AstraZeneca

Clinical Study Protocol

Drug Substance	MEDI4736 and AZD5069
Study Code	D4198C00003
Edition Number	5.0
Date	08 February 2018

A Phase Ib and II Open-Label, Multi-Center Study of MEDI4736 Evaluated in Different Combinations in Patients with Metastatic Pancreatic Ductal Adenocarcinoma

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VERSION HISTORY

Version 5.0, 08 February 2017
Main changes to the protocol are summarised below,

Substantial changes:

1. Synopsis, Section 2.2 (Secondary objectives of Cohort 1 and Cohort 2), Section 8.4.3.2 (Pharmacokinetic analysis)
   - **Rationale for change**: Serum and plasma are used as matrices for PK analysis. Standard noncompartment methods will not be used due to low volume of data
2. Section 1.3.2.1 (Potential risks MEDI4736), Section 6.7.1.1 and Appendix E
   - **Rationale for update**: updated to reflect MEDI4736 (Durvalumab) Investigational Brochure Edition 12
3. Section 1.3.2.2 (Potential risks AZD5069)
   - **Rationale for change**: Neutropenia/Neutrophil count decreased is considered expected for regulatory purposes in the respiratory indication only, and not yet in the oncology population (change arising from alignment with the CTFG Guidelines).
4. Section 8.4.2.3 (Safety assessments) and Section 8.5.1 (Efficacy data)
   - **Rational for change**: Additional sensitivity analysis for Overall Response Rate was removed as it will not be conducted due to lack of meaningful contribution to the interpretation of the data

In addition, there are non-substantial changes made in the protocol amendment that are listed below. These are inclusive of administrative changes made to the amendment, clarifying existing protocol text and correcting existing discrepancies between different sections of protocol.

Please note: Minor clerical corrections are not detailed in this Summary of Changes document.

Non substantial changes:

1. Section 8.4.2.4 (Secondary endpoints): Corrected errors in disease control rate

Version 4.0, 17 July 2017
Main changes to the protocol are summarised below,

Substantial changes:

1. Synopsis, Section 1.2, Section 6.7.: Language was updated to reflect the initial dosing of AZD5069 at 80 mg po bid, with provision for dose reductions described in Section 6.7.3. Text throughout protocol has been updated for consistency.
   - **Rationale for update**: updated to reflect that the adopted current RP2D for AZD5069 from the D5660C00004 (SCORES) study. The revised dosing scheme (previously included as Appendix F in the previous version of this

protocol) is now presented in the toxicity management section of our study (section 6.7.3).

2. Synopsis, Section 2 & Section 8: Primary objective was clarified to be inclusive of safety and tolerability of MEDI4736 + AZD5069 in combination, thus separate safety objective was removed.
   - **Rationale for clarification**: the protocol had originally separated out safety as a separate safety objective. This has now been clarified that safety is primary objective which now aligns with the statistical analysis plan for the study.
3. Section 1.1.2: Section has been updated to include the most current clinical data available for MEDI4736.
   - **Rationale for change**: to update background data based on updated IB
4. Synopsis & Section 3.1: Inclusion criteria #3 text was simplified and Cohort 2 progression timeline for prior therapy was removed.
   - **Rationale for change**: Significant simplification and clarification of entry criterion #3 has been taken in response to investigator feedback and queries about eligibility. Limiting the patient population to PDAC patients with metastatic disease and a single prior line of therapy is intended to make the patient population more homogeneous. This will enhance our ability to understand the meaning of responses without compromising the primary endpoint in this initially small study.
5. Section 3.1, section 3.3, Section 4, Section 5.1: Added inclusion criteria #9 (cohort 2) for taking mandatory tumor biopsy in screening period (or <45 days prior to first dosing if adequate tissue samples are available). Text throughout protocol has been updated for consistency.
   - **Rationale for change**: this has been the intent of the original protocol but discrepancy between protocol sections has been addressed and the intent is reflected more clearly via addition of the requirement in eligibility criteria and in schedule of procedures.

In addition, there are non-substantial changes made in the protocol amendment that are listed below. These are inclusive of administrative changes made to the amendment, clarifying existing protocol text and correcting existing discrepancies between different sections of protocol.

Please note: Minor clerical corrections are not detailed in this Summary of Changes document.

Non substantial changes:

1. Synopsis: Statistical methods for Cohort 1 narratives will be replaced with programmed listings.
2. Section 1.1.3: Section formatting was corrected.
3. Section 3.1 & Section 7.2: Inclusion criteria #7 SI units were added.
4. Section 4, Section 5.1: Clarification for archival tumor sample at screening, that they are mandatory to be collected, if available.
5. Section 4: Clarification regarding sample requirements.

6. Section 5.5: Clarification that there will be no exploratory biomarker research on samples from cohort 1 patients.
7. Section 5.5.1.2: Clarification on sample handling.
8. Section 5.5.1.1: Clarification that there will be no exploratory biomarker research on samples from cohort 1 patients.
9. Section 5.5.3: AZD5069 data will also be pooled with biomarker data from other studies.
10. Appendix F deleted since text was incorporated in Section 6.7.3.

Version 3.0, 14 December 2016
Main changes to the protocol are summarised below,

All Sections: Language has been updated to reflect the current enrolment status of Cohort 1 as recruitment has been permanently stopped in this Cohort.

All Sections: Language has been updated to reflect the how analysis of Cohort 1 will change as recruitment was stopped after only 3 patients had been enrolled.

Synopsis: Added an additional International Coordinating Investigator for Cohort 2.

Synopsis, Objectives Cohort 1: Objectives have been updated as only 3 patients will be available for analysis.

Synopsis, Objectives Cohort 2: Objectives have been updated to reflect the new exploratory objectives for the Cohort 2 population.

Synopsis, Investigational product, dosage and mode of administration: Section has been updated to include language on how dosing will be managed in Cohort 2, including details regarding a dosing regimen currently being established in study D4660C00004.

Section 1.1.2: Language has been added to clarify that MEDI4736 may also be referred to as durvalumab throughout the protocol and other study documents. AstraZeneca has recently agreed upon this non-proprietary name.

Section 1.1.3: Section has been updated to include the most current clinical data available for AZD5069.

Section 1.1.4: Section has been updated to include the most current clinical data available for AZD5069.

Section 1.2.1: Section has been updated to include the most current clinical data available for MEDI4736.

Section 1.2.3: Language has been edited to clarify the rationale for combination dosing with MEDI4736 and AZD5069.

Section 1.2.4: Section has been updated to include the most current clinical data available for AZD5069.

Section 1.3.1.2: Section has been updated to include the most current clinical data available for AZD5069.

Section 1.4: Pharmacokinetics has been added to the list of evaluable data to remain consistent with the study objectives.

Section 1.4.1: Section has been updated to reflect the current status of Cohort 1.

Figure 1: Figure has been updated to reflect the fact that recruitment into Cohort 1 was permanently stopped after 3 patients had been enrolled.

Objectives, Cohort 1: Objectives have been updated as only 3 patients will be available for analysis.

Objectives, Cohort 2: Objectives have been updated to reflect the new exploratory objectives for the Cohort 2 population.

Section 3.1: Inclusion criteria #3 Cohort 2 progression timeline for prior therapy was updated to $\leq$ 6 months.

Section 3.2: Exclusion criteria #11 was update to include chemotherapy induced nausea and vomiting.

Section 3.2: Exclusion criteria #14 was updated to remove “psoriasis not requiring systemic treatment”.

Section 3.2: Exclusion #16 was updated to include prostate cancer.

Section 3.2: Exclusion #19 was updated to match the most current PSSR language for MEDI4736.

Section 3.9: Discontinuation criteria #9 was updated to remove “and Investigator determination that the patient is no longer benefiting from treatment with IP”.

Table 2: Updated to remove all PK and biomarker collection requirements as these are no longer required for the objectives of the Cohort 1 population.

Table 3: Updated to include the collection of circulating soluble factors (serum and plasma), Pharmacogenetic sample, ctDNA and updated collection times of MDSC and PBMCs.

Table 4: Updated to remove all PK, immunogenicity and biomarker collection requirements as these are no longer required for the objectives of the Cohort 1 population.

Table 5: Updated to include the collection of ctDNA.

Section 5.2.3: Updated to specify that 12-Lead ECGs will be recorded in triplicate for Cohort 2 at specified times.

Section 5.4.5: Updated to reflect current AstraZeneca standard sample storage language.

Section 5.4.7: Updated to reflect current AstraZeneca standard sample storage language.

Section 5.5: Updated to reflect which samples will be analysed for each Cohort.

Section 5.5.1.1: Updated to specify tumor biopsy requirements for the Cohort 2 population, including mandatory and optional samples and the types of potential analyses to be conducted on the collected tissue.

Section 5.5.1.2: Updated to further define the exploratory biomarker plan for the Cohort 2 population.

Section 5.6: Pharmacogentics section was added as this is now a requirement for the Cohort 2 population.

Section 6.7.1.1: Added a header to separate "Adverse events of special interest" from the previous paragraph.

Section 6.7.3: Added toxicity management for AZD5069 40 mg starting dose.

Section 7.1: Updated the dosage table to reflect an additional AZD5069 tablet strength.

Section 7.1.3: Updated to reflect that an additional AZD5069 tablet strength is available.

Section 7.2.1.2: Updated to reflect that a 20mg dose of AZD5069 may be used in the study.

Section 7.2.3: Removed all DLT evaluation language. As the Cohort has been closed for enrollment, no further consideration of DLT is required.

Section 7.2.5: Section added to include DLT information for Cohort 2.

Section 8.2.1: Updated to reflect the currently enrollment status of Cohort 1.

Table 10: Updated the probability table data.

Section 8.2.2: Updated the wording surrounding DLT criteria and patient numbers.

Table 11: Updated the probability table data.

Table 12: Added table of Posterior Probabilities of True DLT Incidence > 33% with Various priors as well as explanatory text.

Section 8.3, Table 13: Updated to reflect that the Full analysis set will be used in some outcome variables.

Section 8.4.1.3: The disease control rate will be evaluated at 6 and 12 months, instead of 3 months.

Section 8.4.3.3: Section was updated to clarify how immunogenicity results will be analysed.

Section 8.5: Clarified that data from Cohort 1 will only be listed.

Section 11: The list of references was update where required.

Appendix E: Updated to include the most current version of "MEDI4736 Dosing Modification and Toxicity Management Guidelines".

Appendix F: Added information regarding the dose toxicity management and alternative dosing regimen for AZD5069 80 mg BID currently under exploration.

Version 2.0, 29 Mar 2016
Main changes to the protocol are summarised below,

- Version history and appendices are added due to template update (toxicity management guidelines to stay as Appendix E).
- Clarification of section 1.2.4 and 7.2.1.2 regarding dose of AZD5069 used in this study.
- Updating of section 1.3.2.1 regarding reference to IB for latest risk profile of MEDI4736.
- Updating of section 1.3.2.2 to be consistent with the recent AZD 5069 IB v8.0 changes (addendum dated 13 December, 2015).
- Clarification of section 3.1 and protocol synopsis regarding inclusion criteria #3, 9.
- Clarification of section 3.2 regarding exclusion criteria #14, 15, 20.
- Clarification of criteria to replace withdrawn patients in cohort 1/2 in section 3.3 and definition of 'evaluable patient' for Cohort 2 clarified.
- Clarification of section 3.8 regarding use, type and period of contraceptions before, during and after the trial.
- ECG frequency for Cohort 2 modified on Table 3.

- Clarification of footnote b, d, j of Table 2 & 3.
- Removal of section regarding the tumor assessment in patients who omit day 15 dose administrationsection 5.1.
- Removal of the requirements for central reading of scans in section 5.1.1.
- ECG frequency for Cohort 2 updated to screening and day 1 of each cycle to match the evaluation on Study D5660C00004.
- Clarification of vital signs collection time point pre-dose, during and post-dose in section 5.2.4.
- Amending sections 5.4.5, 5.4.7, 5.5.5 regarding the Biobank used in the study.
- Clarification that the recording of adverse events in section 6.3 also refers to the AESIs.
- Clarification of AESIs associated with MEDI4736 in section 6.7.1.
- Removal of dose reduction or modification guidance of AZD5069 in section 6.7.3 as this document does not exist.
- Clarification of MEDI4736 dosage and strength in section 7.1.
- Removal of table 9 from section 7.1.1
- Removal of the omission of day 15 treatment in case of patient toxicity in section 7.2.1.1.
- Figure 3 updated to correct week schedule of MEDI4736 dose 7.
- Added clarification in section 7.7 that the use of cannabinoids must be avoided in patients administered with AZD5069 alone and in combination with MEDI4736.
- Removal of the overall survival text from section 8.4.1.2, as it is the duplicate of the paragraph in section 8.4.1.3.
- Corrected errors in disease control rate and progression free survival calculation in section 8.4.1.3.
- Removal of "lesions <2 cm biopsied within the screening period (fresh tumor biopsy)" as a non-measurable lesion in Appendix D as it does not pertain to imaging/RECIST.
- Clarification of section 9.3 regarding the start date of the study.

- Removal of sPD-L1 tests thoughout the protocol as sPD-L1 will no longer be analyzed in the study.
- Updated toxicity management guidelines in Appendix E to current version (dated 02 Oct 2015).
- Minor administrative changes and inconsistency errors throughout the protocol.

Version 1.0, 24 Aug 2015 Changes to the protocol are summarised below,
Initial creation

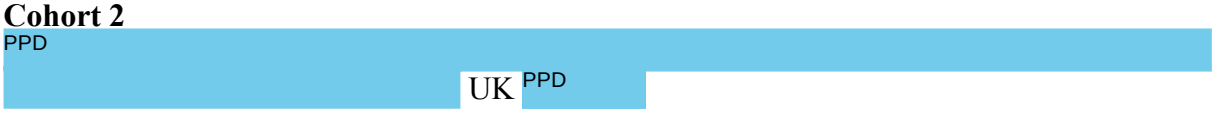
PROTOCOL SYNOPSIS

A Phase Ib and II Open-Label, Multi-Center Study of MEDI4736 Evaluated in Different Combinations in Patients with Metastatic Pancreatic Ductal Adenocarcinoma

International Coordinating Investigators

Cohort 1

Cohort 2



Number of patients planned

This study will consist of 2 cohorts. Cohort 1 has enrolled 3 patients who received MEDI4736 in combination with nab-paclitaxel + gemcitabine. Cohort 2 will enroll approximately 16 evaluable patients to receive MEDI4736 in combination with AZD5069, a CXC chemokine receptor-2 inhibitor.

Study period		Phase of development
Estimated date of first patient enrolled	Q4 2015	Ib and II
Estimated date of last patient completed	Q4 2018	Ib and II

Study design

This study will evaluate the safety, tolerability, pharmacodynamics, and antitumor activity of MEDI4736 in combination with chemotherapy and novel anticancer agents in patients with pancreatic ductal adenocarcinoma (PDAC).

This study will consist of 2 independent cohorts, each of which will run at separate times.

Cohort 1 is a Phase Ib, open-label, dose exploration assessment of the safety, tolerability, antitumor activity, and pharmacokinetics (PK) of MEDI4736 in combination with the nab-paclitaxel + gemcitabine chemotherapy regimen in patients with metastatic PDAC who are treatment-naïve. Initially, 3 patients have been enrolled into a safety run-in period and will also be evaluated for anti-tumor efficacy of this combination. At present, no further expansion of this cohort is planned.

Cohort 2 is a Phase II, open-label, multicenter assessment of the safety and preliminary antitumor activity of MEDI4736 in combination with AZD5069 in patients with metastatic PDAC whose disease has progressed on 5-fluoropyrimidine (5-FU)-containing or gemcitabine-containing first-line chemotherapy. Initially, 6 evaluable patients will be enrolled into a safety run-in period. The dosing regimen employed will be that established by the D5660C00004 trial currently in progress. This regimen involves initial dosing of AZD5069 at 80 mg po bid, with provision for dose reductions described in Section 6.7.3 of the protocol. After this, approximately 10 additional evaluable patients will be enrolled providing defined safety criteria are met.

Tumor assessments will be performed every 8 weeks ±7 days (Cohort 1) or every 6 weeks ±7 days (Cohort 2) for the first 48 weeks relative to the date of first infusion and then every 12 weeks ±7 days thereafter for both cohorts until confirmed progressive disease (PD), with categorization of objective tumor response by Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1).

Objectives

Cohort 1: First-line, Phase Ib, MEDI4736 + nab-paclitaxel + gemcitabine chemotherapy

Primary objective:	**Outcome measure:**
To assess the safety and tolerability of MEDI4736 in combination with nab-paclitaxel + gemcitabine	Occurrence of dose-limiting toxicities AEs, physical examinations, laboratory findings (including clinical chemistry, hematology, and urinalysis), vital signs (including blood pressure and pulse), electrocardiograms (ECGs)

Secondary objectives:	**Outcome measures:**
To assess the efficacy of MEDI4736 in combination with nab-paclitaxel + gemcitabine in terms of ORR, DoR, DCR, PFS, and OS	ORR, DoR, DCR, and PFS using Investigator assessments according to RECIST 1.1, and OS.
To assess the PK of MEDI4736 and the combination of MEDI4736 and nab-paclitaxel + gemcitabine	Concentration of MEDI4736/nab-paclitaxel + gemcitabine in serum or plasma and PK parameters (such as peak concentration and trough, as data allow; sparse sampling only)

Cohort 2: Second-line, Phase II, MEDI4736 + AZD5069

Primary objective:	**Outcome measure:**
To assess the safety, tolerability and ORR of MEDI4736 + AZD5069 in combination.	Occurrence of dose-limiting toxicities AEs, physical examinations, laboratory findings (including clinical chemistry, hematology, and urinalysis), vital signs (including blood pressure and pulse), electrocardiograms (ECGs), and ORR using Investigator assessments according to RECIST 1.1

Secondary objectives:	**Outcome measures:**
To further assess the efficacy of MEDI4736 +AZD5069 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
To investigate the relationship between PD-L1 expression by IHC and efficacy parameters	ORR, DoR, DCR, and PFS across PD-L1 expression using Investigator assessments according to RECIST 1.1 OS
To investigate the immunogenicity of MEDI4736 in combination with AZD5069	Presence of ADAs for MEDI4736 (confirmatory results: positive or negative; titers)
To assess the PK of MEDI4736 and the combination of MEDI4736 and AZD5069	Concentration of MEDI4736/AZD5069 in serum or plasma and PK parameters (such as peak concentration and trough, as data allow; sparse sampling only)

Exploratory objectives:	**Outcome measures:**
Evaluate changes in blood-borne biomarkers that may correlate with treatment or clinical response	Assessments may include, but are not limited to, measurement of gene expression, immune cell types, soluble factors such as cytokines and chemokines, T-cell receptor repertoire, circulating tumor DNA and activation and proliferation markers at baseline and with treatment.
Evaluate tumor-based biomarkers in archival tumor samples that may correlate with treatment or prospectively identify patients likely to respond to treatment	Assessments may include tumor genetics, characterisation of immune infiltrates, gene expression signatures, T cell repertoire, or other stratification markers.
To collect and store deoxyribonucleic acid (DNA) for future exploratory research	Future exploratory research may include but is not limited to exploration of genes/genetic variation that may influence response (i.e. distribution, safety, tolerability and efficacy) to treatment.

Exploratory objectives:	Outcome measures:
Collect and store tumor, blood, plasma, and serum samples or analyse surplus blood or tissue including patient-specific archival tumor tissue, if available	Samples may be used for potential future exploratory research into factors that may influence development of the tumor or response to treatment (where response is defined broadly to include efficacy, tolerability, or safety). In the event that additional tumor molecular profiling is required to understand further any response to treatment, AstraZeneca may request a sample of the most recent tumor biopsy for additional research. Any sample collection can be discontinued or suspended at the discretion of the Sponsor, without need for a protocol amendment.

Target subject population

Cohort 1: Patients (aged ≥18 years) with histologically or cytologically confirmed metastatic PDAC who have received no previous systemic chemotherapy, targeted therapy, immunotherapy, or investigational agents (except adjuvant or neoadjuvant therapy if progression occurred >6 months from last treatment for adjuvant or surgery for neoadjuvant).

Cohort 2: 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 prior standard first-line 5-FU-containing or gemcitabine-containing chemotherapy.

Duration of treatment

Treatment in both cohorts will be administered until confirmed PD, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. In cases of toxicity and at the Investigator's discretion, patients will be permitted to stop treatment with one agent of their combination therapy regimen and continue treatment with the other agent as monotherapy, using the same dose and regimen as previously administered. These patients may continue to receive MEDI4736 alone (until confirmed PD, withdrawal of consent, or another discontinuation criterion is met), or nab-paclitaxel + gemcitabine alone (Cohort 1 only) or AZD5069 alone (Cohort 2 only) (until the first assessment of disease progression [ie, unconfirmed PD], withdrawal of consent, or another discontinuation criterion is met).

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

Investigational product, dosage, and mode of administration

<u>Cohort 1: First-line, Phase Ib, MEDI4736 + nab-paclitaxel + gemcitabine chemotherapy</u>

- 1.5 g MEDI4736 via intravenous (IV) infusion every 4 weeks (q4w), starting at Week 0, until confirmed PD or another discontinuation criterion is met.

- 125 mg/m^2 nab-paclitaxel and 1000 mg/m^2 gemcitabine via IV infusion, both administered on Days 1, 8 and 15 of each 28-day cycle (ie, 1 cycle = weekly for 3 weeks, then 1 week off) until confirmed PD or another discontinuation criterion is met (Patients receiving nab-paclitaxel + gemcitabine as monotherapy, without MEDI4736, will receive treatment until the first assessment of disease progression [ie, unconfirmed PD], withdrawal of consent, or another discontinuation criterion is met).

Cohort 2: Second-line, Phase II, MEDI4736 + AZD5069

- 1.5 g MEDI4736 via IV infusion q4w, starting at Week 0, until confirmed PD or another discontinuation criterion is met.

- The current recommended Phase 2 dose (RP2D) determined for AZD5069 in the dose escalation phase of Study D5660C00004 will be employed. This regimen entails initial dosing of AZD5069 at 80 mg po bid with defined dose reduction criteria based on peripheral blood neutrophil counts. Details of these criteria are described in Secion 6.7.3. Dosing will continue until confirmed PD or another discontinuation criterion is met.

Statistical methods

Cohort 1: First-line, Phase Ib, MEDI4736 + nab-paclitaxel + gemcitabine

Safety and tolerability, and the occurrence of dose limiting toxicity, will be evaluated through adverse events (AEs), physical examinations, laboratory and vital sign measures, and electrocardiograms. Secondary endpoints, including objective response rate (ORR), duration of response (DoR), disease control rate (DCR), and progression-free survival (PFS), will be summarized based on Investigator assessments according to RECIST 1.1. PFS, overall survival (OS), and DoR will be described using programmed listings due to the capping of enrollment at 3 patients for this arm.

Similarly, immunogenicity results will be provided as a programmed listing capturing which patients develop detectable anti-MEDI4736, anti-nab-paclitaxel or anti-gemcitabine antibodies.

PK concentration data will be listed for each patient and each dosing day.

Cohort 2: Second-line, Phase II, MEDI4736 + AZD5069

Safety and tolerability will be evaluated through adverse events (AEs), physical examinations, laboratory and vital sign measures, and electrocardiograms, using summary statistics. Secondary endpoints, including ORR, DoR, DCR, PFS, proportion of patients alive and progression-free after 3 months (PFS3) and proportion of patients alive and progression-free after 6 months (PFS6), will be summarized based on Investigator assessments according to RECIST 1.1. PFS, PFS3, PFS6, OS, proportion of patients alive at 6 months from first dose (OS6), proportion of patients alive at 12 months (OS12), and DoR rates and their medians will

be calculated and plotted using Kaplan-Meier estimates, with 95% CIs. Efficacy parameters will also be summarized and explored as appropriate according to PD-L1 expression levels.

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

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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
AUCss	Area under the plasma drug concentration-time curve at steady state
β-hCG	Beta-human chorionic gonadotropin
BCRP	Breast cancer resistance protein
bid	Twice daily
BoR	Best objective response
BP	Blood pressure
CD	Cluster of differentiation
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
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
CXCL17	Chemokine (C-X-C motif) ligand 17
CXCR2	CXC chemokine receptor-2
CYP	Cytochrome P450
DCR	Disease control rate

Abbreviation or special term	Explanation
DLT	Dose-limiting toxicity
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
EGFR	Epidermal growth factor receptor
ESMO	European Society for Medical Oncology
EU	European Union
FOLFIRINOX	Multidrug combination of leucovorin, fluorouracil, irinotecan, and oxaliplatin
fT_3	Free triiodothyronine
fT_4	Free thyroxine
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's Brochure
ICAM2	Intercellular adhesion molecule 2
ICF	Informed consent form
ICH	International Conference on Harmonisation
IFN-γ	Interferon-gamma
IgG	Immunoglobulin G
IHC	Immunohistochemical
IL	Interleukin
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

Abbreviation or special term	Explanation
IWRS	Interactive Web Response System
LFT	Liver function test
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 enrollment
OS12	Proportion of patients alive at 12 months from enrollment
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-1	Programmed cell death 1
PDAC	Pancreatic ductal adenocarcinoma
PD-L1	Programmed cell death ligand 1
PFS	Progression-free survival
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
PI	Principal Investigator
PK	Pharmacokinetics
PR	Partial response
PS	Performance status
q2w	Every 2 weeks

Abbreviation or special term	Explanation
q3w	Every 3 weeks
q4w	Every 4 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks
q12w	Every 12 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
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
SoC	Standard of care
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). MEDI4736 may also be referred to by its recently agreed on, non-proprietary name (durvalumab) in this protocol and elsewhere. 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 with PDAC (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.

To date durvalumab has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Section 1.3.2.1 and Section 6.7. Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.1.3 AZD5069

AZD5069 is a highly selective and potent small-molecule CXC chemokine receptor-2 (CXCR2) antagonist. CXCR2 was recently identified as a novel target for modulating tumor immunity (Di Mitri et al 2014, Highfill et al 2014). Tumor signaling of PD-1 (CD279) on T cells and expansion of myeloid-derived suppressor cells (MDSCs) are major mechanisms of tumor immune escape. CXCR2 regulates the trafficking of MDSCs to the tumor (Highfill et al 2014), and CXCR2 inhibition was found to retard tumor progression both alone and in combination with docetaxel (Di Mitri et al 2014). Further, when tumor trafficking of MDSCs was inhibited by CXCR2 deficiency anti-PD-1 treatment induced significant antitumor effects in established tumors (Highfill et al 2014).

Studies have suggested that CXCR2 is expressed in various PDAC cell lines and is primarily involved in enhancing the proliferation and survival of cancer cells through the autocrine and paracrine effect (Steele et al 2016, Takamori et al 2000). Specifically, expression of CXCR2 is increased in later stages of PDAC, indicating that CXCR2 is involved with the growth and proliferation of this tumor type (Hussain et al 2010). Based on these findings, blocking the CXCR2 pathway could be used therapeutically to enhance antitumor immune responses in patients with PDAC. Results of multiple nonclinical studies have supported this hypothesis, as well. Blocking the CXCR2 complex reduced cell proliferation and cell invasion of PDAC cells (Wang et al 2013) and has also been demonstrated to prolong survival in a state-of-the-art GEMM model of pancreatic cancer (Steele et al 2016).

Most recently, preliminary data from the dose escalation part the D5660C00004 trial in solid tumor patients treated in combination with AZD5069 and MEDI4736 has been obtained. As of 7 July 2016, safety and limited efficacy information from 11 subjects initially treated with AZD5069 40 mg bid and an additional 12 subjects started on AZD5069 80 mg bid was available. During this portion of the trial, an initial RP2D of 80 mg po bid in combination with durvalumab was agreed upon by the safety review committee.

AZD5069 was also previously evaluated in Phase I studies involving healthy volunteers, as well as patients with chronic obstructive pulmonary disease (COPD) and with bronchiectasis. There have also been 2 Phase II studies in patients with chronic or neutrophilic asthma. A Phase Ib/II study (Study D5660C00004) of AZD5069 in combination with MEDI4736 in patients with advanced solid malignancies and squamous cell carcinoma of the head and neck is currently being conducted under Investigational New Drug Application 125391.

As of April 2015, AZD5069 has been studied in 8 completed Phase I clinical studies in a total of 255 healthy volunteers, of whom 202 received AZD5069 (single doses up to 200 mg; multiple doses up to 80 mg twice daily (bid) for up to 7 days and 100 mg bid for up to 6.5 days). Three 4-week studies have been conducted in patients: 87 patients with COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stage II to III) who received50 mg and 80 mg bid/placebo, 52 patients with bronchiectasis (80 mg bid/placebo), and 5 patients with neutrophilic asthma (45 mg bid). A Phase II efficacy study in 640 patients with persistent uncontrolled asthma has also been completed (478 patients received AZD5069

at doses of 5 mg bid, 15 mg bid, or 45 mg bid, while 162 patients received placebo for 6 months).

Details on the safety profile of AZD5069 are summarized in section 1.3.2.2. Refer also to the current AZD5069 IB for a complete summary of nonclinical and clinical information. No additional expected risks from the combination of AZD5069 with durvalumab treatment have been identified at this time.

1.1.4 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.

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 CTL-mediated apoptosis through Fas- or perforin/granzyme-mediated pathways (Emens and Jaffee 2005).

Chemotherapy, even at conventional doses, can eliminate 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 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), adoptive cell therapy (eg, T cells expressing chimeric antigen receptors), and vaccines (eg, sipuleucel-T).

CXC chemokines display pleiotropic effects in mediating immune response, angiogenesis, and metastases and deregulation of CXC chemokines occurs in late-stage PDAC (Fokas et al 2015). The CXCR2 ligand, CXCL5, is overexpressed in patients with PDAC and is significantly correlated with advanced disease stage and poor outcome. CXCR2-knockout mice harboring PDAC presented impaired recruitment of endothelial progenitor cells from bone marrow that resulted in decreased angiogenesis and tumor growth. (Hiraoka et al 2011) showed that the chemokine (C-X-C motif) ligand 17 (CXCL17) mediated intratumoral infiltration of immature dendritic cells, while the intercellular adhesion molecule 2 (ICAM2) facilitated CD8+ cell-mediated cytotoxicity and tumor cell killing. Interestingly, during tumorigenesis progression from precursor lesions to PDAC, downregulation of CXCL17 and ICAM2 tempered immune response that led to immune tolerance. Furthermore, blockade of TGF-β receptor II in a mutant Kras mouse model resulted in an aggressive disease phenotype with increased secretion of CXCL1 and CXCL5 ligands. Of note, CXCR2 expression was higher in stromal fibroblasts compared to epithelial cells, whereas signaling attenuation using a CXCR2 inhibitor decreased vessel density and improved survival in tumor-bearing mice.

Recent work from Highfill and others (Highfill et al 2014) shows that murine rhabdomyosarcoma (RMS) primarily induces the expansion of granulocytic $CXCR2^{+}CD11b^{+}Ly6G^{hi}$ MDSCs, and demonstrates that CXCR2 is required for trafficking of these MDSCs to the tumor bed.

In addition, a study reported by Steele et al. demonstrated an important potential role for CXCR2 in pancreatic ductal adenocarcinoma (Steele et al 2016). Their work demonstrated that high expression of CXCR2 at the tumor border was associated with more rapid progression in 44 patients. Using a genetically modified mouse model of this disease (KPC mice, *LSL-Kras$^{G12D/+}$; LSL-Trp53$^{R172H/+}$; Pdx1-Cre*), these investigators further demonstrated the presence of CXCR2-expressing myeloid cells within developing tumors and that simultaneous small molecule inhibition of CXCR2 by AZ13381758, (an AZD5069 congener) and gemcitabine can significantly enhance survival.

MDSC-mediated suppression of antitumor immunity is a local phenomenon limited to the tumor bed because inhibition of MDSC trafficking to the tumor enhances the potency of PD-1 checkpoint blockade (Highfill et al 2014). This work identifies CXCR2 as a new target for therapies aimed at inhibiting MDSC recruitment and provides a rationale for combining immune checkpoint inhibitors with agents designed to prevent MDSC-mediated immune suppression for cancer therapy.

Based on the preliminary clinical efficacy and safety data observed in the pancreatic cancer cohort of Study 1108, this study is being conducted to determine the safety and tolerability of the combination of MEDI4736 with chemotherapy or novel anticancer agents in patients with 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 dose rationale

A dose of MEDI4736 20 mg/kg every 4 weeks (q4w) is supported by in-vitro data, non-clinical activity, clinical pharmacokinetics (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 every 2 weeks (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 soluble PD-L1 [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. For further information on immunogenicity, please see the current IB.

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 area under the plasma drug concentration-time curve (AUC) at steady state (AUC_{ss}) (4 weeks). Median maximum plasma concentration at steady state ($C_{max,ss}$) is expected to be higher with 20 mg/kg q4w (~1.5 fold), and median trough plasma concentration at steady state ($C_{trough,ss}$) 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 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

Overall, cumulatively, 765 out of 1,744 patients (43.9%) reported SAEs in the monotherapy programme. The most frequently reported SOCs were Neoplasms Benign, Malignant and Unspecified (including Cysts And Polyps) (n = 218; 12.5%) [likely in relation to the underlying cancer], Respiratory, Thoracic and Mediastinal Disorders (n = 195 11.2%) and Infections and Infestations (n = 163 9.3%). The most frequently reported SAEs were Dyspnoea (n=62), Pneumonia (n=53) and NSCLC (n=50) (artefact most likely representing progressive disease rather than an SAE). Possible immune-mediated adverse events (AEs) included: GI events (diarrhoea, colitis, enteritis, enterocolitis, pancreatitis and pancreatitis acute), endocrine events (adrenal insufficiency, hyperthyroidism, hypothyroidism, and hypopituitarism), hepatic events (autoimmune hepatitis, hepatitis, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, liver injury and hepatic laboratory abnormality SAEs), renal events (acute kidney injury, renal failure) and respiratory events (ILD and pneumonitis). Other SAEs reported were axonal neuropathy (1), myocarditis (1) and tumour flare (1).

Partial efficacy data are available for Study CD-ON-MEDI4736-1108. Tumor assessments were based on RECIST v1.1 (Eisenhauer et al 2009). A total of 456 of 694 subjects with

advanced solid tumors treated with durvalumab 10 mg/kg Q2W were evaluable for response (defined as having ⩾ 24 weeks follow-up, measurable disease at baseline, and ⩾ 1 follow-up scan, or discontinued due to disease progression or death without any follow-up scan). In PD-L1 unselected patients, the ORR, based on investigator assessment per RECIST v1.1, ranged from 0% in uveal melanoma to 20.0% in bladder cancer, and DCR-24w ranged from 4.2% in TNBC to 39.1% in advanced cutaneous melanoma.). PD-L1 status was known for 383 of the 456 response evaluable subjects. Across the PD-L1-positive tumors, ORR was highest (> 10%) for bladder cancer, advanced cutaneous melanoma, HCC (33.3% each), NSCLC (26.7%), and SCCHN (18.2%). Moreover, in the PD-L1-positive subset, DCR-24w was highest (> 10%) in advanced cutaneous melanoma. Response rates to durvalumab 10 mg/kg IV Q2W among 30 patients with pancreatic adenocarcinoma at more than 24 weeks of followup were 2/30 subjects treated (6.7%), with a disease control rate of 5/30 (16.7%).

1.2.1.1 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 (5^{th}, median, and 95^{th} 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.

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) is included in the current study.

1.2.2 Rationale for combination MEDI4736 and chemotherapy (nab-paclitaxel + gemcitabine)

The use of combination chemotherapy has been a mainstay of oncology therapy by distributing different stages of the cell reproduction cycle. Recently, targeted agents have been combined rationally with other targeted or chemotherapeutic agents, and current

investigations are now adding immunotherapeutics to broaden responses as well as to treat resistance.

Cytotoxic chemotherapy have been shown to modulate the immune response by several mechanisms such as stimulating T-cell activation via increasing the expression of MHC-1 molecules (Liu et al 2010), stimulating dendritic cell maturation (Liu et al 2010), inducing immunogenic cell death, a form of cell death that induces dendritic cells to stimulate tumor antigen presentation to T cells (Kroemer et al 2013); and reducing the immunosuppressive function of regulatory T cells (Zhang et al 2008) and MDSCs (Kodumudi et al 2010). Combining MEDI4736, a PD-L1 antagonist, with cytotoxic agents, such as nab-paclitaxel and gemcitabine, may provide complementary benefit in mounting an effective antitumor immunity by promoting the antigen presentation, increasing the production of protective T cells and overcoming immunosuppression in the tumor bed (Mellman et al 2011). A variety of approaches for combining PD-1 pathway blockers with other agents have been explored over the past few years in an effort to both improve the efficacy of therapy and/or position the treatment regimen for testing in treatment-naïve patients with a variety of cancers. Approaches have included combinations with other checkpoint inhibitors (such as ipilimumab), immunostimulatory cytokines (eg, interferon-gamma [IFN-γ]), cytotoxic chemotherapy, anti-angiogenic inhibitors, and small-molecule molecularly targeted therapies, many with promising results and an acceptable toxicity profile (Philips and Atkins 2015).

CheckMate 012 [ClinicalTrials.gov identifier: NCT01454102] is a multi-arm Phase I study of nivolumab with various anticancer agents or as monotherapy. Preliminary results from 4 treatment arms from this study have been presented recently at the 2014 American Society of Clinical Oncology annual meeting.

In the platinum doublet arm, where 3 platinum-based chemotherapy regimens (cisplatin + gemcitabine, cisplatin + pemetrexed, and carboplatin + paclitaxel) were combined with nivolumab (n=56 patients), the ORR was 33% to 50%, 24-week PFS 36% to 71% and 1-year OS was 59% to 87% (Antonia et al 2014b). No DLTs were seen in the first 6 weeks of treatment, but 45% of patients had Grade 3 or 4 toxicities and 7% (n=4 patients) had pneumonitis. Based on these preliminary results, the antitumor activity of first-line nivolumab in combination with platinum doublets is highly promising. In the erlotinib and nivolumab arm, chemotherapy-naïve patients (n=21 patients) with epidermal growth factor receptor (EGFR) mutations were enrolled. A total of 20 patients had prior treatment with first-line erlotinib. The ORR was 19%, and the 24-week PFS was 51% (Rizvi et al 2014). Interestingly, of those with acquired erlotinib resistance, 3 patients (15%) had a PR, 9 patients (45%) achieved stable disease (SD), and 1 patient had an unconventional immune-related response. Grade 3 toxicities were reported in 19% of patients (there were no Grade 4 toxicities). Common side effects included skin rash, fatigue, paronychia, diarrhea, and skin fissures. While this combination has shown encouraging activity, the data are preliminary and validation and comparison with the third-generation EGFR tyrosine-kinase inhibitors in tumors harboring T790M mutations is still needed. Further work on the interaction between tumors harboring T790M mutations and the tumor microenvironment and immune checkpoints would also be of interest.

1.2.3 Rationale for combination of MEDI4736 and AZD5069

Combining a PD-L1 antagonist, MEDI4736, with an agent targeting immunosuppression in the tumor bed, AZD5069, is a complementary antitumor strategy, as the 2 immunotherapeutics may reasonably be expected to restore effective antitumor immunity by two separate but related mechanisms: these are promoting the effector function of T-cell responses (MEDI4736) and hindering immune escape in the tumor bed (AZD5069).

The combination of MEDI4736 with AZD5069 will be tested in this study to evaluate the safety and tolerability in patients the second-line treatment of patients with PDAC, a patient population with a limited benefit from chemotherapy. PK, immunomodulatory, and PD parameters, as well as clinical activity and biomarkers that may correlate with activity or prospectively identify patients likely to respond to the various treatments, will also be evaluated. The results from this study will form the basis for decisions for future studies.

1.2.4 AZD5069 dose rationale

The recommended Phase 2 dose levels (RP2D) of AZD5069 as determined in Study D5660C00004 (SCORES study) will be employed.

This entails initial dosing of AZD5069 at 80 mg po bid in combination with durvalumab using defined dose reduction criteria based on peripheral blood neutrophil counts. Details of this management are described Section 6.7.3. Briefly, it entails starting at AZD5069 80 mg bid and carefully monitoring neutrophil counts during the first weeks of treatment. Short dosing holds are the first response to absolute neutrophil counts $<0.5 \times 10^9$/l (referred to hereafter as Grade 4 neutrophil reductions).

In the face of prolonged Grade 4 neutrophil reductions unresponsive to dose holds, use of G-CSF is allowed twice at any given dose level; subsequent dose reductions to the next lower dosing level (80 mg bid→40 mg bid or 40 mg bid→20 mg bid) are then mandated. Of note, Grade 3 neutrophil reductions (ANC $0.5\text{-}1.0 \times 10^9$/l) without clinically significant infection are tolerated within the dose reduction scheme.

This dosing regime was developed over more than one year of experience treating patients in the SCORES trial without serious infectious complications of AZD5069 neutrophil reductions as described below.

In the SCORES study, an initially established RP2D of AZD5069 40 mg bid was arrived after observation of a single dose limiting toxicity of Grade 3 neutropenia without infectious complications (9 patients initially treated at that dose level). Among the 11 mixed solid tumor patients who received AZD5069 + Durvalumab at the next dosing level (80 mg bid), 2 exhibited reversible Grade 3 or 4 neutropenia again not associated with infectious complications during the DLT evaluation window; one complete remission of a tumor type (ER^+ breast cancer) rarely responsive to PD-(L)1 inhibition was also observed.

Because reduced peripheral blood neutrophil counts associated with CXCR2 inhibition by AZD5069 result from redistribution of mature neutrophils (myelokathexis or failure of bone

marrow release) and not from absolute reductions in the total body pool of granulocytes available to respond to infectious agents, the Safety Review Committee in the SCORES trial subsequently decided to enroll an additional cohort of up to 12 evaluable patients under a new dosing schedule for AZD5069 (80 mg bid with scheduled dose holds and titration for each patient). Based on the absence of clinically significant infections in six additional patients and also on the accumulating experience with AZD5069 in oncology patients, the dosing scheme beginning with AZD5069 80 mg po bid reproduced and outlined in Section 6.7.3 here was declared the new RP2D.

Preliminary efficacy results in the SCORES trial suggest potential benefit from the combination of AZD5069 with Durvalumab. As of 7 July 2016, 23 patients with mixed solid tumors had received AZD5069 in combination with MEDI4736 for a minimum of 6 weeks. These included 11 patients at 40 mg bid and 12 at 80 mg bid. Preliminary data at that time suggested 1 patient in the AZD5069 40 mg bid cohort had stable disease as a best response. There were 3 patients with stable disease, 2 patients with partial responses, and 1 patient with a complete response in the AZD5069 80 mg bid cohort. Efficacy analysis of these patients is ongoing.

Due to the very acute, rapidly progressive nature of pancreatic ductal adenocarcinoma, patients in the D4198C00003 study will begin receiving both AZD5069 and Durvalumab on day 1 of the first treatment cycle (no initial 7 day run-in on AZD5069 alone, as in the D5660C00004 study). Dosing will continue until confirmed PD or another discontinuation criterion is met.

In study D5660C00004, following a single dose administration, maximum AZD5069 plasma concentrations (Cmax) were observed with a median time to maximum (Tmax) occurring at 2 hrs (range: 0.5-8 hr). As assessed by geometric mean CV%, there was moderate between-subject variability in Cmax and AUC, with values ranging from 31 to 46%. As the dose increased from 40 mg (capsule) to 80 mg (tablet), Cmax and AUC0-8, increased by 2.9 and 2.57 fold, respectively. A similar trend was observed with the metabolite AZ13587715 PK..

In further support of the proposed dosing, a significant body of data from healthy volunteers and pulmonary patients also describes the safety of AZD5069 during long term administration. As of April 2015, AZD5069 had been studied in 8 completed Phase I clinical studies in a total of 255 healthy volunteers, of whom 202 received AZD5069 (single doses up to 200 mg; multiple doses up to 80 mg bid for up to 7 days and 100 mg bid for up to 6.5 days).

In addition, three major trials in pulmonary patients were completed in 87 patients with COPD (GOLD Stage II-III) (50 mg and 80 mg bid/placebo), 52 patients with bronchiectasis (80 mg bid/placebo), and in a Phase II efficacy study in 640 patients with persistent uncontrolled asthma (478 patients received AZD5069 at doses of 5 mg, 15 mg bid, or 45 mg bid, while 162 patients received placebo for 6 months). In the asthma trial, approximately 70% of patients enrolled during the first portion of the study completed a planned optional 6-month safety extension, even though that portion of the study was terminated early due to a lack of efficacy. A small study of 4 patients involving comparison of neutrophils in sputum, serum, and bronchial tissue in patients with neutrophilic asthma has also been completed.

In these pulmonary studies, up to ~30% decreases in blood neutrophil counts were seen in pulmonary patients (COPD, bronchiectasis and asthma studies) without evidence of any increase in infections that might have been related to drop in neutrophil counts. For further information concerning the healthy volunteer and pulmonary studies, please consult the current version of the Investigators Brochure for AZD5069.

1.3 Benefit/risk and ethical assessment

The following sections include summaries of the potential benefits and risks associated with MEDI4736 monotherapy and AZD5069 monotherapy, 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).

1.3.1.2 AZD5069

AZD5069 is being evaluated in the D5660C00004 (SCORES) trial and so far a complete remission in one patient with a tumor type (ER+ breast cancer) that rarely responds to PD-(L)1 blockade alone has been identified. In addition, a strong basis for expecting efficacy has been documented in preclinical literature for a number of tumor types (pancreatic, rhabdomyosarcoma, prostate). Blocking the CXCR2 complex has reduced cell proliferation and CXCR2 expression is increased in later stages of PDAC, so strong antagonism to this chemokine receptor may favorably affect host cell immune responses to PDAC tumors. Modest reductions in the numbers of peripheral blood neutrophils are to be expected and may actually prove to reflect dosing of AZD5069 at levels adequate to reduce intratumoral TANs and MDSCs, which have been hypothesized to play an important role in the tumor microenvironment, potentially downregulating host immune responses to malignancies as well as affecting tumor cell senescence.

Additional data on patients with solid tumors will be available from Study D5660C00004 prior to initiation of treatment in this study.

1.3.2 Potential risks

1.3.2.1 MEDI4736

Risks with MEDI4736 (durvalumab) include, but are not limited to, diarrhea/colitis and intestinal perforation, pneumonitis/ILD, endocrinopathies (hypo- and hyper-thyroidism, type I diabetes mellitus, hypophysitis and adrenal insufficiency) hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/pruritus/dermatitis, myocarditis, myositis/polymyositis, other rare or less frequent inflammatory events including neurotoxicities, infusion-related reactions, hypersensitivity reactions and infections/serious infections.

For information on all identified and potential risks with MEDI4736 (durvalumab) please always refer to the current version of the MEDI4736 (durvalumab) IB.

In monotherapy clinical studies AEs (all grades) reported very commonly (≥ 10% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, asthenia, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 9% of patients experienced an AE that resulted in permanent discontinuation of MEDI4736 (durvalumab) and approximately 6% of patients experienced an SAE that was considered to be related to MEDI4736 (durvalumab) by the study investigator.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (please see Section 6.7).

A detailed summary of MEDI4736 (durvalumab) monotherapy AE data can be found in the current version of the MEDI4736 (durvalumab) IB.

1.3.2.2 AZD5069

Identified risks that are currently regarded as expected terms for regulatory reporting purposes and comprise the reference safety information for AZD5069 are as follows:

Respiratory indications (non-oncology)

- Neutropenia
- Neutrophil count decreased

A reduction in blood neutrophil counts has been seen in healthy volunteers and patients participating in respiratory studies with AZD5069. Data from healthy volunteers indicate a dose related effect. The reductions in blood neutrophil counts have been asymptomatic, with a return to baseline values following the completion of the dosing regimen. In some cases this reduction in blood neutrophil counts led to neutrophil levels falling below the lower limit of the laboratory reference range.

While reduction of neutrophils in peripheral blood or sputum could have an impact on host defense with regard to infections, studies with AZD5069 in healthy subjects, and in respiratory patients with COPD, bronchiectasis, and asthma did not show an increased rate of overall infections compared with placebo. The reduction in blood neutrophil counts in these patients was modest in magnitude compared to that associated with cytoreductive therapeutics commonly employed in oncology clinics.

Oncology indications

So far in the clinical program of AZD5069 in oncology indications, although reductions in peripheral blood neutrophil counts have been observed in the ongoing D5660C00004 trial, these have been non serious, reversible, and not associated with significant clinical symptoms. No serious reports suggestive of neutrophil count decreased or neutropenia have been reported to data cut-off. *Therefore, in the oncology indications, neutropenia/neutrophil count decreased is **not** currently considered expected for regulatory reporting purposes.*

For information on potential risks of AZD5069 and further information on the safety profile of AZD5069, please refer to the current AZD5069 IB Section 6, Summary of data and guidance for the Investigators.

1.3.2.3 Overall benefit and risk assessment

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

The combination of nab-paclitaxel + gemcitabine has been approved in patients with newly diagnosed advanced pancreatic cancer based on the data generated from the 861 patients enrolled in the Phase III MPACT trial, demonstrating a median OS of 8.5 months (95% CI, 7.89 to 9.53) for the nab-paclitaxel + gemcitabine group compared with 6.7 months (95% CI, 6.01 to 7.23) for the gemcitabine monotherapy group (HR for death =0.72; 95% CI, 0.62 to 0.83; $p<0.001$). In the nab-paclitaxel + gemcitabine group, the median duration (range) of treatment was 3.9 months (0.1 to 21.9 months) compared with 2.8 months (0.1 to 21.5 months) in the gemcitabine group. The most frequently reported nonhematologic AEs related to treatment with the nab-paclitaxel + gemcitabine combination included fatigue (54%), alopecia (50%), and nausea (49%). Grade 3 or higher neutropenia, leukopenia, fatigue, and peripheral neuropathy were reported more often in the nab-paclitaxel + gemcitabine group compared with the gemcitabine monotherapy group. Peripheral neuropathy was the AE with the most notable difference between the 2 treatment groups. It was cumulative and rapidly reversible in most patients after temporary discontinuation of nab-paclitaxel and subsequent dose reduction. None of the patients experienced Grade 4 peripheral neuropathy. The rate of discontinuation of nab-paclitaxel due to peripheral neuropathy (all grades) was 8%. Overall, 10% of the patients had a dose reduction of nab-paclitaxel as a result of peripheral neuropathy.

While this will be the first study investigating the treatment of AZD5069 (in combination with MEDI4736) in patients with metastatic PDAC and further data in patients with solid tumors

will be available from Study D5660C00004, data in other CXCR2 inhibitors showed retardation of tumor progression both alone and in combination with docetaxel (Di Mitri et al 2014). Additionally, preclinical animals models have demonstrated the blocking both CXCR2 and PD-L1 versus PD-L1 blockade alone demonstrated significant antitumor effects in established tumors (Highfill et al 2014). Reduction of neutrophils in peripheral blood has been reported in AZD5069 trials and in general in this class of compound and could have an impact on host defense with regard to infections. However, so far studies with AZD5069 in healthy patients and in patients with COPD and bronchiectasis did not shown an increased rate of overall infections compared with placebo.

Treatment with agents targeting PD-1/PD-L1 (such as MEDI4736) 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. Thus, combining MEDI4736 with chemotherapy, AZD5069, or other agents may potentially offer complementary antitumor 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, nab-paclitaxel, gemcitabine, and AZD5069).

No important risks have been identified in the human studies of AZD5069 to date.

The toxicity profile of MEDI4736 monotherapy includes fatigue, nausea, diarrhea, decreased appetite, dyspnea, pyrexia, 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.

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 (1) the safety and tolerability of adding MEDI4736 to first-line SoC and (2) MEDI4736 + AZD5069 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 and potentially extending survival.

1.4 Study design

This study will evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and antitumor activity of MEDI4736 in combination with chemotherapy and novel anticancer agents in patient with PDAC. This study will consist of two independent study cohorts. Cohort 1 is a first-line, Phase Ib assessment of MEDI4736 in combination with chemotherapy. Cohort 2 is a second-line, Phase II assessment of MEDI4736 + AZD5069 with a safety run-in.

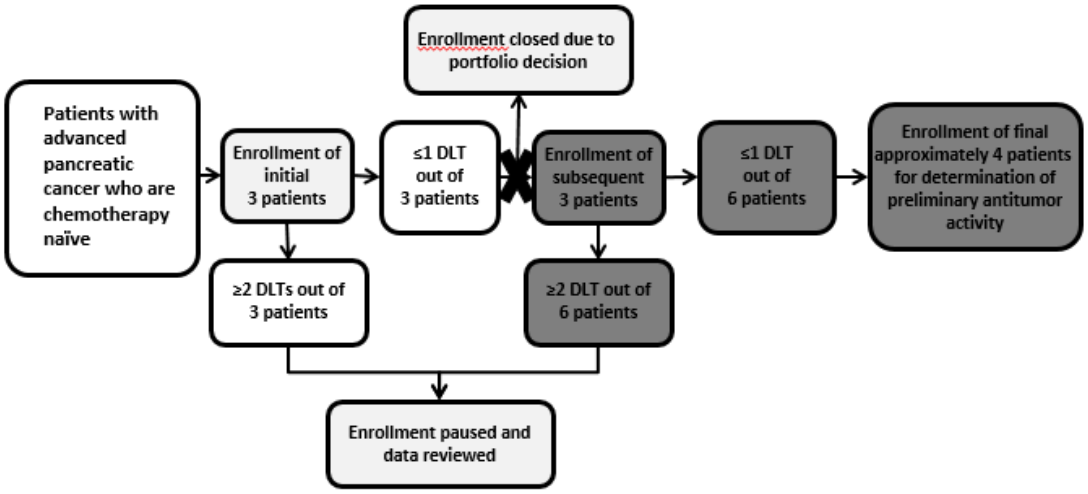
1.4.1 Cohort 1: First-line, Phase Ib, MEDI4736 + nab-paclitaxel + gemcitabine chemotherapy

Cohort 1 is a Phase Ib, open-label, dose exploration assessment of the safety, tolerability, antitumor activity, and PK of MEDI4736 in combination with the nab-paclitaxel + gemcitabine chemotherapy regimen in patients with metastatic PDAC who are treatment-naïve (defined as no prior exposure to systemic chemotherapy, targeted therapy, immunotherapy, or investigational agents [except adjuvant or neoadjuvant therapy if >6 months from last treatment]) (Von Hoff et al 2013). A schematic diagram of the Cohort 1 as initially designed Figure 1.

To date, 3 patients have been enrolled into a safety run-in period to evaluate safety, tolerability, and antitumor activity. All three patients tolerated therapy through the study's defined DLT window. Their treatment and evaluation with respect to primary and secondary objectives will continue until such time as unacceptable toxicity or progressive disease is observed. Enrollment of this cohort is currently closed due to portfolio decisions that are not related to safety or observed efficacy. See Section 7.2.4 for details on the definition of DLTs.

Doses and treatment regimens are described in Section 7.2. Assessments will be conducted as indicated in Table 2 and Table 4

Figure 1 Cohort 1 (first-line, Phase Ib MEDI4736 + nab-paclitaxel + gemcitabine chemotherapy) design



1.4.2 Cohort 2: Second-line, Phase II, MEDI4736 + AZD5069

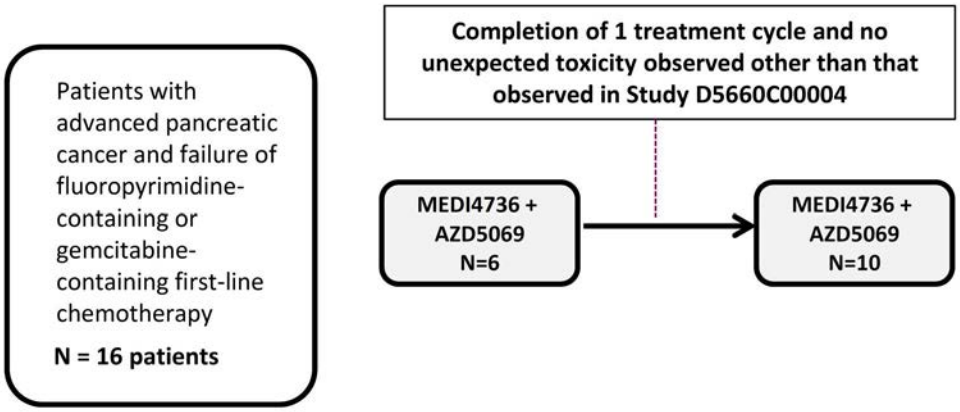
Cohort 2 is a Phase II, open-label, multicenter assessment of the safety and preliminary antitumor activity of MEDI4736 in combination with AZD5069 in patients with metastatic PDAC whose disease has progressed on a 5-FU-containing or gemcitabine-containing first-

line chemotherapy. Cohort 2 will enroll approximately 16 evaluable patients. A schematic diagram of the Cohort 2 design is shown in Figure 2.

Initially, approximately 6 patients will be enrolled into a safety run-in period to evaluate safety, tolerability, and antitumor activity. After the initial 6 patients complete 1 treatment cycle, if no unexpected toxicity meeting DLT criteria, approximately 10 additional patients will be enrolled to determine preliminary antitumor activity. All patients in this cohort, including those in the safety run-in, will be included in the preliminary antitumor activity analysis.

Doses and treatment regimens are further described in Section 7.2. Assessments will be conducted as indicated in Table 3 and Table 5.

Figure 2 Cohort 2 (second-line, Phase II MEDI4736 + AZD5069) design



2. STUDY OBJECTIVES

2.1 Primary objectives

2.1.1 Cohort 1: First-line, Phase Ib, MEDI4736 + nab-paclitaxel + gemcitabine chemotherapy

Primary objective:	Outcome measure:
To assess the safety and tolerability of MEDI4736 in combination with nab-paclitaxel + gemcitabine	Occurrence of dose-limiting toxicities AEs, physical examinations, laboratory findings (including clinical chemistry, hematology, and urinalysis), vital signs (including blood pressure and pulse), electrocardiograms (ECGs)

2.1.2 Cohort 2: Second-line, Phase II, MEDI4736 + AZD5069

Primary objective:	Outcome measure:
To assess the safety, toleratility and ORR for MEDI4736 + AZD5069 in combination.	Occurrence of dose-limiting toxicities AEs, physical examinations, laboratory findings (including clinical chemistry, hematology, and urinalysis), vital signs (including blood pressure and pulse), electrocardiograms (ECGs), and ORR using Investigator assessments according to RECIST 1.1.

2.2 Secondary objectives

2.2.1 Cohort 1: First-line, Phase Ib, MEDI4736 + nab-paclitaxel + gemcitabine chemotherapy

Secondary objectives:	Outcome measures:
To assess the efficacy of MEDI4736 in combination with nab-paclitaxel + gemcitabine in terms of ORR, DoR, DCR, PFS, and OS	ORR, DoR, DCR, and PFS using Investigator assessments according to RECIST 1.1OS
To assess the PK of MEDI4736 and the combination of MEDI4736 and nab-paclitaxel + gemcitabine	Concentration of MEDI4736/nab-paclitaxel + gemcitabine in blood and noncompartmental PK parameters (such as peak concentration and trough, as data allow; sparse sampling only)

2.2.2 Cohort 2: Second-line, Phase II, MEDI4736 + AZD5069

Secondary objectives:	Outcome measures:
To further assess the efficacy of MEDI4736 +AZD5069 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
To investigate the relationship between PD-L1 expression by IHC and efficacy parameters	ORR, DoR, DCR, and PFS across PD-L1 expression using Investigator assessments according to RECIST 1.1, OS
To investigate the immunogenicity of MEDI4736 in combination with AZD5069	Presence of ADAs for MEDI4736 (confirmatory results: positive or negative; titers)
To assess the PK of MEDI4736 and the combination of MEDI4736 and AZD5069	Concentration of MEDI4736/AZD5069 in blood and noncompartmental PK parameters (such as peak concentration and trough, as data allow; sparse sampling only)

2.3 Exploratory objectives

2.3.1 Cohort 1: First-line, Phase Ib, MEDI4736 + nab-paclitaxel + gemcitabine chemotherapy

Not applicable.

2.3.2 Cohort 2: Second-line, Phase II, MEDI4736 + AZD5069

Exploratory objectives:	Outcome measures:
Evaluate changes in blood-borne biomarkers that may correlate with treatment or clinical response	Assessments may include, but are not limited to, measurement of gene expression, immune cell types, soluble factors such as cytokines and chemokines, T-cell receptor repertoire, circulating tumor DNA and activation and proliferation markers at baseline and with treatment.
Evaluate tumor-based biomarkers in archival tumor samples that may correlate with treatment or prospectively identify patients likely to respond to treatment	Assessments may include tumor genetics, characterisation of immune infiltrates, gene expression signatures, T cell repertoire, or other stratification markers.
To collect and store deoxyribonucleic acid (DNA) for future exploratory research	Future exploratory research may include but is not limited to exploration of genes/genetic variation that may influence response (i.e. distribution, safety, tolerability and efficacy) to treatment.

Exploratory objectives:	Outcome measures:
Collect and store tumor, blood, plasma, and serum samples or analyse surplus blood or tissue including patient-specific archival tumor tissue, if available	Samples may be used for potential future exploratory research into factors that may influence development of the tumor or response to treatment (where response is defined broadly to include efficacy, tolerability, or safety). In the event that additional tumor molecular profiling is required to understand further any response to treatment, AstraZeneca may request a sample of the most recent tumor biopsy for additional research. Any sample collection can be discontinued or suspended at the discretion of the Sponsor, without need for a protocol amendment.

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.

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.)

Cohort 1 (first-line, Phase Ib, MEDI4736 + nab-paclitaxel + gemcitabine chemotherapy): treatment-naïve patients with metastatic PDAC who have received no previous systemic chemotherapy, targeted therapy, immunotherapy, or investigational agents (except adjuvant or neoadjuvant therapy if progression occurred >6 months from last treatment or surgery, respectively)

Cohort 2: Patients with metastatic PDAC will have received no more than 1 prior systemic chemotherapy regimen.

4. Life expectancy ≥ 12 weeks.

5. ECOG PS of 0 or 1

6. 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.

7. Adequate organ and bone marrow function as defined below:

   - Hemoglobin ≥9 g/dL
   - Albumin ≥3 g/dL
   - Absolute neutrophil count ≥1500/mm3 [≥1.5 x 109/l]
   - Platelet count ≥100000/mm3 [≥100 x 109/l]
   - Serum bilirubin ≤1.5 × 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 ≤2.5 × ULN; for patients with hepatic metastases, ALT and AST ≤5 × ULN
   - Serum creatinine ≤1.5 mg/dL or calculated creatinine clearance ≥40 mL/min as determined by the Cockcroft-Gault equation

8. 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 of age would be considered post-menopausal if they have been amenorrheic for 12 months or more without an alternative medical cause, following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).
   - Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more without an alternative medical cause, following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

9. Ability to undergo during screening a tumor biopsy (mandatory during screening period or taking place <45 days before beginning treatment) that is adequate for biomarker analysis. See Section 3.3 for further specifics concerning tissue samples.

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. For patients with biliary obstruction caused by PDAC, the intervention of stent placement or percutaneous biliary drainage is allowed.

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 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. 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) and chemotherapy induced nausea and vomiting

12. Cohort 2 only: Has received any potent and moderate cytochrome P450 (CYP)3A4 inhibitors, potent and moderate CYP3A4 inducers, P-glycoprotein (P-gp) substrates (digoxin and dabigatran), breast cancer resistance protein (BCRP) substrates (topotecan), sensitive CYP2B6 substrates (bupropion and efavirenz), warfarin and coumarin derivatives, or herbal supplements (see Section 7.7 for list of drugs) within 14 days of the first dose of study treatment

13. History of organ transplant that requires use of immunosuppressive agents.

14. Active autoimmune disorders , or prior documented severe autoimmune or inflammatory disorders requiring immunosuppressive treatment (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. The following are exceptions to this criterion:

    - Patients with vitiligo or alopecia
    - diabetes mellitus type I or resolved childhood asthma/athopy
    - Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement
    - Any chronic skin condition that does not require systemic therapy
    - Patients without active disease in the last 5 years may be included but only after consultation with the study physician

15. 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, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.

16. Other malignancy within 5 years except for noninvasive malignancies such as cervical carcinoma in situ, non-melanomatous carcinoma of the skin, prostate cancer or ductal carcinoma in situ of the breast that has/have been surgically cured.

17. 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).

18. History of active primary immunodeficiency.

19. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

20. Active infection including hepatitis B, hepatitis C, or human immunodeficiency virus (HIV).

21. 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.

22. 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).

23. Known allergy or hypersensitivity to IP formulations or to other human monoclonal antibodies.

24. Any condition that, in the opinion of the Investigator, would interfere with evaluation of IP or interpretation of patient safety or study results.

25. 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, or prior randomization or treament in previous MEDI4736 and/or tremelimumab clinical trials regardless of treatment arm assignment.

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrollment

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.

2. Obtain a unique 7-digit enrollment number, beginning with 'E#' (ie, the "E-Code"). 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 electronic Case Report Forms (eCRFs).

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

Note: In Cohort 2 only, patients must be able to undergo a tumor biopsy during screening (mandatory). Tumor lesions used for biopsies should not be target lesions. 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. More specific details of collecting tumor biopsy samples can be found in the laboratory/pathology manual.

Patients in both cohorts 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 cannot be reused. Withdrawn patients will not be replaced after the DLT period in cohort 1 and the safety run-in period for cohort 2. Patients in cohort 1 could be replaced if they do not meet the evaluable patient criteria (section 7.2.3) or withdraw from study during the DLT period (28 days) for reason other than toxicity. Patients in cohort 2 could be replaced during the safety run-in period if they do not complete the first cycle because of withdrawal from the study for reason other than toxicity related to the study drug.

3.4 Procedures for handling incorrectly enrolled 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 initiated on treatment and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is 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 to participate in Cohort 1 or Cohort 2 will be enrolled sequentially in that cohort. The cohorts will run at separate times.

Every effort should be made to minimize the time between enrollment and starting study drug. It is recommended that patients commence study drug as soon as possible after enrollment.

If a patient discontinues participation in the study, then their enrollment 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. Restricted therapies are described in Section 7.7.

1. Female patients of childbearing potential who are sexually active with a nonsterilized male partner must use at least one highly effective method of contraception from screening and must agree to continue using such precautions for 180 days after the final dose of IP (MEDI4736 and/or AZD5069). Patients receiving MEDI4736 in combination with nab-paclitaxel + gemcitabine (Cohort 1) must follow the contraceptive method guidelines reported in this paragraph, for their respective sex, from screening and for a minimum of 180 days, or according to local contraceptive recommendations for nab-paclitaxel or gemcitabine (whichever is longer) after last dose of therapy. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. In addition, female patients should refrain from breastfeeding and egg cell donation throughout this period.

    - 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).

- It is strongly recommended for non-sterilised male partners of a female patient to use a male condom plus spermicide throughout this period.

2. Nonsterilized males who are sexually active with a female partner of childbearing potential must use use a male condom plus spermicide from screening through 180 days after receipt of the final dose of IP. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. In addition, male patients must refrain from sperm donation for 180 days after the final dose of IP, or according to local recommendations for nab-paclitaxel or gemcitabine (whichever is longer) for patients in cohort 1.

3. It is strongly recommended for female partners (of childbearing potential) of male patients to use a highly effective method of contraception throughout this period (Table 1). Highly effective methods of contraception are described in Table 1. A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Not all methods of acceptable contraception are highly effective. Note that some contraception methods are not considered highly effective (e.g. male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

4. **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 Highly Effective methods of contraception (<1% failure rate)

Barrier/Intrauterine methods	Hormonal methods
Copper T intrauterine device	Etonogestrel implants: e.g. Implanon or Norplan
Levonorgesterel-releasing intrauterine system (eg, Mirena®)d	Intravaginal device: e.g. ethinylestradiol and etonogestrel
	Medroxyprogesterone injection: e.g. Depo-Provera
	Normal and low dose combined oral contraceptive pill
	Norelgestromin/ethinylestradiol transdermal system
	Cerazette (desogestrel)

[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 and Section 7.2
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. Patients receiving nab-paclitaxel + gemcitabine or AZD5069 as single agent therapy will discontinue treatment at first assessment of PD [ie, unconfirmed PD].

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 4and Table 5). 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 4and Table 5) 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. 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 to be used to for screen failures (ie, patients who failed screening procedures). Screen-failed patients may be rescreened once. 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.

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 4 and Table 5) should be contacted by telephone every 2 months as an alternative. Withdrawn patients will not be replaced.

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, Cohort 2 may be stopped if the criteria to proceed are not met (see Section 8.2.2). 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 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 treatment periods in this study are presented in Table 2 and Table 3, and the procedures for the follow-up period are presented in Table 4and Table 5.

Table 2 Schedule of assessments for Cohort 1 (first-line, Phase Ib, MEDI4736 + nab-paclitaxel + gemcitabine chemotherapy) treatment period

	Screening	C1			C2			C3			C4, C5, C6, etc			
		Window for each assessment: ±3 days, window for tumor assessment: ±7 days												For details see Section
Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Week (on Day 1 of the week)	**-4 to -1**	**0**	**1**	**2**	**4**	**5**	**6**	**8**	**9**	**10**	**12**	**13**	**14**	
Informed consent														
Written informed consent: study procedures/assignment of patient identification number	X													4.1
Study Procedures														
Physical examination (full)[a]	X				X			X			X			5.2.2
Targeted physical exam (based on symptoms)[a]		At all visits and as clinically indicated												5.2.2
Vital signs (pre-, during, and post-infusion vital signs assessments)[b]	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	5.2.1
Hematology[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.1

	Screening	C1			C2			C3			C4, C5, C6, etc			
		Window for each assessment: ±3 days, window for tumor assessment: ±7 days												For details see Section
Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Week (on Day 1 of the week)	**-4 to -1**	**0**	**1**	**2**	**4**	**5**	**6**	**8**	**9**	**10**	**12**	**13**	**14**	
Thyroid function tests (TSH, fT3, and fT4)[e]	X	X			X			X			X			5.2.1
Urinalysis[f]	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[h]	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			5.3.1
AE/SAE assessment	X	X	All visits											6.3
Treatment administration														
MEDI4736[j]		X			X			X			X			7.2.1.1
Gemcitabine[j]		X	X	X	X	X	X	X	X	X	X	X	X	7.2.1.1
Nab-paclitaxel[j]		X	X	X	X	X	X	X	X	X	X	X	X	7.2.1.1
Other laboratory assessments and assays														
Mandatory tumor biopsy (newly acquired or archival <3 years old)[l]	X													5.5.1.1
Archival tumor sample, if available, for patients who submit a newly acquired biopsy at screening	X													5.5.1.1

	Screening	C1			C2			C3			C4, C5, C6, etc			
		Window for each assessment: ±3 days, window for tumor assessment: ±7 days												For details see Section
Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Week (on Day 1 of the week)	**-4 to -1**	**0**	**1**	**2**	**4**	**5**	**6**	**8**	**9**	**10**	**12**	**13**	**14**	
Tumor assessment (CT or MRI)[m]	X	q8w for the first 48 weeks relative to first infusion, and q12w thereafter, until confirmed disease progression												5.1

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.

[a] Body weight recorded at all physical examinations.

[b] Blood pressure and pulse will be evaluated prior to the beginning of infusion with MED4736, approximately 30 minutes during the infusion with MEDI4736 (halfway through infusion), and 1 hour after the end of infusion with MEDI4736 (prior to start of nab-paclitaxel). Blood pressure and pulse will be evaluated upon completion of infusion with nab-paclitaxel and gemcitabine. Body temperature and respiratory rate will be evaluated pre-dose (prior to each infusion for each component IP). Vital sign assessment should implement on designated time point -5 minutes for pre-dose, ±5 minutes during treatment and +5 minutes post 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 first dose they do not need to be repeated at Day 1. Results for safety bloods must be available and reviewed before commencing an infusion. Gamma glutamyltransferase tested at screening, Day 1 (to be tested only if Day 1 is more than 3 days from screening visit) 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 tests 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] Patient will receive MEDI4736 as a 60-minute infusion, administered prior to chemotherapy every 4 weeks until confirmed PD, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. The recommended dose of nab-paclitaxel is 125 mg/m^2 intravenously on Days 1, 8 and 15 of each 28-day cycle and 1000 mg/m2 gemcitabine on Days 1, 8 and 15 of each 28-day cycle immediately after nab-paclitaxel. Patients may continue to receive MEDI4736 alone until confirmed PD, and nab-paclitaxel + gemcitabine alone until first assessment of PD.

[k] To be performed in Cycle 4 only.

[l] The newly acquired or archival (<3 years) sample must be received by the central laboratory prior to dosing. Sample is mandatory if medically feasible.

[m] 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 q8w ±7 days for the first 48 weeks (relative to the date of the first infusion) and then q12w ±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 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.

Table 3 Schedule of assessments for Cohort 2 (second-line, Phase II, MEDI4736 + AZD5069)

	Screening	C1		C2		C3	C4, C5, C6, etc	
		Window for each assessment: ±3 days, window for tumor assessment: ±7 days						
Day	**-28 to -1**	**1**	**8**	**1**	**8**	**1**	**1**	**For details see Section**
Week (on Day 1 of the week)	**-4 to -1**	**0**	**1**	**4**	**5**	**8**	**12**	
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	5.2.2
Vital signs (pre-, during, and post-infusion vital signs assessments)[b]	X	X		X		X	X	5.2.4
Electrocardiogram[c]	X	X		X		X	X	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	5.2.1
Hematology[d]	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	5.2.1
Urinalysis[f]	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[h]	X[h]	As clinically indicated					5.2.5
Coagulation parameters[i]	X	As clinically indicated						5.2.1

	Screening	C1		C2		C3	C4, C5, C6, etc	
		Window for each assessment: ±3 days, window for tumor assessment: ±7 days						
Day	**-28 to -1**	**1**	**8**	**1**	**8**	**1**	**1**	**For details see Section**
Week (on Day 1 of the week)	**-4 to -1**	**0**	**1**	**4**	**5**	**8**	**12**	
Monitoring								
ECOG performance status	X	X		X		X	X	5.3.1
AE/SAE assessment	X	X	All visits					6.3
Pharmacokinetics								
MEDI4736 PK sample (serum)		X[j]		X[j]		X[j]	X[j,k]	5.4.2
AZD5069 PK sample (plasma)		X[j]		X[j]		X[j]	X[j,k]	5.4.2
Treatment administration								
MEDI4736[l]		X		X		X	X	7.2.1.2
AZD5069[l]		Twice daily						7.2.1.2
Other laboratory assessments and assays								
Immunogenicity assessment for MEDI4736 only (ADA sampling [including ADA neutralizing antibodies] to identify ADA responses in patient circulation)		X		X		X	X[k]	5.4.6
Circulating soluble factors (serum)		X		X			X[m]	5.5.1.1
Circulating soluble factors (plasma)		X		X			X[m]	5.5.1.1
Mandatory tumor biopsy (newly acquired)[n]	X			X[o]				5.5.1.1
Archival tumor sample	X							5.5.1.1
MDSC	X	X		X		X		5.5.1.2
miRNA/mRNA (to examine immune cell gene expression profiles in circulation)		X		X				5.5.1.2
PBMCs	X	X	X	X				5.5.1.2
Pharmacogenetic (PGx) Sample		X[p]						5.6.1
ctDNA (plasma)	X	X[r]				X	X[s]	5.5.1.2

	Screening	C1		C2		C3	C4, C5, C6, etc	
		Window for each assessment: ±3 days, window for tumor assessment: ±7 days						
Day	**-28 to -1**	**1**	**8**	**1**	**8**	**1**	**1**	**For details see Section**
Week (on Day 1 of the week)	**-4 to -1**	**0**	**1**	**4**	**5**	**8**	**12**	
Tumor assessment (CT or MRI)[q]	X	q6w for the first 48 weeks relative to first infusion, and q12w thereafter, until confirmed disease progression						5.1

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.

[a] Body weight recorded at all physical examinations.

[b] Blood pressure and pulse will be evaluated prior to the beginning of the infusion, 30 minutes during infusion (halfway through infusion), and at the end of the infusion. A 1-hour observation period is recommended after the first infusion of MEDI4736. If no clinically significant infusion reactions are observed during or after the first infusion, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after infusion). 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). Vital sign assessment should implement on designated time point -5 minutes for pre-dose, ±5 minutes during treatment and +5 minutes post 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 first dose they do not need to be repeated at Day 1. Results for safety bloods must be available and reviewed before commencing an infusion. At any time per the Investigator's clinical judgment, more frequent serum or plasma chemistry, hematology, or LFT monitoring are allowed as clinically indicated. Gamma glutamyltransferase tested at screening, Day 1 (to be tested only if Day 1 is more than 3 days from screening visit) 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 tests 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 Cycle 1 Day 1 and Cycle 7 Day 1 (Week 24), 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 after end of MEDI4736 infusion). On Cycle 2 Day 1 (Week 4), Cycle 3 Day 1 (Week 8), and Cycle 4 Day 1 (Week 12), PK samples will be collected pre-dose (within 60 minutes prior to treatment with any IP only). On the day pre-dose PK samples are collected, the morning dose of AZD5069 must be administered at the study center and the exact time of administration recorded.

[k] To be performed in Cycles 4 and 7 only.

[l] Patients will receive MEDI4736 as a 60 minute infusion, administered prior to chemotherapy every 4 weeks until confirmed PD, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Patients will receive AZD5069 bid (ie, in the morning and in the evening of each day). AZD5069 should be administered 2 hours before or 2 hours after food. MEDI4736 infusions will take place in the morning at least 30 minutes after the morning administration of AZD5069. Patients may continue to receive MEDI4736 alone until confirmed PD, and AZD5069 alone until first assessment of PD.

[m] To be performed in Cycle 4 only.

[n] The newly acquired (mandatory during screening period or taking place <45 days before beginning treatment). An optional tumor biopsy on progression may also be obtained.

[o] Newly acquired tumor sample to be collected at Week 4 (-1 week/+2 weeks)

[p] A single 9ml sample of venous blood for genetic analysis will be collected at pre-dose of Cycle 1 Day 1. The date and time of collection of each sample will be recorded. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

[q] 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 ±7 days for the first 48 weeks (relative to the date of the first infusion) and then q12w ±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 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.

[r] ctDNA should be collected pre-dose at C1D1

[s] ctDNA should be collected on Day 1 of odd cycles, from C5 onward.

Table 4 Schedule of follow up assessments for Cohort 1 (first-line, Phase Ib, MEDI4736 + nab-paclitaxel + gemcitabine chemotherapy)

Evaluation	Time since last dose of IP								
	Day (±3)	Months (±1 week)						12 months and every 2 months (±2 weeks)	For details see Section
	30	2	3	4	6	8	10		
Physical examination[a]	X								5.2.2
Vital signs (temperature, respiratory rate, blood pressure, and pulse)	X								5.2.4
Weight	X								5.2.2
AE/SAE assessment	X	X	X						6.3
Concomitant medications	X	X	X						7.7
Survival status: for all patients, including phone contact with patients who refuse to return for evaluations and agree to be contacted[b]		X		X	X	X	X	X	5.1
Urine hCG or serum β-hCG	X								5.2.5
Hematology	X	X	X						5.2.1
Serum or plasma chemistry	X	X	X						5.2.1
Thyroid function tests (TSH, fT_3, and fT_4)[c]	X								5.2.1
Tumor assessment (CT or MRI)	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: q8w ±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.								5.1

[a] Full physical exam.
[b] Post-progression, patients will be followed for survival contact every 2 months (8 weeks) until death or until the end of the study.
[c] fT_3 and fT_4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

Table 5 Schedule of follow up assessments for Cohort 2 (second-line, Phase II, MEDI4736 + AZD5069)

Evaluation	Time since last dose of IP								
	Day (±3)	Months (±1 week)						12 months and every 2 months (±2 weeks)	For details see Section
	30	2	3	4	6	8	10		
Physical examination[a]	X								5.2.2
Vital signs (temperature, respiratory rate, blood pressure, and pulse)	X								5.2.4
Weight	X								5.2.2
AE/SAE assessment	X	X	X						6.3
Concomitant medications	X	X	X						7.7
Subsequent anticancer therapy	X	X	X	X	X	X	X	X	5
Survival status: for all patients, including phone contact with patients who refuse to return for evaluations and agree to be contacted[b]		X		X	X	X	X	X	5.1
Urine hCG or serum β-hCG	X								5.2.5
Hematology	X	X	X						5.2.1
Serum or plasma chemistry	X	X	X						5.2.1
Thyroid function tests (TSH, fT_3, and fT_4)[c]	X								5.2.1
Pharmacokinetic assessment (MEDI4736 only)			X						5.4.2
Immunogenicity assessment for MEDI4736 only (ADA sampling [including ADA neutralizing antibodies] to identify ADA responses in patient circulation)			X		X				5.4.6
Circulating soluble factors	X								5.5.1.2
miRNA/mRNA (to examine immune cell gene expression profiles in circulation)	X								5.5.1.2
PBMCs	X								5.5.1.2
ctDNA (plasma)	X								5.5.1.2

Evaluation	Time since last dose of IP								
	Day (±3)	Months (±1 week)						12 months and every 2 months (±2 weeks)	For details see Section
	30	2	3	4	6	8	10		
Tumor assessment (CT or MRI)	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. 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 ± 7days for the first 48 weeks and q12w ± 7 days thereafter (per **Table 3**) until confirmed PD by RECIST 1.1. Please refer to **Table 3** for timings of confirmatory scans.								5.1

[a] Full physical exam.
[b] Post-progression, patients will be followed for survival contact every 2 months (8 weeks) until death or until the end of the study.
[c] fT_3 and fT_4 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.

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 and Table 3.

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. For Cohort 2, tumor biopsies and archival tissue (the latter only if available) are mandatory for entry into the study (see Table 3 for details). 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 5

4.2 Treatment period

All procedures to be conducted during the treatment period for both cohorts will be performed according to the assessment schedules (see Table 2 and Table 3).

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 and Table 3.

4.3 Follow-up period

All procedures to be conducted during the follow-up period for both cohorts will be performed according to the assessment schedule (see Table 4 and Table 5).

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, proportion of patients alive and progression-free after 3 months (PFS3), and proportion of patients alive and progression-free after 6 months (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 D. OS, proportion of patients alive at 6 months from enrollment (OS6), and proportion of patients alive at 12 months from enrollment (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 8 weeks (q8w ±7 days; Cohort 1) or every 6 weeks (q6w ±7 days; Cohort 2) for the first 48 weeks relative to the date of the first infusion, and q12w ±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 in patients receiving MEDI4736 as monotherapy or in combination with nab-paclitaxel + gemcitabine or AZD5069; confirmation is not required for patients receiving nab-paclitaxel + gemcitabine or AZD5039 monotherapy. 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 schedules of assessments (Table 4 and Table 5). In addition, all patients will be contacted in the week following data cutoff to confirm survival status.

It is important to follow the assessment schedule as closely as possible. Refer to the study plans (Table 2 and Table 3 [screening and the treatment period], and Table 4 and Table 5 [follow up]) and Appendix D.

5.1.1 Central reading of scans

For both cohorts, an Investigator's assessment of all scans using RECIST 1.1 will be conducted (see Section 8.5 for the analysis methods). Sites will be required to store electronic copies of all scans.

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 5).

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 6 (clinical chemistry) Table 7 (hematology), and Table 8 (urinalysis).

Table 6 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 ≥2 × ULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin

b At baseline and as clinically indicated

Table 7 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 8 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 ≥3 × ULN together with total bilirubin ≥2 × ULN, refer to Appendix C 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 ≥1.5 × 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 3). 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 Electrocardiograms

Resting 12-lead ECGs will be recorded according to the assessment schedules (see Table 2 and Table 3). 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.

For Cohort 1, ECGs will be recorded at screening and as clinically indicated.

For Cohort 2, 12-Lead ECGs will be recorded in triplicate at screening and day 1 of each treatment cycle.

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 5)

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.

For Cohort 1, BP and pulse will be evaluated prior to the beginning of infusion with MED4736, approximately 30 minutes during the infusion with MEDI4736 (halfway through infusion), and 1 hour after the end of infusion with MEDI4736 (prior to start of nab-paclitaxel). Blood pressure and pulse will be evaluated upon completion of infusion with nab-paclitaxel and gemcitabine.

For Cohort 2, BP and pulse will be evaluated prior to the beginning of the infusion, 30 minutes during infusion (halfway through infusion), and at the end of the infusion. A 1-hour observation period is recommended after the first infusion of MEDI4736. If no clinically significant infusion reactions are observed during or after the first infusion, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after infusion). 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). Vital sign assessment should implement on designated time point -5 minutes for pre-dose, ±5 minutes during treatment and +5 minutes post 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 5). 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 ECOG performance status

ECOG PS will be assessed at the times specified in the assessment schedules (see Table 2 and Table 3) 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.

5.4 Pharmacokinetics

5.4.1 Collection of samples

Blood samples for determination of MEDI4736 concentration in serum, and nab-paclitaxel, gemcitabine and AZD5069 concentration in plasma will be obtained according to the assessment schedules (see Table 2 through Table 5).

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

5.4.2 Determination of drug concentration of nab-paclitaxel, gemcitabine, and AZD5069

Samples for determination of nab-paclitaxel, gemcitabine, and AZD5069 will be analyzed by Covance on behalf of Clinical Bioanalysis Alliance, AstraZeneca R&D, using appropriate bioanalytical methods.

Full details of the analytical methods used will be described in separate bioanalytical reports. All samples still within the known stability of the analytes of interest at the time of receipt by the bioanalytical laboratory will be analyzed.

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

5.4.3 Storage and destruction of pharmacokinetic samples for nab-paclitaxel, gemcitabine, and AZD5069

PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

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 clinical study report (CSR) but separately in a bioanalytical validation report.

5.4.4 Determination of drug concentration of MEDI4736

Samples for determination of MEDI4736 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.

5.4.5 Storage and destruction of pharmacokinetic samples for MEDI4736

Samples will be stored for a maximum of 15 years from the end of study, after which they will be destroyed.

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-assigned Biobank).

5.4.6 Collection of samples to measure the presence of ADAs

The presence of ADAs for MEDI4736 will be assessed in serum samples taken according to the assessment schedules (see Table 2 through Table 5).

Samples will be measured for the presence of ADAs and ADA-neutralizing antibodies for MEDI4736 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-naive validation samples will be used.

5.4.7 Storage and destruction of ADA samples

Samples will be stored for a maximum of 15 years from the end of study, after which they will be destroyed.

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-assigned Biobank).

5.5 Biomarker analysis

The patient's consent to the use of donated biological samples is mandatory. For Cohort 1, only clinical chemistry, anti-drug antibody determinations (MEDI4736), and pharmacokinetic parameters (MEDI4736, gemcitabine, and paclitaxel) will be measured where collected. For Cohort 2 only, the uses of these samples will in addition include the biomarker measurements described below.

Mandatory tumor and blood sample collections for the purpose of evaluating exploratory biomarkers (potential patient selection and mechanistic biomarkers) are described in Section 5.5.1. Samples will be taken according to the assessment schedules (see Table 2 through Table 5).

Biomarkers that have demonstrated the potential to identify patients who are likely to respond to treatment with IP (from other MEDI4736 monotherapy or other 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. There will be no exploratory biomarker research on samples from Cohort 1 patients.

5.5.1 Collection of samples

Any sample collections listed in this section may be discontinued at any time during the study at the Sponsor's discretion. See Table 2 to 5 for a schedule of sample collections.

Details of sample collection, processing, shipping, and storage for all sample collections below will be described in the Laboratory Manual.

5.5.1.1 Collection of samples for evaluation of potential patient selection markers

There will be no exploratory biomarker research on samples from Cohort 1 patients. For Cohort 2, provisions of biopsy 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 (Cohort 2 only) as described in the proceeding section. A newly acquired tumor biopsy is mandatory during screening period or taking place <45 days before beginning treatment.

  Samples should be collected via an image-guided core needle (18 gauge or larger is preferred). 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 viable tumor for downstream analyses.

  Tumor lesions planned for biopsy should may be used as index lesions for assessment of disease.

- Cohort 2 only, MANDATORY on treatment biopsy: on-treatment collection of tumor biopsies are required if clinically feasible at the timepoints indicated in Table 3 and Table 5. On treatment biopsy timing may be refined with emerging PK and/or pharmacodynamic data during the course of the trial. Failure to to obtain sufficient on-treatment tumor samples after making best efforts to biopsy the tumor will not be considered a protocol deviation. The Investigator must consult with the Study Physician if such sampling is not feasible.

- Cohort 2 only, MANDATORY archived tumor tissue: Archived tumor tissue (formalin-fixed, paraffin-embedded) for evaluation of tumor genetics and/or tumor PD-L1 expression, where such samples exist in a quantity sufficient to allow for analysis.

- Cohort 2 only, OPTIONAL: Tumor biopsy at the time of progression is encouraged. Additional tumor biopsies collected as part of clinical care (eg, for mixed responses or upon PD) can be submitted for further analysis.

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

See the Laboratory Manual for further details of requirements.

Tissue obtained as part of screening procedures for establishing PD-L1 expression may be analyzed for additional, exploratory markers /signatures at baseline and on-treatment that may correlate with response or treatment. These include but are not limited to tumor genetics, gene expression signatures (e.g. IFN-gamma signature), markers of immune suppression or activation (e.g. FoxP3 T regulatory cells, increased CD8 T effector cells, ARG1 or other markers of MDSCs that may change on treatment, particularly in response to AZD5069

therapy (Highfill et al 2014), markers of stromal architecture changes (Steele et al 2016) and T cell repertoire changes.

Tumor biopsies will be stored at AstraZeneca Research and Development or an appropriate vendor selected by AstraZeneca. Core biopsies and/or archived tissue may be used for correlative studies such as IHC assay for e.g. immune or stromal analysis, tumor mutation analysis, ribonucleic acid (RNA) analysis, proteomic analysis, immunophenotyping, and assessment of immunodiversity. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

5.5.1.2 Collection of blood samples from Cohort 2 (AZD5069 plus MEDI4736) for exploratory analyses

Blood for exploratory biomarker analyses will be obtained according to the assessment schedules presented in Table 3 and Table 5. 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. 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 blood biomarker plan is described by sample type below.

Whole blood gene expression (miRNA/mRNARNA)

Whole blood samples will be obtained at baseline and on-treatment as outlined in Table 3 and Table 5 from all patients. These samples will be used to evaluate gene expression and/or immunophenotypic changes based on genomic DNA methylation patterns associated with clinical response or treatment using nucleic acid-directed methods. Changes reflecting a potential increase in an active immune response, e.g. TH1 response, are likely to be a focus. Similar procedures may be completed using select peripheral blood mononuclear cell (PBMC) samples described below.

Circulating Myeloid derived suppressor cells (MDSC)

Flow cytometry will be carried out to quantify baseline and on-treatment circulating MDSC subtypes as baseline or decrease from baselinemay predict clinical benefit from therapy (Highfill et al 2014).

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, 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 deoxyribonucleic acid.

Soluble factors

Serum and plasma will be obtained at baseline and on- treatment as outlined in 3 and 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, CXCL9, and CXCL10 and factors associated with AZD5069 treatment (e.g. rises in CXCL8 and CXCL1). High pretreatment expressions (concentrations) of such factors may indicate active immune responses that may be augmented by checkpoint inhibitor immunotherapies; correlations with outcome data may identify patients likely to receive benefit or, alternatively,identifypatients likely to suffer drug-related AEs. Plasma samples may also be used to evaluate circulating free DNA (cfDNA) as a potential patient selection or clinical response marker.

Serum and plasma may also be used for the detection/quantification of autoantibodies (against tumor-associated antigens). Seroconversion following treatment could 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.

Circulating tumor DNA

A 10mL blood sample will be taken at each of the timepoints to provide plasma and will be used for the extraction and analysis of circulating tumor DNA (ctDNA), for the analysis of predictive biomarkers, pharmacodynamic biomarkers to interrogate changes in genetic alterations and potential mechanisms of resistance and for diagnostic purposes.

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 biomarker 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 AZD5069 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 B.

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-assigned 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

5.6.1 Collection of pharmacogenetic samples

The subject's consent to participate in the pharmacogenetic research components of the study is mandatory.

The blood sample for genetic research will ideally be obtained from the subjects at Day 1 Cycle 1, prior to dosing. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an adverse event (AE), such subjects would be important to include in any genetic analysis. If for any reason the sample is not drawn at Day 1 Cycle 1, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

5.6.2 Storage, re-use and destruction of pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication.

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 subject enrolment/randomisation 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 when the subject has requested disposal/destruction of collected samples not yet analysed.

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 AAppendix A Additional Safety Information

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6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

AEs (including AESIs) 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 (including AESIs) 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 AAppendix A Additional Safety Information

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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 ≥3 × ULN together with total bilirubin ≥2 × ULN may need to be reported as SAEs. Please refer to Appendix C 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 IB for MEDI4736.

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.
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.
- All toxicities will be graded according to NCI CTCAE, Version 4.03.

6.7.1 MEDI4736

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 Sections 6.7.2 and 6.7.3 and the Dosing Modification and Toxicity Management Guidelines in Appendix E).
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

In addition, there are certain circumstances in which MEDI4736 should be permanently discontinued (see section 3.9 of this protocol and the Dosing Modification and Toxicity Management Guidelines in Appendix E).

Following the first dose of IP, subsequent administration of MEDI4736 can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines in Appendix E of the protocol. These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to MEDI4736 regimen by the reporting investigator.Dose reductions are not permitted. In case of doubt, the Investigator should consult with the Study Physician.

6.7.1.1 Adverse events of special interest (AESIs)

Adverse events of special interest (AESIs) are events of scientific and medical interest specific to the further understanding of the MEDI4736 safety profile and require close monitoring and rapid communication by the Investigator to AstraZeneca. MEDI4736 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 this IP.

AESIs for MEDI4736 include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with MEDI4736 monotherapy and combination therapy. An immune-related adverse event (irAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate aetiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

If the Investigator has any questions in regards to an adverse event (AE) being an irAE, the Investigator should promptly contact the Study Physician.

AESIs observed with MEDI4736 include:

- Diarrhea/Colitis and intestinal perforation
- Pneumonitis / ILD
- Hepatitis/transaminase increases
- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis / serum lipase and amylase increases Myocarditis
- Myositis / Polymyositis
- Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, haematological and rheumatological events.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological aetiology are also considered AESIs.

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the MEDI4736 Investigator Brochure. More specific guidelines for their evaluation and treatment are described in detail in Appendix E.

Information on MEDI4736 AESIs and guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for MEDI4736 are provided in the Dosing Modification and Toxicity Management Guidelines in Appendix E. The most current version of the TMGs is also available through the following link: https://tmg.azirae.com. In addition a version of the current TMGs is maintained within the Site Master File. Please contact your clinical trial associate for information on how to gain access to this website.

6.7.2 Nab-paclitaxel + gemcitabine

Nab-paclitaxel and gemcitabine are associated with a number of unwanted effects. In case an AE can reasonably be attributed to nab-paclitaxel or gemcitabine, dose adjustment should be attempted before adjusting the MEDI4736 dose. Management of severe and/or intolerable suspected adverse reactions may require dose alterations and should be performed in agreement with the Summary of Product Characteristics and hospital protocol procedure.

Toxicities related to nab-paclitaxel + gemcitabine treatment should be managed as per local guidelines and the relevant approved labelling.

6.7.3 AZD5069

AZD5069, an inhibitor of CXCR2, acts by modulating neutrophil migration. Therefore, effects on blood neutrophil count, including reduction in their number (neutropenia), infections (especially requiring administration of outpatient oral or IV antibiotics) are deemed events of special interest, as are ECG abnormalities occuring after treatment with AZD5069.

Patients will initiate dosing of AZD5069 as 80 mg BID oral tablets. If a patient experiences a clinically significant and/or unacceptable toxicity, dosing of AZD5069 will be interrupted or the dose reduced with supportive therapy administered as required. For non neutropenic toxicities, if the toxicity resolves or reverts to a lower CTCAE grade within 21 days of onset and the patient is showing clinical benefit, dosing may be resumed as per Table 9 and Table 10 for events other than neutropenia associated with AZD5069. If the toxicity does not resolve to CTCAE grade 2 (grade 1 for liver function tests) after 21 days, study treatment should be permanently discontinued and the patient should be followed up for safety.

A maximum of 2 dose reductions from 80 mg bid (Figure 3) will be allowed for an individual patient. If the dose reduction is not tolerated, study treatment should be permanently

discontinued and the patient should be followed up for safety. The lowest dose of AZD5069 that may be administered is 20 mg BID.

If a patient experiences a clinically significant and/or unacceptable toxicity at these dose levels, study treatment should be permanently discontinued and the patient should be followed up for safety.

Table 9 Dose modifications for toxicity (non neutropenic and non liver toxicity events)

Examples (including and not limited to)			
Toxicity	**Recovery**	**Re-dosing**	**Notes**
Grade 3	G2[a] ≤21 days	Restart at dose level -1	If second event, then discontinue drug
	G2[a] >21 days	Discontinue study drug treatment	
Grade 4		discontinue study drug treatment	

[a] Patients starting with an abnormal baseline may restart when the lab/AE returns to pretreatment status. If thrombocytopenia is accompanied by bleeding, discontinue study drug treatment. Abbreviation: G=grade.

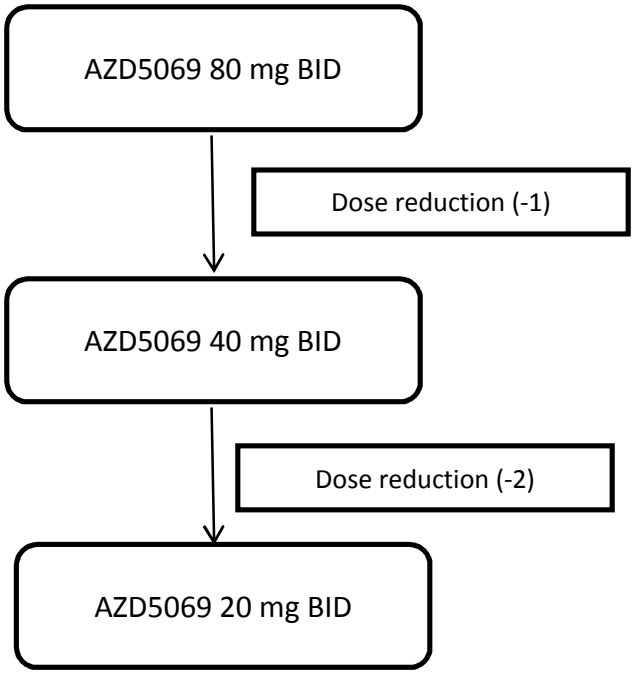
Table 10 Dose modifications for elevations in liver function tests

Toxicity	**Recovery**	**Re-dosing**	**Notes**
Grade 3	G1[a] ≤21 days	Restart at dose level -1	If second event discontinue drug
	G1[a] >21 days	Discontinue study drug treatment	
Grade 4 – and assessed by the Investigator as related to study treatment		Discontinue study drug treatment	

[a] Patients starting with an abnormal baseline may restart when the lab/AE returns to pretreatment status. If thrombocytopenia is accompanied by bleeding, discontinue study drug treatment.
Abbreviation: G=grade.

All dose reductions must be discussed case-by-case by the Investigator and the Sponsor Study Team Physician. Until this discussion occurs, dosing of study treatment must be interrupted temporarily.

Figure 3 Dose-reductions levels for AZD5069 toxicity management



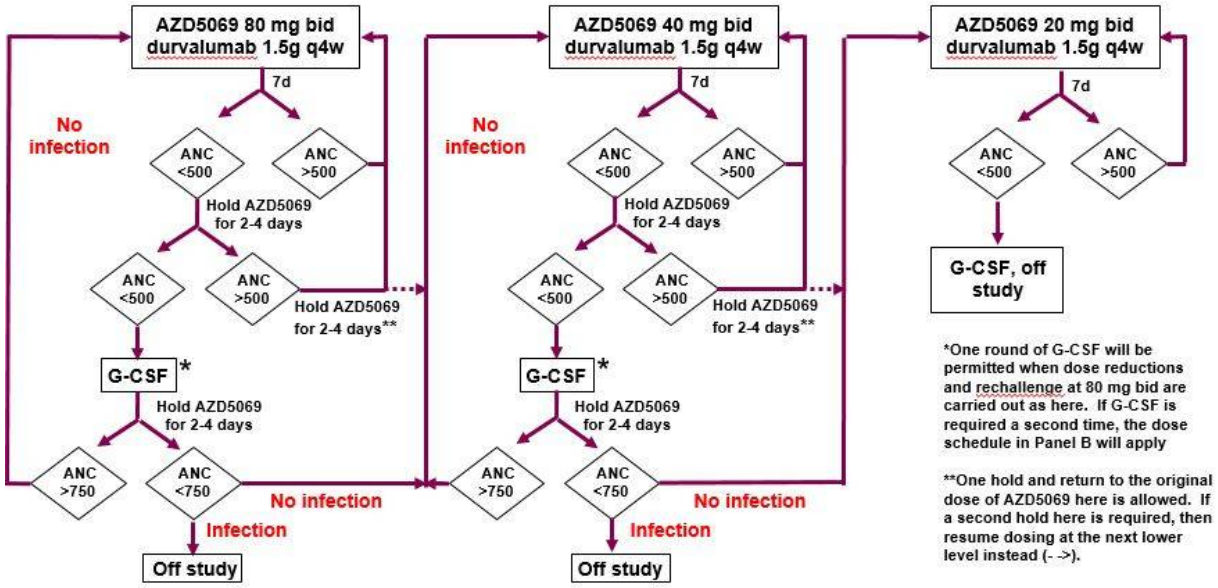
Management of neutropenia associated with AZD5069 should be according to Figure 4. It entails carefully monitoring neutrophil counts during the first weeks of treatment, with short dosing holds as the first response to absolute neutrophil counts <0.5 x 10^9/l (Grade 4 neutrophil reductions).

In the face of prolonged Grade 4 neutrophil reductions unresponsive to dose holds, use of G-CSF is allowed twice at any given dose level; subsequent dose reductions to the next lower dosing level (80 mg bid→40 mg bid or 40 mg bid→20 mg bid) are then mandated. Of note, Grade 3 neutrophil reductions (ANC 0.5-1.0 x 10^9/l) without clinically significant infection are tolerated within the dose reduction scheme.

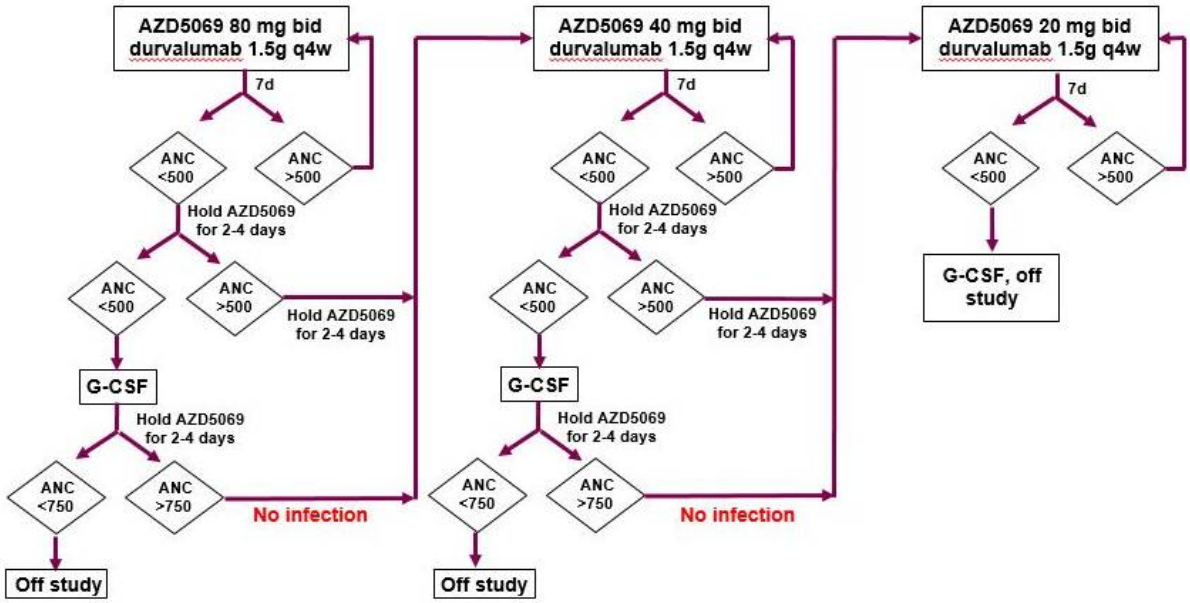
Figure 4 Management of neutropenic toxicities

Toxicity management for Grade 3 and Grade 4 AZD5069- related neutropenic events is as illustrated below in the Panels A and B.

PANEL A



PANEL B



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 AZD5069. Nab-paclitaxel and gemcitabine will be sourced locally.

Investigational product	Dosage form and strength
MEDI4736	50 mg/mL solution for infusion after dilution
Nab-paclitaxel	IV (as sourced locally)
Gemcitabine	IV (as sourced locally)
AZD5069	10 mg tablets for oral use
AZD5069	40 mg tablets for oral use

7.1.1 MEDI4736

MEDI4736 will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL MEDI4736, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must 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. Total time from needle puncture of the MEDI4736 vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

A dose of 1.5 g will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final MEDI4736 concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Remove 30.0 mL of IV solution from the IV bag prior to addition of MEDI4736. Next, 30.0 mL of MEDI4736 (ie, 1.5 g of MEDI4736) is added to the IV bag such that final concentration is

within 1 to 20 mg/mL (IV bag volumes 100 to 1000 mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

In the event that either preparation time or infusion time exceeds the time limits outlined in the table, a new dose must be prepared from new vials. MEDI4736 does not contain preservatives, and any unused portion must be discarded.

No incompatibilities between MEDI4736 and polyvinylchloride, or polyolefin IV bags have been observed.

All details can be found in the Drug Handling Instructions.

7.1.2 Nab-paclitaxel + gemcitabine

The nab-paclitaxel + gemcitabine will be sourced as commercially available material/locally sourced, prescribed according to local regulations, and will be administered according to prescribing information or treatment guidance in general use by the Investigating site. Under certain circumstances when local sourcing is not feasible, nab-paclitaxel + gemcitabine will be supplied centrally by AstraZeneca. This will be labeled with local language translated text in accordance with regulatory guidelines.

7.1.3 AZD5069

AZD5069 will be supplied as 40-mg and 10-mg oral tablets.

7.2 Dose and treatment regimens

7.2.1 Treatment regimens

7.2.1.1 Cohort 1: First-line, Phase Ib, MEDI4736 + nab-paclitaxel + gemcitabine chemotherapy

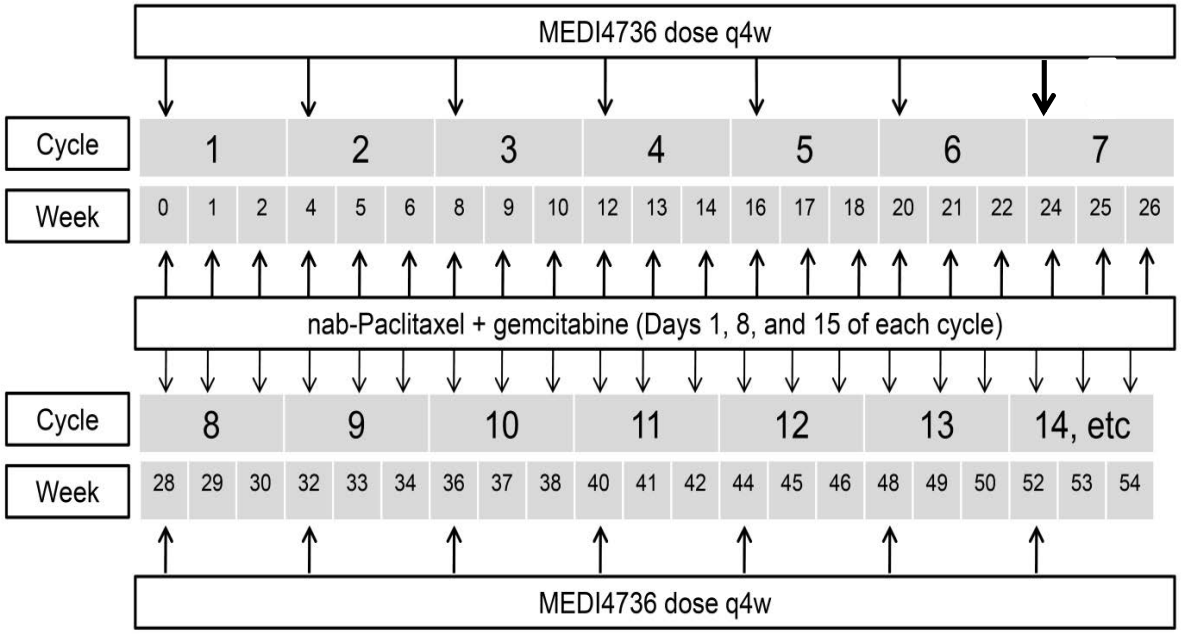
Patients in Cohort 1 will receive 1.5 g MEDI4736 by IV infusion q4w (ie, Day 1 of each 28-day cycle).

The recommended dose of nab-paclitaxel in combination with gemcitabine is 125 mg/m^2 via IV infusion over 30 minutes on Days 1, 8, and 15 of each 28-day cycle. The concurrent recommended dose of gemcitabine is 1000 mg/m^2 via IV infusion over 30 minutes immediately after the completion of nab-paclitaxel administration on Days 1, 8, and 15 of each 28-day cycle. The tumor assessment schedule will not be altered (ie, assessments will continue to be q8w ±7 days relative to the date of first infusion per Table 2).

MEDI4736 will be administered first as a 1-hour infusion. The nab-paclitaxel + gemcitabine infusion will start approximately 1 hour after the end of the MEDI4736 infusion. Nab-paclitaxel will be administered first as a 30- to 40-minute infusion, immediately followed by gemcitabine as a 30- to 40-minute infusion.

The dosing schedule for Cohort 1 is presented in Figure 5. The duration of treatment is described in Section 7.2.2.

Figure 5 Cohort 1 dosing schedule



7.2.1.2 Cohort 2: Second-line, Phase II, MEDI4736 + AZD5069

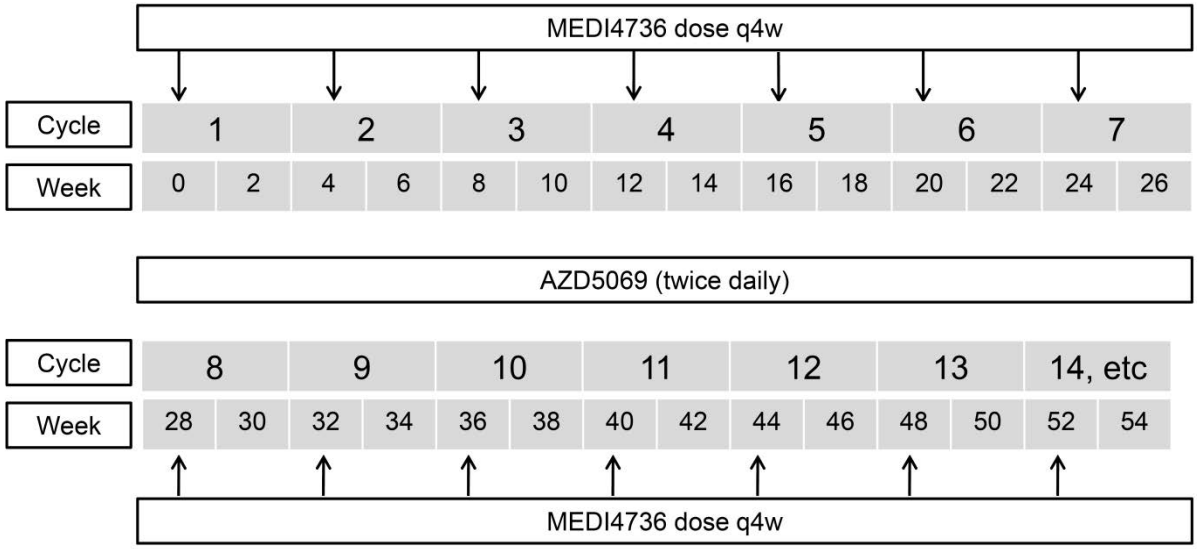
Patients in Cohort 2 will receive 1.5 g MEDI4736 by IV infusion q4w (ie, Day 1 of each 28-day cycle) and AZD5069 administered at a starting dose of 80 mg orally bid (with dose reductions to 40 mg bid or 20 mg bid for toxicity allowable) in the morning and the evening of each day; see Figure 6.

The morning dose of AZD5069 will be administered at least 30 minutes before the infusion of MEDI4736. A 1-hour observation period is recommended after the first infusion of MEDI4736. If no clinically significant infusion reactions are observed during or after the first infusion, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after infusion).

In all cases, AZD5069 should be administered with at least two hours of fasting before and one hour fasting after each dose (3 hour interval without food consumption) at approximately the same time each day (within a +/- 2 hours window). Patients may have glucose (sugar tablets) and/or juice (except for grapefruit juices or juices containing grapefruit or Seville oranges) if they show signs or symptoms of hypoglycaemia after they have received AZD5069 in the fasted state. Water will be restricted from 1 hour predose until 1 hour postdose, except for the water administered with AZD5069. This fasting restriction may be removed only when data showing there is no clinically relevant effect of food on the PK of AZD5069 becomes available.

The duration of treatment is described in Section 7.2.2.

Figure 6 Cohort 2 dosing schedule



7.2.2 Duration of treatment

Treatment in both cohorts will be administered beginning on Day 1 until the following conditions are met:

1. Confirmed PD
2. Unacceptable toxicity
3. Withdrawal of consent, or
4. Another discontinuation criterion is met

In cases of toxicity and at the Investigator's discretion, patients will be permitted to stop treatment with one agent of their combination therapy regimen and continue treatment with the other agent as monotherapy, using the same dose and regimen as previously administered. These patients may continue to receive MEDI4736 alone (until confirmed PD, withdrawal of consent, or another discontinuation criterion is met), or nab-paclitaxel + gemcitabine alone (Cohort 1 only) or AZD5069 alone (Cohort 2 only) until the first assessment of disease progression [ie, unconfirmed PD], withdrawal of consent, or another discontinuation criterion is met.

Patients who the Sponsor and Investigator determine may not continue treatment 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 via telephone for death until end of study.

Treatment through initial assessment of progression is allowed only with MEDI4736 as monotherapy or in combination with AZD5069 and nab-paclitaxel/gemcitabine. Treatment through initial progression is not permitted for monotherapy AZD5069 and nab-paclitaxel/gemcitabine alone. 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 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 PS 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.

7.2.3 Enrollment and stopping criteria for Cohort 1 (first-line, Phase Ib, MEDI4736 + nab-paclitaxel + gemcitabine chemotherapy)

Initially, 3 patients will be enrolled into Cohort 1. The DLT period is defined as the first treatment cycle (28 days). The population evaluable for safety will consist of all patients who complete the first treatment cycle (DLT period, as described above) and/or discontinue study treatment early due to a DLT and who have not missed ≥2 administrations of gemcitabine.

Because Cohort 1 is now limited to 3 patients who have completed the evaluation period, no further consideration of DLT is required.

7.2.4 Definition of dose-limiting toxicity for Cohort 1 (first-line, Phase Ib, MEDI4736 + nab-paclitaxel + gemcitabine chemotherapy)

A DLT is defined as any of the below listed laboratory abnormalities or AEs clearly related to the administration of MEDI4736 occurring during the DLT period.

The following will be considered a DLT regardless of duration or reversibility:

- Liver transaminase elevation ≥ 5 × but ≤ 8× ULN that does not downgrade to Grade 2 within 5 days after onset with optimal medical management, including systemic corticosteroids

- Transaminase elevation > 8× ULN or total bilirubin > 5 × ULN

Patients experiencing a DLT during the DLT period may continue treatment after dose adjustment (see Section 6.7) if there is a potential benefit from treatment.

Immune-related adverse events (irAEs)

- Any Grade 4 irAE not attributed to local tumor response (eg, inflammatory reaction attributed to local tumor response or inflammatory reaction at sites of metastatic disease or lymph nodes).
- Any Grade ≥3 colitis
- Any ≥ Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 7 days of the initiation of maximal supportive care.
- Any Grade 3 irAE, excluding colitis or pneumonitis, that does not downgrade to Grade ≤1 or baseline status (for patients who entered the study with an existing laboratory abnormality) within 14 days.

Non-Immune-related Adverse Event (Non-irAE)

- Any Grade ≥3 non-irAE toxicity that does not downgrade to Grade ≤1 or baseline status (for patients who entered the study with an existing laboratory abnormality) within 14 days.

The definition of DLT excludes the following conditions:

- Vitiligo, alopecia, rash, and Grade 3 electrolyte abnormalities that are reversed with appropriate medical intervention within 7 days or derived from a suboptimal prophylactic and curative therapy.
- Grade 4 electrolyte abnormalities lasting less than 24 hours.
- Grade 3 and 4 toxicity nausea, vomiting, and diarrhea lasting less than 72 hours. Grade 3 and 4 diarrhea will be considered DLTs if considered as an irAE.
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy, and the patient is asymptomatic.
- Grade 3 inflammatory reaction attributed to a local antitumor response (eg, inflammatory reaction at sites of metastatic disease or lymph nodes).
- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management.

- Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 5 days. Grade 3 or Grade 4 febrile neutropenia that can be reasonably attributed to background chemotherapy (Section 6.7.2).

- Grade 3 or 4 lymphopenia

- Grade 4 thrombocytopenia (platelet count ≤25000/mm^3 [≤25 x 10^9/l]) or Grade 3 thrombocytopenia (platelet count 25000-50000/mm^3 [25-50 x 10^9/l]) not associated with any bleeding, not requiring transfusion, lasting less than 7 days, and/or can be reasonably attributed to background chemotherapy (Section 6.7.2).

irAEs are defined as AEs of an immune nature (ie, inflammatory) in the absence of a clear alternative etiology. In the absence of a clinically significant abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT. Laboratory abnormalities that are not deemed to be clinical significant will not be considered a DLT.

7.2.5 Definition of dose-limiting toxicity for Cohort 2 (MEDI4736 + AZD5069)

For patients in Cohort 2 to be deemed evaluable, a patient must have received 50% of planned doses of AZD5069 during the DLT evaluation period as well as the MEDI4736 infusion and have remained active on trial at the end of Day 28 of the study cycle 1.

The DLT evaluation period for Cohort 2 will be defined as the time from the first dose of AZD5069 and MEDI4736 to the end of Cycle 1 (ie, 28 days total) or until a patient experiences a DLT, whichever occurs first.

Dose-limiting toxicity **criteria for MEDI4736:**

A DLT is defined as any of the below listed laboratory abnormalities or **AEs clearly related to the administration of MEDI4736** occurring during the DLT period.

The following will be considered a DLT regardless of duration or reversibility:

- Liver transaminase elevation ≥ 5 × but ≤ 8× ULN that does not downgrade to Grade 2 within 5 days after onset with optimal medical management, including systemic corticosteroids.

- Transaminase elevation > 8× ULN or total bilirubin > 5 × ULN

Patients experiencing a DLT during the DLT period may continue treatment after dose adjustment (see Section 6.7) if there is a potential benefit from treatment.

Immune-related adverse events (irAEs)

- Any Grade 4 irAE not attributed to local tumor response (eg, inflammatory reaction attributed to local tumor response or inflammatory reaction at sites of metastatic disease or lymph nodes).

- Any Grade ≥3 colitis

- Any ≥ Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 7 days of the initiation of maximal supportive care.

- Any Grade 3 irAE, excluding colitis or pneumonitis, that does not downgrade to Grade ≤1 or baseline status (for patients who entered the study with an existing laboratory abnormality) within 14 days.

Non-Immune-related Adverse Event (Non-irAE)

- Any Grade ≥3 non-irAE toxicity that does not downgrade to Grade ≤1 or baseline status (for patients who entered the study with an existing laboratory abnormality) within 14 days.

The definition of DLT excludes the following conditions:

- Vitiligo, alopecia, rash, and Grade 3 electrolyte abnormalities that are reversed with appropriate medical intervention within 7 days or derived from a suboptimal prophylactic and curative therapy.

- Grade 4 electrolyte abnormalities lasting less than 24 hours.

- Grade 3 and 4 toxicity nausea, vomiting, and diarrhea lasting less than 72 hours. Grade 3 and 4 diarrhea will be considered DLTs if considered as an irAE.

- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy, and the patient is asymptomatic.

- Grade 3 inflammatory reaction attributed to a local antitumor response (eg, inflammatory reaction at sites of metastatic disease or lymph nodes).

- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management.

- Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 5 days. Grade 3 or Grade 4 febrile neutropenia that can be reasonably attributed to background chemotherapy (Section 6.7.2).

- Grade 3 or 4 lymphopenia.

- Grade 4 thrombocytopenia (platelet count ≤25000/mm [≤25 x 10^9/l]) or Grade 3 thrombocytopenia (platelet count 25000-50000/mm^3 [25-50 x 10^9/l]) not associated with any bleeding, not requiring transfusion, lasting less than 7 days, and/or can be reasonably attributed to background chemotherapy (Section 6.7.2).

irAEs are defined as AEs of an immune nature (ie, inflammatory) in the absence of a clear alternative etiology. In the absence of a clinically significant abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT. Laboratory abnormalities that are not deemed to be clinical significant will not be considered a DLT.

Dose-limiting toxicity **criteria for AZD5069:**

A DLT is defined as any AE that occurs from the first dose of AZD5069 up to the end the DLT evaluation period, that is **judged by the Investigator to be AZD5069 related** (ie, unrelated to PD, intercurrent illness, or concomitant medications), and that is assessed as grade 3 or worse according to the National Cancer Institute (NCI) CTCAE, with the following exceptions:

- Increases in transaminase levels (serum glutamic oxaloacetic transaminase [SGOT]/AST and serum glutamic-pyruvic transaminase [SGPT]/ALT) are DLT if:
  - SGOT/AST and/or SGPT/ALT increase to >15×ULN at any time, and/or
  - SGOT/AST and/or SGPT/ALT increase to >10× to 15×ULN over a span of 14 consecutive days, and/or
  - SGOT/AST and/or SGPT/ALT increase to >ULN, and 1 or more of the following conditions is met and not explained by other causes:
    (a) Total bilirubin increased to >2×ULN
    (b) New appearance of eosinophilia (>5%)
    (c) Clinical signs of functional liver impairment
- Nausea, vomiting, and diarrhoea will be considered a DLT only if assessed as grade 3 or worse after optimal prophylactic or treatment measures have been prescribed.
- Fatigue will not be considered a DLT.
- Neutropenia will be considered a DLT only:

- If in the context of grade 3 febrile neutropenia (ie, absolute neutrophil count [ANC] 500-1000/mm3 [0.5-1.0 x 109/l] with a single temperature of more than 38.3ºC (101ºF) or a sustained temperature of at least 38ºC (100.4ºF) for more than 1 hour;

- If in the context of grade 4 febrile neutropenia (ie, ANC <500/mm3 [<0.5 x 109/l] with life-threatening consequences that indicate urgent intervention);

- If assessed as grade 3 or worse (ie, ANC 0.5-1.0 x 109/l) and associated with an infection that is clinically severe, associated with sepsis or requiring hospitalization. Grade 3 non febrile neutropenia with clinically minor (as judged by the investigator) infection need not be regarded as DLT.; or

- If assessed as grade 4 (ie, ANC <500/mm3 [0.5 x 109/l]) for more than 5 days.

- Thrombocytopenia will be considered a DLT only:

  - If assessed as grade 3 or worse (ie, platelet count <50000/mm3 [<50 x 109/l]) and associated with bleeding, or

  - If assessed as grade 4 (ie, platelet count <25000/mm3 [<25 x 109/l]).

Any other grade 3 or grade 4 laboratory evaluations that are asymptomatic will be considered a DLT only if assessed by the Investigator as clinically significant.

Any toxicity judged by the Investigator to be AZD5069 related (ie, causality rated as possible or greater) that requires study treatment to be discontinued for more than 10 consecutive days will be considered a DLT.Management of toxicity for MEDI4736 related events is described in Appendix E

Management of neutropenia associated with AZD5069 is described in Section 6.7.3.

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 source documentation and 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. The administration of all medications (including study drug) and details of treatment with investigational product should be recorded in the appropriate sections of the eCRF.

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 source documentation and 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 PD-1, PD-L1, and PD-L2, CXCR2 inhibitors, and therapeutic anticancer vaccines through 90 days after the last dose during the study	Should not be given during the study
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)

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
Best supportive care (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

As detailed in the IB for AZD5069, patients who are treated with AZD5069 should avoid coadministration of drugs that are known potent or moderate CYP3A4 inhibitors, potent or moderate CYP3A4 inducers, P-gp substrates with narrow therapeutic index, sensitive CYP2B6 substrates, warfarin or any other coumarin derivatives, BCRP-substrates that reduce blood neutrophils, Seville orange or grapefruit products, and any herbal medications. Please refer to local prescribing information for other drugs that may interact with either nab-paclitaxel or gemcitabine.

For each patient enrolled in Cohort 2, the Investigator has to assess both the patient's medication history for any such products as well as the patient's anticipated need or likelihood to consume such products at any time throughout the study.

Restrictions apply starting 14 days prior to the first dose of AZD5069 and last for as long as the patient is treated with AZD5069 and until 24 hours after the last dose of AZD5069.

See Table 11 for a list of the main potent or moderate CYP3A4 inhibitors, potent or moderate CYP3A4 inducers, P-gp substrates with narrow therapeutic index, sensitive CYP2B6 substrates, warfarin or any other coumarin derivatives, and BCRP-substrates that reduce blood neutrophils.

Patients administered AZD5069 alone and in combination with MEDI4736 must not consume Seville orange marmalade, Seville orange juice, grapefruit, grapefruit juice, grapefruit marmalade, or other Seville orange or grapefruit products. In addition the use of cannabinoids must be avoided in patients administered AZD 5069 alone and in combination with MEDI4736.

Any further questions regarding concomitant treatments in patients treated with AZD5069 should be referred to the Study Physician.

Table 11 Prohibited medications and foods for patients who receive AZD5069

Class	Examples (including and not limited to)	
Potent/moderate CYP3A4 inhibitors	Amprenavir	Imatinib
	Aprepitant	Indinavir
	Atazanavir	Indinavir/ritonavir
	Atazanavir/ritonavir	Itraconazole
	Boceprevir	Ketoconazole
	Casopitant	Ledipasvir
	Cimetidine	Lomitapide
	Ciprofloxacin	Lopinavir/ritonavir
	Clarithromycin	Mibefradil
	Cobicistat (gs-9350)	Nefazodone
	Conivaptan	Nelfinavir
	Crizotinib	Netupitant
	Cyclosporine	Posaconazole
	Danoprevir/ritonavir	Ritonavir
	Darunavir	Saquinavir
	Darunavir/ritonavir	Saquinavir/ritonavir
	Diltiazem	Schisandra sphenanthera
	Dronedarone	Telaprevir
	Elvitegravir/ritonavir	Telithromycin
	Erythromycin	Tipranavir/ritonavir
	Fluconazole	Tofisopam
	Fosamprenavir	Troleandomycin
	Grapefruit juice	Verapamil
	Idelalisib	Voriconazole
Potent/moderate CYP3A4 inducers	Avasimibe	Modafinil
	Bosentan	Nafcillin
	Carbamazepine	Phenytoin
	Efavirenz	Rifampin
	Etravirine	St. John’s wort
Sensitive CYP2B6 substrates	Bupropion	Efavirenz
P-gp substrates with narrow therapeutic index	Digoxin	Dabigatran
Coumarin derivatives	Acenocoumarol	Warfarin
	Phenprocoumon	
BCRP substrates that reduce blood neutrophils	Topotecan	
Any herbal medications		

Table 11 Prohibited medications and foods for patients who receive AZD5069

Class	Examples (including and not limited to)	
Seville orange or grapefruit products	Seville orange marmalade Seville orange juice	Grapefruit Grapefruit juice Grapefruit marmalade

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 AZD5069 and MEDI4736 therapy up to completion of a patient's treatment period (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

8.2.1 Cohort 1: First-line, Phase Ib, MEDI4736 + nab-paclitaxel + gemcitabine chemotherapy

The sample size is set to screen patients for major toxicity that occurs in a large portion of the population, using the conventional 3 + 3 design. The total number of patients in dose level 1 is 3 patients.

Based on binomial probabilities, the probability of observing 0 or more patients with a toxicity event in 3 patients (6 patients respectively) can be seen in Table 12.

Table 12 Probability of observing toxicity event

Incidence of DLTs	Probability of observing X out of Y (X/Y) patients with DLT					
	0/3	≤1/3	≥2/3	0/6	≤1/6	≥2/6
30%	34.30%	78.40%	21.60%	11.80%	42.00%	58.00%
50%	12.50%	50.00%	50.00%	1.60%	10.90%	89.10%
70%	2.70%	21.60%	78.40%	0.10%	1.10%	98.90%

8.2.2 Cohort 2: Second-line, Phase II, MEDI4736 + AZD5069

The sample size is set to screen patients for major toxicity that occurs in a large portion of the population, using the approximately 6 to 16 evaluable patients in total. A cohort of 6 patients will be recruited sequentially at the planned dose level. Should safety and tolerability be acceptable (if there are 3 or fewer patients exhibiting DLT criteria) following assessment of the initial 6 patients, approximately 10 further patients will be recruited, to target approximately 16 evaluable patients in total.

Based on binomial probabilities, the probability of observing 0 or more patients with a toxicity event in 6 patients (6 patients respectively) can be seen in Table 13.

Table 13 Probability of observing toxicity events in 6 or 16 patients

Incidence of DLTs	Probability of observing X out of Y (X/Y) patients with DLT					
	0/6	≤1/6	⩽2/6	⩾3/6	≤2/16	≥3/16
1%	94.10%	99.90%	100%	0%	98.90%	1.10%
5%	73.50%	96.70%	99.80%	0.20%	81.10%	18.90%
10%	53.10%	88.60%	98.40%	1.60%	51.50%	48.50%
20%	26.20%	65.50%	90.10%	9.90%	14.10%	85.90%
30%	11.80%	42%	74.40%	25.60%	2.60%	97.40%
50%	1.60%	10.90%	34.40%	65.60%	0%	100%
70%	0.10%	1.10%	7%	93%	0%	100%

When the true incidence is 30% the chance of observing at least 3 DLTs out of 6 patients is 25.6% assuming no prior information.

While the estimates in Table 13 are true for the assumed true DLT incidences, there is prior information in the AZD5069 program. In particular there have been 23 patients treated with

at least one of the durvalumab combinations in Trial D5660C00004. About half of the patients treated with the AZD5069/durvalumab combination were treated with a tolerated dose which will continue to be developed, the empirical priors were discounted by about 50%. The table below presents posterior probabilities that the true DLT incidence is at least 33%. Three sets of posterior proibabilities are shown. The posterior priobabilities based on a non-informative prior are presented as an initial case. Since we do have prior data, the more relevant posterior probabilities are shown in the last two columns of Table 14. The probabilities under Trial 4 amendment 2 reflect the DLT information documented in the current version of the AZD5069 IB. In the last column, posterior probabilities based on the original (more conservative) DLT definition are presented.

Table 14 Posterior Probabilities of True DLT Incidence > 33% with Various Priors

Data	Non-informative	Trial 4 Amendment 2	Trial 4 original (conservative)
0/6 DLT	6.06%	0.05%	1.45%
1/6 DLT	26.96%	0.51%	5.56%
2/6 DLT	57.83%	2.57%	14.82%
3/6 DLT	83.18%	8.31%	30.02%
4/6 DLT	95.66%	19.63%	49.09%
5/6 DLT	99.35%	36.34%	67.86%
6/6 DLT	99.96%	55.55%	82.66%

With 3 patients out of 6 experiencing DLTs there is a 30.02% chance that the true DLT incidence is > 33% under the original Trial D5660C00004 DLT definition, which was changed to accommodate an Oncology population as opposed to the original COPD population. The data supporting this change is outlined in the current AZD5069 IB. With this in mind, the same posterior probability quoted for 3 patients out of 6 experiencing DLTs, the posterior probability that the true incidence is at least 33% is only 8.31%. Based on this, we will continue Cohort 2 in this trial if in 6 patients we see no more than 3 DLTs.

8.3 Definitions of analysis sets

Definitions of the analysis sets for each outcome variable are provided in Table 15

Table 15 Summary of outcome variables and analysis populations

Outcome variable	Population
Efficacy data	
ORR	Efficacy Analysis Set
DoR, DCR, PFS, PFS3, PFS6, OS, OS6, OS12, and symptom endpoints	Efficacy Analysis Set
Demography	Safety Analysis Set
PK data	PK analysis set
Safety Data	
Exposure	Safety analysis set
AEs	Safety analysis set
Laboratory measurements	Safety analysis set
ECOG PS	Safety analysis set
Vital signs	Safety analysis set

8.3.1 Full analysis set

The Full Analysis Set will include all patients enrolled to receive treatment (ie, the intent-to-treat [ITT] population) and will classify them on the basis of allocated treatment, regardless of the treatment actually received. Patients who were enrolled to receive treatment who did not subsequently go on to receive study treatment are included in the ITT population.

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. PK 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.

8.3.4 Efficacy analysis set

The Efficacy analysis set (EAS) will include patients who received at least 1 dose of IP and with no important protocol deviation that could impact the efficacy evaluation. These deviations will be discussed and stated during the Data Review Meeting prior to database lock (DBL).

8.4 Outcome measures for analyses

8.4.1 Calculation or derivation of efficacy variables

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 overall 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 (either because the scan was unreadable or taken before Day 15 of Cycle 2), the patient will be assigned an overall 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, PFS3, and PFS6) will be derived from the overall visit response date and the scan dates.

Progression of TLs will be calculated in comparison to when the tumor burden was at a minimum (ie, smallest sum of diameters previously recorded on study, including baseline). In the absence of progression, tumor response (CR, PR, SD) will be calculated in comparison to the baseline tumor measurements obtained before starting treatment.

For TL measurements, if $\leqslant$ one-third of the TL sizes are missing then a scaling up rule will be applied as follows:

- If $\leq$ one-third of all lesions recorded at baseline are missing, the results will be scaled up (based on the nadir sizes, including baseline) to give an estimated sum of diameters and this will be used in calculations. (This is equivalent to comparing the visit sum of diameters of the nonmissing lesions to the nadir sum of diameters excluding the lesions that are missing and determining at what rate the lesions are changing.)

- If > one-third of all lesions recorded at baseline are missing, the TL response will be NE. However, if the sum of nonmissing TL diameters would result in PD (ie, if using a value of 0 for missing lesions the sum of diameters has still increased by >20% or more compared to the smallest sum of diameters on study); PD takes precedence over NE.

- Only responses of PR, SD, PD, or NE will be permitted if any of the TL data are missing.

An overall visit response of CR is defined when all TL and NTL lesions present at baseline have disappeared (with the exception of lymph nodes which must be less than 10 mm to be considered nonpathological) and no new lesions have developed since baseline. An overall visit response of PR is defined when the sum of diameters of the TLs has decreased by 30% or more compared to baseline (with no evidence of progression) and the NTLs are at least stable with no evidence of new lesions. To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.

Stable disease is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of not less than 35 days.

When the Investigator is in doubt as to whether PD has occurred and therefore reassesses the patient at a later date, the date of the initial scan should be declared as the date of progression if the repeat scans confirm progression.

Please refer to Appendix D for the definitions of CR, PR, SD, NE, and PD.

8.4.1.2 Primary endpoints

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:

Corrected calcium (mmol/L) = Total calcium (mmol/L) + ([40 – albumin (G/L)] × 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.

8.4.2.4 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 6 or 12 months is defined as the percentage of patients who have a best objective response (BoR) of CR or PR in the first 6 or 12 months, respectively, or who have demonstrated SD for a minimum interval of 24 or 48 weeks, respectively (-7 days, ie, 161 or 329 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 first progression event.

Progression-free survival (PFS)

PFS (per RECIST 1.1 using Investigator assessments) will be defined as the time from the date of first dose 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 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 Day 1 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.

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.

Overall survival

OS is defined as the time from the date of initial treatment 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.

Proportion of patients alive at 6 months

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

Proportion of patients alive at 12 months

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 D. 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 D) 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 within 17 weeks (ie, 16 weeks ±7 days) weeks for Cohort 1 and 13 weeks (ie, 12 weeks ±7 days) for Cohort 2 after enrollment, then BoR will be assigned to the PD category. For patients who die with no evaluable RECIST assessments, if the death occurs >17 weeks (ie, 16 weeks ±7 days) for Cohort 1 and >13 weeks (ie, 12 weeks ±7 days) for Cohort 2 after the date of enrollment, then BoR will be assigned to the NE category.

Progression events that have been censored due to them being >17 weeks for Cohort 1 and >13 weeks for Cohort 2 after the last evaluable assessment will not contribute to the BoR derivation.

8.4.3 Calculation or derivation of pharmacokinetic variables

8.4.3.1 Population pharmacokinetics and exposure-response/safety analysis

A population PK model analysis might be performed using a nonlinear mixed-effects modelling approach if data allowed. 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.

8.4.3.2 Pharmacokinetic 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. 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.

8.4.3.3 Immunogenicity analysis

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patient who develop detectable ADAs against MEDI4736 when they are treated with MEDI4736 in combination with nab-paclitaxel + gemcitabine or MEDI4736 in combination with AZD5069. 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.

8.4.4 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.

8.5 Methods for statistical analyses

Descriptive statistics will be used for all variables, as appropriate, and will be presented by cohort. 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 cohort.

Since Cohort 1 enrollment was stopped with only 3 patients, data from this cohort will be listed only.

8.5.1 Efficacy data

Objective response rate

Objective Response rate (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 Efficacy 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.
The Objective Response rate (ORR) will be estimated with 95% exact CIs. The programmatically derived ORR will be based on Investigator assessments, and using all scans regardless of whether they were scheduled or not.

The analysis population for ORR will be the efficacy Analysis Set.

Summaries will be produced that present the number and percentage of patients with a tumor response (CR/PR) .

8.5.1.1 Duration of response

Descriptive data (relevant to Cohorts 1 and 2) will be provided for the DoR in responding patients, including the associated Kaplan-Meier curves (without any formal comparison of cohorts or p-value attached).

8.5.1.2 Disease control rate

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

8.5.1.3 Progression-free survival

Kaplan-Meier plots of PFS will be presented for each cohort Summaries of the number and percentage of patients experiencing a PFS event and the type of event (RECIST 1.1 or death) will be provided along with median PFS for each cohort (if calculable).

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

The PFS3 and PFS6 will be calculated using Kaplan-Meier estimates, as the cumulative probability of progression-free survival to each of those time periods for each cohort. 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.

8.5.1.5 Overall survival

Kaplan-Meier plots of OS will be presented for each cohort. 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).

8.5.1.6 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 for each cohort. 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.

8.5.2 Safety data

Safety and tolerability data will be presented by cohort 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 cohort and CTCAE grade. Additionally, data presentations of the rate of AEs per person-years at risk may be produced.

Other safety data will be assessed in terms of physical examination, clinical chemistry, hematology, vital signs, and ECGs. Exposure to MEDI4736, nab-paclitaxel + gemcitabine, and AZD5069 will be summarized. Time on study and MEDI4736, nab-paclitaxel + gemcitabine, and AZD5069 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.

8.5.3 Pharmacokinetic data

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

8.5.3.1 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, anti-nab-paclitaxel, anti-gemcitabine, or anti-AZD5069 antibodies. The immunogenicity titer and neutralizing ADA data will be listed for samples confirmed positive for the presence of anti-MEDI4736, anti-nab-paclitaxel, anti-gemcitabine, or anti-AZD5069 antibodies.

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

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.

8.5.4 Biomarker data

The relationship of PD-L1 expression and if applicable, of exploratory biomarkers to ORR, DoR, DCR, OS, PFS, PFS3, and PFS6 will be presented for a subset of patients in the efficacy analysis set 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.

8.5.5 Interim analysis

Cohort 1: First-line, Phase Ib, MEDI4736 + nab-paclitaxel + gemcitabine chemotherapy

Not applicable.

Cohort 2: Second-line, Phase II, MEDI4736 + AZD5069

Not applicable.

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 clinical study protocol (CSP) and related documents with the

investigational staff and train them in any study-specific procedures, including use of IVRS/IWRS and WBDC.

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 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.

9.2.3 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 Q1 2016 and to end by Q4 2018.

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.

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 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.

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.

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.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the PI 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 ICF, 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.

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Appendix A 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.

Appendix B 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.

Appendix C Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

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.

Definitions

Potential Hy's Law (PHL)
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3 × upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥2 × 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 ≥3 × ULN **together with** TBL ≥2 × 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.

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 ≥3 × ULN
- AST ≥3 × ULN
- TBL ≥2 × 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 Appendix C 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 (Appendix C for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

Follow-up

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.

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

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

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 Appendix C

[#] 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.

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 Appendix C

If No: follow the process described in Appendix C

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 Appendix C

[#] 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.

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.

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

Introduction

This appendix details the implementation of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines (Eisenhauer et al 2009) for the D4198C00003 study with regards to Investigator assessment of tumor burden including protocol-specific requirements for this study.

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 baseline[1]).
- 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.
- Previously irradiated lesions that have not demonstrated progression[2]
- Brain metastasis

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

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.

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 16, and those excluded from tumor assessments for this study are highlighted with the rationale provided.

Table 16 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.

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 D4198C00003 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.

Clinical examination
In the D4198C00003 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.

X-ray
Plain X-ray
In the D4198C00003 study plain X-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

Ultrasound
In the D4198C00003 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.

Endoscopy and laparoscopy
In the D4198C00003 study, endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor assessment.

Tumor markers
In the D4198C00003 study, tumor markers will not be used for tumor response assessments as per RECIST 1.1.

Cytology and histology
In the D4198C00003 study histology will not be used as part of the tumor response assessment as per RECIST 1.1.

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 D4198C00003 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.

FDG-PET scan

In the D4198C00003 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 uptake[3] 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.

Tumor response evaluation

Schedule of evaluation

RECIST assessments will be performed using CT/MRI assessments of the chest and abdomen, and the pelvis only when suspected or when there is 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 the start of study treatment, and ideally should be performed as close as possible to the start of study treatment (see Table 2 and Table 3 of the Clinical Study Protocol). Follow-up assessments will be performed every 8 weeks (±7 days; Cohort 1) or every 6 weeks (±7 days; Cohort 2) for the first 48 weeks relative to the date of the first infusion, and every 12 weeks ±7 days thereafter until confirmed objective disease progression. In Cohort 1, if Day 15 treatment administration is delayed due to patient toxicity (see Clinical Study Protocol Section 7.2.1.1), tumor assessments will not be altered (ie, assessments will continue to be every 8 weeks ±7 days relative to the date of first infusion per Table 2 of the Clinical Study Protocol).

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.

Target lesions

Documentation of target 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.

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.

Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumor visit response for TL (see Table 17).

Table 17 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.

Non-target lesions

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 (Table 18).

Table 18 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.

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.

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.

Evaluation of overall visit response

The overall visit response will be derived using the algorithm shown in Table 19

Table 19 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).

Confirmation of Progression

In the D4198C00003 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:

- ≥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 ≥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 ≥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.

Central Review

The Contract Research Organization appointed by AstraZeneca will provide specification for radiological imaging protocols in standard acquisition guidelines documentation.

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.

Appendix E MEDI4736 Dosing Modification and Toxicity Management Guidelines Immune-Mediated, Infusion Related, And Non Immune-Mediated Reactions

Table 20 Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy With Tremelimumab or Tremelimumab Monotherapy) 1 November 2017 Version

General Considerations

Dose Modifications	Toxicity Management
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03. In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ⩽10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/study regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing **Grade 1** No dose modification **Grade 2** Hold study drug/study regimen dose until Grade 2 resolution to Grade ⩽1. If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes to Grade ⩽1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per Investigator or treating physician's clinical judgement. 3. Doses of prednisone are at ⩽10 mg/day or equivalent. **Grade 3** Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below. **Grade 4** Permanently discontinue study drug/study regimen.	It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table: – It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. – Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. – Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events. – For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ⩾3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper). – More potent immunosuppressives such as TNF inhibitors (e.g., infliximab) (also refer to the individual sections of the imAEs for specific type of

Note: For Grade ⩾3 asymptomatic amylase or lipase levels, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).	immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids. – With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. – Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; imAE immune-mediated adverse event; IV intravenous; NCI National Cancer Institute; PO By mouth.

Pediatric Considerations

Dose Modifications	Toxicity Management
The criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity is the same for pediatric patients as it is for adult patients, as well as to permanently discontinue study drug/study regimen if unable to reduce corticosteroid ≤ a dose equivalent to that required for corticosteroid replacement therapy **within 12 weeks** after last dose of study drug/study regimen	– All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended. – The recommendations for dosing of steroids (i.e., mg/kg/day) and for IV IG and plasmapheresis that are provided for adult patients should also be used for pediatric patients. – The infliximab 5 mg/kg IV dose recommended for adults is the same as recommended for pediatric patients ≥ 6 years old. For dosing in children younger than 6 years old, consult with a pediatric specialist. – For pediatric dosing of mycophenolate mofetil, consult with a pediatric specialist. – With long-term steroid and other immunosuppressive use, consider need for PJP prophylaxis, gastrointestinal protection, and glucose monitoring.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider Pulmonary and Infectious disease consult.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If still no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for

[a]ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.

			treatment of cancer-related infections [Category 2B recommendation])[a] – Consider pulmonary and infectious disease consult. – Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious disease consult; consider, as necessary, discussing with study physician. – Hospitalize the patient. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks' dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Diarrhea/Colitis	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.

Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only)	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day) (Colitis: abdominal pain; mucus or blood in stool)	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks[a]. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Grade 3 or 4 (Grade 3 diarrhea: stool frequency of ≥7 over baseline per day; Grade 4 diarrhea: life threatening	**Grade 3** Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration.

	consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medi-cal intervention indi-cated, peritoneal signs; Grade 4 colitis: life-threatening consequences, urgent intervention indicated)	can be resumed after completion of steroid taper. **Grade 4** Permanently discontinue study drug/study regimen.	– Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g., infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in HCC patients**	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	Grade 1 (AST or ALT >ULN and ≤3.0×ULN and/or TB > ULN and ≤1.5×ULN)	• No dose modifications. • If it worsens, then treat as Grade 2 event.	**For Grade 1:** – Continue LFT monitoring per protocol.
	Grade 2 (AST or ALT >3.0×ULN and ≤5.0×ULN and/or TB >1.5×ULN and ≤3.0×ULN)	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to Grade ≤1 in 1 to 2 days, consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional work up and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss

[b]FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

		with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Grade 3 or 4 (Grade 3: AST or ALT >5.0×ULN and ≤20.0×ULN and/or TB >3.0×ULN and ≤10.0×ULN) (Grade 4: AST or ALT >20×ULN and/or TB >10×ULN)	**For Grade 3:** For elevations in transaminases ≤8 × ULN, or elevations in bilirubin ≤5 × ULN: • Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.[b] **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (i.e., mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Perform hepatology consult, abdominal workup, and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. See instructions at **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients** bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg – For HCV+ patients: evaluate quantitative HCV viral load – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load >2000 IU/ml – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥2-fold – For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above
	Grade 1 (Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline)	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as Grade 2 event. For all grades, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	
	Grade 2 (Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline)	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1 or baseline.	**For Grade 2:** – Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion.

(Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline)	• If toxicity worsens, then treat as Grade 3 or Grade 4. If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper.	– Consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
Grade 3 (Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline) (Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)	• Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	**For Grade 3:** – Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider, as necessary, discussing with study physician. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

	Grade 4 (Isolated AST or ALT >20×ULN, whether normal or elevated at baseline)	Permanently discontinue study drug/study regimen.	**For Grade 4:** **Same as above** **(except would recommend obtaining liver biopsy early)**
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR): - **Manage dosing for Grade 1 transaminase rise as instructed for Grade 2 transaminase rise** - **Manage dosing for Grade 2 transaminase rise as instructed for Grade 3 transaminase rise** - **Grade 3-4: Permanently discontinue study drug/study regimen**			
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade**	**General Guidance**	**For Any Grade:** – Consult with nephrologist. – Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections). – Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.
	Grade 1 (Serum creatinine > 1 to 1.5 × baseline; > ULN to 1.5 × ULN)	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.

Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
Grade 3 or 4 (Grade 3: serum creatinine >3.0 × baseline; >3.0 to 6.0 × ULN; Grade 4: serum creatinine >6.0 × ULN)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine on daily basis. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Rash (excluding bullous skin formations)	**Any Grade** (refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED.**
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen. **For Grade 4:**	**For Grade 3 or 4:** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for

		Permanently discontinue study drug/study regimen.	treatment of cancer-related infections [Category 2B recommendation]).[a] − Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** − Consider consulting an endocrinologist for endocrine events. − Consider, as necessary, discussing with study physician. − Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). − Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). − For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. − If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
	Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** − Monitor patient with appropriate endocrine function tests. − For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). − If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at

		subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until patient is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	**For Grade 2 (including those with symptomatic endocrinopathy):** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency)	**For Grade 3 or 4:** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones).

		can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	– For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). – Perform symptomatic treatment with neurological consult as appropriate. –
	Grade 1	No dose modifications.	**For Grade 1:** – See "Any Grade" recommendations above.
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Obtain neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent.

		If toxicity worsens, then treat as Grade 3 or 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper.	– If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (e.g., IV IG).
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consider, as necessary, discussing with study physician. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., IV IG). – Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade**	**General Guidance**	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely

		indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Grade 1	No dose modifications.	**For Grade 1:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult.
Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:*

			○ It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. ○ Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Consider, as necessary, discussing with study physician. – Recommend hospitalization. – Monitor symptoms and obtain neurological consult. *MYASTHENIA GRAVIS:* ○ Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. ○ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. ○ If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* ○ It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. ○ Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider, as necessary, discussing with the study physician.

		– Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)
Grade 1 (asymptomatic with laboratory (e.g., BNP) or cardiac imaging abnormalities)	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 (no definitive findings):** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. - Consider using steroids if clinical suspicion is high.
Grade 2, 3 or 4 (Grade 2: Symptoms with mild to moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated)	- If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen.	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.

	(Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support))	If Grade 3-4, permanently discontinue study drug/study regimen.	– Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Myositis/Polymyositis ("Poly/myositis")	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the

AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease;

		muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
Grade 1 (mild pain)	- No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	Hold study drug/study regimen dose until resolution to Grade ≤1. - Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Grade 3 or 4 (pain associated with severe weakness;	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation.

	limiting self-care ADLs)	Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** - Permanently discontinue study drug/study regimen.	– Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether patient may require IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

imAE immune-mediated adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Infusion-Related Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade:** − Manage per institutional standard at the discretion of investigator. − Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1:** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2:** The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2:** − Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. − Consider premedication per institutional standard prior to subsequent doses. − Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** − Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

CTCAE Common Terminology Criteria for Adverse Events; IM intramuscular; IV intravenous; NCI National Cancer Institute.

Non–Immune-Mediated Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."
AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.

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