, and safety will be evaluated if data allow.

8.5.7 Pharmacokinetic/pharmacodynamic relationships

If the data are suitable, the relationship between PK exposure and efficacy/safety parameters may be investigated graphically or using an appropriate data modelling approach.

8.5.8 Biomarker data

The relationship of PD-L1 expression and if applicable, of exploratory biomarkers to ORR, DoR, DCR, PFS, PFS2, PFS3, and PFS6 will be presented for a subset of patients in the ITT population who are evaluable for each biomarker.

This will be assessed using similar summary and graphical representations to those that are outlined for the efficacy outputs in Sections 8.5.1.

PD-L1 expression determined by IHC assay will be reported in the CSR. Summaries and analyses for exploratory biomarkers will be documented in a separate analysis plan and will be reported outside the CSR in a separate report.

8.5.9 Healthcare resource use

An exploratory health economic analysis of hospital episodes including type of contact (hospitalization, outpatient, or day case), reason, length of stay by ward type (including intensive care unit), procedures, and tests may be undertaken to examine the impact of disease

and treatment on resource use to primarily support the economic evaluation of MEDI4736 and MEDI4736 + tremelimumab in comparison to SoC. The analysis will be reported separately.

8.5.10 Interim analysis

An interim analysis when 15 evaluable patients are observed in Part A will use predictive probability to determine whether either arm may stop (based on <10% predictive probability of meeting the minimum criteria to initiate Part B). Should it become obvious that the continuation criteria have been met prior to completion of enrollment of Part A, then the decision to initiate Part B (either Expansion or the RCT) may be made early.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first patient is enrolled in the study, an AstraZeneca representative will review and discuss the requirements of the CSP and related documents with the investigational staff and train them in any study-specific procedures and IVRS/IWRS, WBDC, and any electronic PRO systems to be utilized.

The PI will ensure that appropriate training relevant to the study is given to all of these staff and that any new information relevant to the performance of this study is forwarded to the staff involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, biological samples are handled in accordance with the Laboratory Manual, and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study), including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)

- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of or destroyed accordingly, and the action is documented and reported to the patient.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the center need information and advice about the study conduct.

9.2.1 Source data

Refer to the CSA for location of source data.

Source data are any data generated as a result of the patient's inclusion in the study (including run-in and/or follow-up related to the study) and include all related medical examinations and other records.

9.2.2 Direct access to source data in Japan

The Head of the study site and the PI/Investigator will cooperate for monitoring and audit by AstraZeneca and accept inspection by the IRB or regulatory authorities. All study documents, such as raw data, will be open for direct access to source data at the request of the monitor and the auditor of AstraZeneca, the IRB, or regulatory authorities.

The monitor(s) will verify data from the eCRFs against source data before the PI signs the eCRFs to ensure accuracy and completeness of documentation and ensure that the PI has submitted the eCRFs to AstraZeneca. If the Investigator wishes to amend the collected eCRFs, the monitor will ensure that the PI has recorded the amendment with signature and date and provided this to AstraZeneca.

9.2.3 Study agreements

The PI at each center should comply with all the terms, conditions, and obligations of the CSA for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of patients. In all other respects not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the PI should be in place before any study-related procedures can take place or before any patients are enrolled.

9.2.4 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

The end of the study is defined as "the last visit of the last patient undergoing the study." The Investigator will be notified by the Sponsor when recruitment is complete.

The study is expected to start in Q3 2015 and to end by Q3 2020.

The study may be terminated at individual centers if the study procedures are not being performed according to Good Clinical Practice (GCP) or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study involving MEDI4736 or tremelimumab.

9.4 Data management by AstraZeneca or delegate

Data management will be performed by a chosen vendor according to the Data Management Plan. AEs and medical/surgical history will be classified according to the terminology of the latest version of MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary. Classification coding will be performed by the chosen vendor.

The data collected through third party sources will be obtained and reconciled against study data.

Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed, and locked, clean file will be declared. Any treatment-revealing data may thereafter be added, and the final database will be locked.

Serious adverse event reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data management of genotype data

Please see [Appendix D](#) for details.

Data associated with human biological samples

Data associated with human biological samples will be transferred from laboratories internal or external to AstraZeneca.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation

(ICH)/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

The applicable regulatory requirements in Japan are “Good Clinical Practice for Trials on Drugs” (Ministry of Health, Labor, and Welfare [MHLW] Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications.

10.2 Patient data protection

The ICF will incorporate wording that complies with relevant data protection and privacy legislation. In some cases, such wording will be in a separate accompanying document.

Please see [Appendix D](#) for further details.

10.3 Ethics and regulatory review

An EC/IRB should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable EC/IRB and to the study site staff.

The opinion of the EC/IRB should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrollment of any patient into the study.

The EC/IRB should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC/IRB annually.

Before enrollment of any patient into the study, the final study protocol, including the final version of the ICF, should be approved by the national regulatory authority or a notification to the national regulatory authority should be approved, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, EC/IRBs, and PIs with safety updates/reports according to local requirements.

Each PI is responsible for providing the EC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the PI so that he or she can meet these reporting requirements.

10.4 Informed consent

The PI(s) at each center will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study
- Ensure each patient is notified that her or she is free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an EC/IRB.

For sites in Japan only

If any new information on the study medication becomes available that may influence the decision of the patient to continue the study, the Investigator(s) should inform the patient of such information immediately, record this in a written form, and confirm with the patient if he or she wishes to continue the participation in the study. In addition, if the Investigator(s) deem it necessary to revise the ICF, he or she should revise it immediately (refer to Section 10.5). The Investigator(s) should re-explain the patients using an updated ICF even if the patients have already been informed of the new information verbally. Written informed consent to continue participation in the study should be provided separately.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca. If it is necessary for the study protocol to be amended, the amendment should be submitted to the Head of the Study Site and be approved by its IRB. If applicable, AstraZeneca should submit a notification to the regulatory authority before it is implemented. If a protocol amendment requires a change to a particular center's Informed Consent Form, then AstraZeneca and the center's IRB should be notified. Approval of the revised ICF by AstraZeneca and by the IRB is required before the revised form is used. If an administrative change is required, such a change should be notified to or approved by each IRB according to local requirements.

10.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an EC/IRB may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and to determine if data were recorded, analyzed, and accurately reported according to the protocol, GCP, ICH guidelines, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

For Japan sites: All study data may undergo a reliability review and onsite-GCP inspection by the regulatory authorities.

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Clinical Study Protocol Appendix B

Drug Substance	MEDI4736 and Tremelimumab
Study Code	D4198C00001
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Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

“Life-threatening” means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient’s death. “Life-threatening” does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability, or incapacity but may jeopardize the patient or may require medical intervention to prevent 1 or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a “reasonable possibility” that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?
- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, or other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A “reasonable possibility” could be considered to exist for an AE where 1 or more of these factors exist.

In contrast, there would not be a “reasonable possibility” of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Ambiguous cases should be considered as being a “reasonable possibility” of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

MEDI4736 DRUG-DRUG INTERACTIONS

There is no information to date on drug-drug interactions with MEDI4736 either pre-clinically or in patients. As MEDI4736 is a monoclonal antibody and therefore a protein, it will be degraded to small peptides and amino acids and will be eliminated by renal and reticuloendothelial clearance. It is therefore not expected that MEDI4736 will induce or inhibit the major drug metabolising cytochrome P450 pathways. As a result, there are no expected pharmacokinetic drug-drug interactions. The mechanism of action of MEDI4736 involves binding to PD-L1, and therefore significant pharmacodynamic drug interactions with the commonly administered concomitant medications are not expected. Despite this, appropriate clinical monitoring in all of the planned clinical studies will be conducted to evaluate any potential drug-drug interactions.

Clinical Study Protocol Appendix C

Drug Substance	MEDI4736 and Tremelimumab
Study Code	D4198C00001
Edition Number	2
Date	17 August 2015

Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance
Document

LABELING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B, or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability or life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens, eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, B, C, D, and E viruses, human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations that require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Clinical Study Protocol Appendix D

Drug Substance MEDI4736 and
Tremelimumab

Study Code D4198C00001

Edition Number 2

Date 17 August 2015

Appendix D
Pharmacogenetics Research

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
CSR	Clinical Study Report
DNA	Deoxyribonucleic acid
LIMS	Laboratory information management system
PGx	Pharmacogenetics

1. BACKGROUND AND RATIONALE

AstraZeneca intends to perform genetic research in the MEDI4736 clinical development program to explore how genetic variations may affect the clinical parameters associated with this drug combination. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Future research may suggest other genes or gene categories as candidates for influencing not only response to MEDI4736, but also susceptibility to pancreatic ductal adenocarcinoma for which MEDI4736 may be evaluated. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to pancreatic ductal adenocarcinoma and MEDI4736 treatment.

2. GENETIC RESEARCH OBJECTIVES

The objective of this research is to collect and store DNA, derived from a blood sample, for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) of MEDI4736 and/or susceptibility to pancreatic ductal adenocarcinoma.

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Selection of genetic research population

3.1.1 Study selection record

All enrolled patients will be asked to participate in this genetic research (Substudy 3 only). Participation is voluntary, and if a patient declines to participate, there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

3.1.2 Inclusion criteria

For inclusion in this genetic research, patients must fulfill all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

3.1.3 Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant

- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

3.1.4 Discontinuation of patients from this genetic research

Specific reasons for discontinuing a patient from this genetic research are:

Withdrawal of consent for genetic research: patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 3.9 of the main Clinical Study Protocol.

3.2 Collection of samples for genetic research

The blood sample for genetic research will be obtained from the patients at baseline after randomization. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), as these patients would be important to include in any genetic analysis. Only 1 sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

If the patient agrees to participate, a 9-mL blood sample will be collected.

3.3 Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years from the date of last patient last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrollment/randomization code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

4. ETHICAL AND REGULATORY REQUIREMENTS

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 10 of the main Clinical Study Protocol.

4.1 Informed consent

The genetic component of this study is optional, and the patient may participate in other components of the main study (Substudy 3 only) without participating in the genetic component. To participate in the genetic component of the study, the patient must sign and date both the consent form for the main study (Substudy 3) and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study center. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that he or she may freely discontinue from the genetic aspect of the study at any time.

4.2 Patient data protection

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a patient's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

5. DATA MANAGEMENT

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyze the samples.

The results from this genetic research may be reported separately from the CSR for the main study.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

7. LIST OF REFERENCES

None

Clinical Study Protocol Appendix E

Drug Substance	MEDI4736 and Tremelimumab
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Appendix E
Actions Required in Cases of Increases in Liver Biochemistry and
Evaluation of Hy's Law

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1. INTRODUCTION

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on the managing liver abnormalities can be found in Section 5.2.1 of the protocol and in the Dosing Modification and Toxicity Management Guidelines.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\geq 3 \times$ upper limit of normal (ULN) **together with** total bilirubin (TBL) $\geq 2 \times$ ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)

AST or ALT $\geq 3 \times$ ULN **together with** TBL $\geq 2 \times$ ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL to be met the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- $ALT \geq 3 \times ULN$
- $AST \geq 3 \times ULN$
- $TBL \geq 2 \times ULN$

If a central laboratory is used

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Section 2 of this appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

If a local laboratory is used

The Investigator will, without delay, review each new laboratory report and if the identification criteria are met will:

- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss, and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. If a central laboratory is used, this includes deciding which the tests available in the Hy's law lab kit should be used.
- Complete the 3 Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term “Hy’s Law”) according to AstraZeneca standard processes.
 - The “Medically Important” serious criterion should be used if no other serious criteria apply
 - As there is no alternative explanation for the HL case, a causality assessment of “related” should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term “Potential Hy’s Law”) applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

6. ACTIONS REQUIRED WHEN POTENTIAL HY’S LAW CRITERIA ARE MET BEFORE AND AFTER STARTING STUDY TREATMENT

This section is applicable to patients with liver metastases who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the patients’ condition[#] compared with the last visit where PHL criteria were met[#]

- If there is no significant change no action is required
- If there is a significant change notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Section 4.2 of this Appendix

[#] A “significant” change in the patient’s condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

7. ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY’S LAW

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study, eg, chronic or progressing malignant disease, severe infection or liver disease, or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Section 6?

If No: follow the process described in Section 4.2 of this Appendix

If Yes:

Determine if there has been a significant change in the patient’s condition[#] compared with when PHL criteria were previously met

- If there is no significant change, no action is required
- If there is a significant change, follow the process described in Section 4.2 of this Appendix

[#] A “significant” change in the patient’s condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of

whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

8. REFERENCES

FDA Guidance for Industry (issued July 2009) “Drug-induced liver injury: Premarketing clinical evaluation”:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>.

Clinical Study Protocol Appendix F

Drug Substance MEDI4736 and Tremelimumab

Study Code D4198C00001

Edition Number 2

Appendix Date 17 August 2015

Appendix F
Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1
Criteria (Response Evaluation Criteria in Solid Tumors)

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1. INTRODUCTION

This appendix details the implementation of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines ([Eisenhauer et al 2009](#)) for the D4198C00001 study with regards to Investigator assessment of tumor burden including protocol-specific requirements for this study.

2. DEFINITION OF MEASURABLE, NON-MEASURABLE, TARGET AND NON-TARGET LESIONS

Only patients with measurable disease at baseline should be included in the study. Measurable disease is defined by the presence of at least one measurable (by RECIST 1.1) lesion which has not been previously irradiated. A tumor lesion in a previously irradiated field can be assessed as measurable disease provided the lesion has been deemed to demonstrate progression.

Measurable:

A lesion, not previously irradiated per the protocol prior to enrollment, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements. A tumor lesion in a previously irradiated field can be assessed as measurable disease provided the lesion has been deemed to demonstrate progression.

Non-measurable:

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm short axis at baseline¹).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Lesions < 2 cm biopsied within the screening period (fresh tumor biopsy)

¹ Nodes with < 10 mm short axis are considered non-pathological and should not be recorded or followed as non-target lesions (NTLs).

- Previously irradiated lesions that have not demonstrated progression²
- Brain metastasis

Special cases:

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.
- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected as target lesions (TLs).

Target lesions:

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TLs at baseline.

Non-target lesions:

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

3. METHODS OF ASSESSMENT

The same method of assessment and the same technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits.

A summary of the methods to be used for RECIST assessment is provided in [Table 1](#), and those excluded from tumor assessments for this study are highlighted with the rationale provided.

² Localized post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated and have not demonstrated progression will not be considered measurable and must be selected as NTL at baseline and followed up as part of the NTL assessment.

Table 1 Summary of methods of assessment

Target lesions	Non-target lesions	New lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Clinical examination	Clinical examination
	X-ray, Chest X-ray	X-ray, Chest X-ray
		Ultrasound
		Bone scan
		FDG-PET

CT Computed tomography; FDG-PET 18-Fluoro-deoxyglucose positron emission tomography; MRI Magnetic resonance imaging.

3.1 CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and identification of any new lesions.

In the D4198C00001 study, the methods of assessment of tumor burden used at baseline and follow-up visits are CT / MRI of the chest and abdomen, pelvis only when suspected or documented disease involvement. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients. CT examination with intravenous contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For brain lesion assessment, MRI is the preferred method.

3.2 Clinical examination

In the D4198C00001 study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as TLs if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

3.3 X-ray

3.3.1 Plain X-ray

In the D4198C00001 study plain X-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

3.4 Ultrasound

In the D4198C00001 study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumor size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

3.5 Endoscopy and laparoscopy

In the D4198C00001 study, endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor assessment.

3.6 Tumor markers

In the D4198C00001 study, tumor markers will not be used for tumor response assessments as per RECIST 1.1.

3.7 Cytology and histology

In the D4198C00001 study histology will not be used as part of the tumor response assessment as per RECIST 1.1.

3.8 Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

In the D4198C00001 study, isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and X-ray is recommended where bone scan findings are equivocal.

3.9 FDG-PET scan

In the D4198C00001 study, 18-Fluoro-deoxyglucose positron emission tomography (FDG-PET) scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive 18-Fluoro-deoxyglucose uptake³ not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

³ A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

4. TUMOR RESPONSE EVALUATION

4.1 Schedule of evaluation

RECIST assessments will be performed using CT/MRI assessments of the chest and abdomen, pelvis only when suspected or documented disease involvement. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before start of study treatment, and ideally should be performed as close as possible to the start of study treatment (see Table 2 of the Clinical Study Protocol). Follow-up assessments will be performed every 6 weeks ($q6w \pm 7$ days) for the first 48 weeks relative to the date of the first infusion, and $q12w \pm 7$ days thereafter until confirmed objective disease progression.

Additional assessments will be performed post confirmed objective disease progression for patients remaining on assigned treatment, re-treatment, or until subsequent cancer therapy according to the clinical study protocol.

Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimize any unintentional bias caused by some patients being assessed at a different frequency than other patients.

4.2 Target lesions

4.2.1 Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts.
- If two or more TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention eg, radiotherapy, embolization, surgery, during the study, the size of the TL should still be provided where possible.

4.2.2 Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumor visit response for TL (see [Table 2](#)).

Table 2 Evaluation of target lesions

Complete Response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progression of disease (PD)	At least a 20% increase in the sum of diameters of TLs, 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.
Not Evaluable (NE)	Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. Note: if the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; SD Stable disease; TL Target lesion.

4.3 Non-target lesions

4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit (see [Table 3](#)).

Table 3 Evaluation of non-target lesions

Complete response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non CR/Non PD	Persistence of one or more NTL.
Progression (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: for patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; NTL Non-target lesion; TL Target lesion.

To achieve “unequivocal progression” on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of stable disease or partial response in TLs, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest “increase” in the size of 1 or more NTLs is usually not sufficient to qualify for unequivocal progression status.

4.4 New lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor.

If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

4.5 Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with “symptomatic deterioration” requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumor assessments where possible until objective disease progression is observed.

4.6 Evaluation of overall visit response

The overall visit response will be derived using the algorithm shown in [Table 4](#).

Table 4 Overall visit response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NE	Non PD or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR Complete response, PR Partial response, SD Stable disease, PD Progression of disease, NE Not evaluable, NA Not applicable (only relevant if there were no non-target lesions at baseline).

5. CONFIRMATION OF PROGRESSION

In the D4198C00001 study, imaging for confirmation of response (complete response or partial response) should be performed at next scheduled visit (and no less than 4 weeks) following the date the criteria for response were first met.

Disease progression requires confirmation. The confirmatory scan should occur preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of progression of disease (PD) in the absence of clinical deterioration.

Progression would be considered confirmed if the following criteria are met:

- $\geq 20\%$ increase in the sum diameters of TLs compared with the nadir at 2 consecutive visits with an absolute increase of 5mm ⁽¹⁾
- And/or significant progression (worsening) of NTLs or new lesions at the confirmatory PD time-point compared with the first time point where progression of NTLs or new lesions identified
- And/or additional new unequivocal lesions at the confirmatory PD time-point compared with the first time point new lesions identified.

⁽¹⁾ The assessment of progression requires a $\geq 20\%$ increase in the sum diameters of target lesions at the first progression timepoint relative to the nadir. The nadir is the smallest sum of diameters, and this may be at baseline or subsequent follow-up assessments. The confirmatory scan confirms the persistence of the $\geq 20\%$ increase relative to the nadir. The minimum absolute increase in the sum of diameters of target lesions is at least 5 mm at both assessments.

In the absence of significant clinical deterioration the Investigator should continue assigned treatment until progression is confirmed. If progression is not confirmed, then the patient should continue on assigned treatment and on treatment assessments.

If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression, then the patient should still continue to be followed until confirmed objective disease progression.

6. CENTRAL REVIEW

The Contract Research Organization appointed by AstraZeneca to perform the independent central review for this study will provide specification for radiological imaging protocols in standard acquisition guidelines documentation.

7. REFERENCES

Eisenhauer et al 2009

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

Clinical Study Protocol Appendix G

Drug Substance	MEDI4736 and Tremelimumab
Study Code	D4198C00001
Edition Number	2
Date	17 August 2015

Appendix G
Patient Reported Outcomes: EORTC QLQ-C30, EORTC QLQ-PAN26,
PRO-CTCAE, and EQ-5D-5L



EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

--	--	--	--

Your birthdate (Day, Month, Year):

--	--	--	--	--	--	--	--	--	--

Today's date (Day, Month, Year):

31

--	--	--	--	--	--	--	--	--	--

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor

Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor

Excellent





EORTC QLQ - PAN26

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Have you had abdominal discomfort?	1	2	3	4
32. Did you have a bloated feeling in your abdomen?	1	2	3	4
33. Have you had back pain?	1	2	3	4
34. Did you have pain during the night?	1	2	3	4
35. Did you find it uncomfortable in certain positions (e.g. lying down)?	1	2	3	4
36. Were you restricted in the types of food you can eat as a result of your disease or treatment?	1	2	3	4
37. Were you restricted in the amounts of food you could eat as a result of your disease or treatment?	1	2	3	4
38. Did food and drink taste different from usual?	1	2	3	4
39. Have you had indigestion?	1	2	3	4
40. Were you bothered by gas (flatulence)?	1	2	3	4
41. Have you worried about your weight being too low?	1	2	3	4
42. Did you feel weak in your arms and legs?	1	2	3	4
43. Did you have a dry mouth?	1	2	3	4
44. Have you had itching?	1	2	3	4
45. To what extent was your skin yellow?	1	2	3	4
46. Did you have frequent bowel movements?	1	2	3	4
47. Did you feel the urge to move your bowels quickly?	1	2	3	4
48. Have you felt physically less attractive as a result of your disease and treatment?	1	2	3	4

Please go to the next page

During the past week:

	Not at all	A little	Quite a bit	Very much
49. Have you been dissatisfied with your body?	1	2	3	4
50. To what extent have you been troubled with side-effects from your treatment?	1	2	3	4
51. Were you worried about your health in the future?	1	2	3	4
52. Were you limited in planning activities, for example meeting friends, in advance?	1	2	3	4
53. Have you received adequate support from your health care professionals?	1	2	3	4
54. Has the information given about your physical condition and treatment been adequate?	1	2	3	4
55. Have you felt less interest in sex?	1	2	3	4
56. Have you felt less sexual enjoyment?	1	2	3	4



Health Questionnaire

English version for the UK

SAMPLE

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about ☐
- I have slight problems in walking about ☐
- I have moderate problems in walking about ☐
- I have severe problems in walking about ☐
- I am unable to walk about ☐

SELF-CARE

- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe 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 doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

PAIN / DISCOMFORT

- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

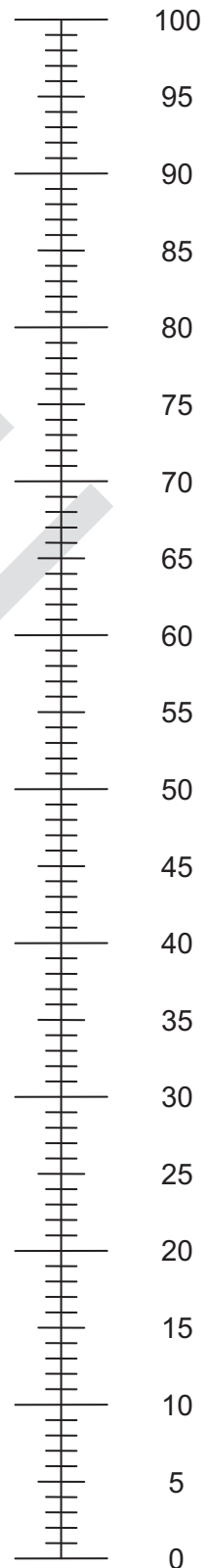
ANXIETY / DEPRESSION

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health
you can imagine



The worst health
you can imagine

PATIENT-REPORTED OUTCOMES VERSION OF THE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (PRO-CTCAE) ITEM LIBRARY

Attention/Memory

- Concentration*
- Memory

Cardio/Circulatory

- Swelling*
- Heart Palpitations

Sleep/Wake

- Insomnia*
- Fatigue*

Neurological

- Numbness & tingling*
- Dizziness

Sexual

- Achieve and maintain erection
- Ejaculation
- Desire
- Orgasm
- Pain w/sexual Intercourse

Cutaneous

- Rash*
- Skin dryness
- Acne
- Hair loss*
- Hand-foot syndrome
- Hives
- Itching
- Nail loss
- Nail ridging
- Nail discoloration
- Sensitivity to sunlight
- Pressure sores
- Radiation skin reaction
- Skin darkening
- Stretch marks

Pain

- General pain*
- Headache*
- Muscle pain
- Joint pain

Respiratory

- Shortness of breath*
- Cough
- Wheezing

Mood

- Anxious*
- Discouraged
- Sad*

Gastro-Intestinal

- Taste changes*
- Decreased appetite*
- Nausea*
- Vomiting*
- Heartburn
- Gas
- Bloating
- Hiccups
- Constipation*
- Diarrhea*
- Abdominal pain
- Fecal incontinence

Gynecologic/Urinary

- Vaginal bleeding
- Missed menstrual periods
- Vaginal discharge
- Vaginal dryness
- Painful urination
- Urinary urgency
- Urinary frequency
- Change in usual urine color
- Urinary incontinence

Miscellaneous

- Breast swelling and tenderness
- Bruising
- Chills
- Increased sweating
- Decreased sweating
- Hot flashes
- Nosebleed
- Pain and swelling at injection site
- Body odor

Visual/Perceptual

- Blurred vision
- Flashing lights
- Visual floaters
- Watery eyes
- Ringing ear

Oral

- Dry mouth*
- Difficulty swallowing
- Mouth/throat sores*
- Cracking at the corners of the mouth (cheilosis)
- Voice quality changes
- Hoarseness



*Denotes core item