AstraZeneca

Statistical Analysis Plan

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A Phase II, Multi-Center, Open-Label Study of Tremelimumab Monotherapy in Patients with Advanced Solid Tumors

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Study Statistician PPD _____ 27JUN2018
Date

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Global Product Statistician PPD

05 July 2018
Date

TABLE OF CONTENTS PAGE

TABLE OF TABLES PAGE

TABLE OF FIGURES PAGE

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AZ	AstraZeneca
AZDD	AZ drug dictionary
BoR	Best objective response
CI	Confidence interval
CR	Complete response
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTC / CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of investigational product due to adverse event
DCO	Data cut-off
DCR	Disease control rate
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	Full analysis set
GGT	gamma-glutamyl transferase
IP	Investigational product
IV	Intravenous
LD	Longest diameter
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NA	Not applicable
NE	Not evaluable
NTL	Non-target lesions

Abbreviation or special term	Explanation
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-L1	Programmed death ligand 1
PDAC	Pancreatic ductal adenocarcinoma
PFS	Progression-free survival
PID	Percentage intended dose
PK	Pharmacokinetic(s)
PR	Partial response
PT	Preferred term
q4w	Every 4 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks
q12w	Every 12 weeks
QTcF	QT interval corrected by the Fridericia's correction formula
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumours.
SAE	Serious adverse event
SD	Stable disease
SOC	System organ class
TL	Target lesions
TNBC	Triple-negative breast cancer
UBC	Urothelial bladder cancer

AMENDMENT HISTORY

Date	Brief description of change
26 August 2016	Version 1.1 Removal of DCR at 12 months. Minor updates to reflect revised protocol.
16 September 2016	Version 1.2 Re-defining the full analysis set to have the definition of the evaluable analysis set in the CSP Removing the evaluable analysis set completely Reinstating analysis of DCR at 12 months Including time to response endpoint and analysis Including time to first AE, duration of AE and time to resolving AEs to Grade ≤1 and ≤ 2. Including time to first AESI and duration of AESIs.
23 September 2016	Other modifications following removal of certain tables and listings and figures following sponsor review.
28 October 2016	Fonts, addressing some comments, implementation of recommendations from Study Statistician
16 December 2016	Version 1.6, Updated for consistency with shells
16 January 2017	Version 1.7, Updated with comments from PPD and responses to the outstanding comments in agreement with PPD
11 March 2017 (v1.7)	Updated AE section to remove tables not produced.
02 January 2018 (v1.8)	Updates from BDR1 and protocol version 3
20April 2018 (v1.10)	Updates from review comments from SAP v0.9, inclusion of extra AE analyses
18Jun2018 (v1.11)	Applied BDR2 comments, added PK analyses, added urinalysis analyses.
22JUN2018 (v2.0)	Final Version

1. STUDY DETAILS

1.1 Study objectives

Primary Objective:	Outcome Measure:
To assess the efficacy of tremelimumab monotherapy in terms of ORR	ORR using Investigator assessments according to RECIST 1.1[a]

[a] Decision to proceed to Stage 2 (ie, enrol 12 additional patients) for each tumor type will be performed based on tumor information recorded in the clinical database by the Investigator according to RECIST 1.1.
Abbr: ORR Objective response rate; RECIST 1.1 Response Evaluation Criteria In Solid Tumors, Version 1.1.

Secondary Objective:	Outcome Measure:
To further assess the efficacy of tremelimumab monotherapy in terms of DoR, DCR, PFS, BoR, and OS	DoR, DCR, PFS[a], and BoR using Investigator assessments according to RECIST 1.1 OS
To assess the efficacy of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy after confirmed PD on tremelimumab monotherapy or during follow-up in terms of ORR, DoR, DCR, PFS, BoR, and OS	ORR, DoR, DCR, PFS, and BoR using Investigator assessments according to RECIST 1.1 OS

[a] Progression status at time analyses of PFS analyses, modified for confirmation of progression (Full Analysis Set.
Abbr: BoR Best objective response; DCR Disease control rate; DoR Duration of response; ORR Objective response rate; OS Overall survival; PD Progressive disease; PFS Progression-free survival;
RECIST 1.1 Response Evaluation Criteria In Solid Tumors, Version 1.1.

Safety Objective:	Outcome Measure:
To assess the safety and tolerability profile of tremelimumab monotherapy	AEs, physical examinations, laboratory findings, vital signs, and ECGs
To assess the safety and tolerability profile of MEDI4736 monotherapy and of MEDI4736 + tremelimumab combination therapy after confirmed PD on tremelimumab monotherapy or during follow-up	AEs and laboratory findings

Abbr: AE Adverse event; ECG Electrocardiogram; PD Progressive disease.

Exploratory Objective:	Outcome Measure:
To assess the PK of tremelimumab monotherapy, MEDI4736 monotherapy, and MEDI4736 + tremelimumab combination therapy	Concentration of tremelimumab and MEDI4736 in blood and non-compartmental PK parameters, such as peak concentration and trough (as data allow, sparse sampling)
To investigate the immunogenicity of tremelimumab and MEDI4736	Presence of ADAs for tremelimumab and MEDI4736 (confirmatory results: positive or negative)
To collect blood and tissue samples for defining biological responses to tremelimumab monotherapy, MEDI4736 monotherapy, and MEDI4736 + tremelimumab combination therapy and for identifying candidate markers that may correlate with likelihood of clinical benefit	Protein expression detected by IHC (eg, PD-L1) Circulating soluble factors (eg, cytokines and autoantibodies) miRNA/mRNA T-cell and MDSC phenotyping

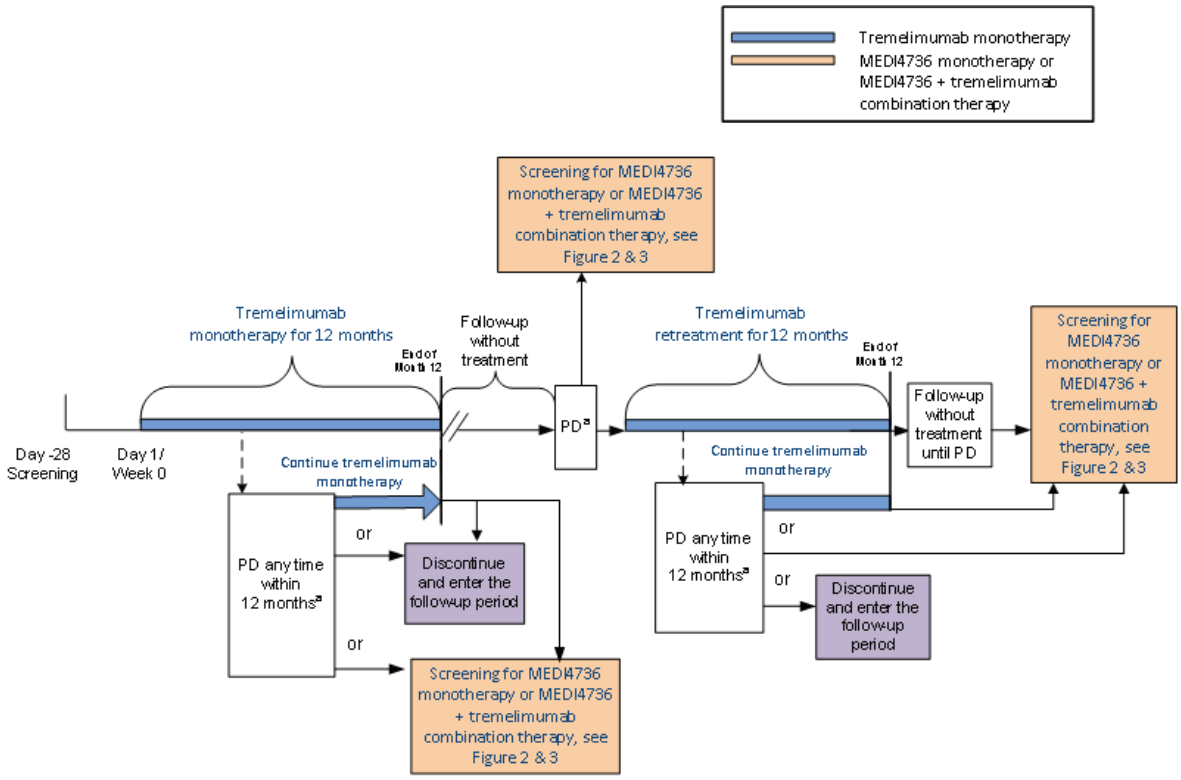
Exploratory objectives are not within the scope of this SAP, and will be the responsibility of AstraZeneca/MedImmune Clinical Pharmacology or Biomarker groups, or designee, and will be reported separately from the main CSR.
Abbr: ADA Anti-drug antibody; IHC Immunohistochemistry; MDSC Myeloid-derived suppressor cell; miRNA Micro-ribonucleic acid; mRNA Messenger ribonucleic acid; PD-L1 Programmed cell death ligand 1; PK Pharmacokinetic(s).

1.2 Study design

This is an open-label, multi-center study to determine the efficacy and safety of tremelimumab monotherapy in the treatment of different patient cohorts with specified advanced solid tumors. If eligible and at the discretion of the Investigator, after confirmed disease progression on tremelimumab monotherapy or during follow-up, patients will have the option of being sequenced to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy, for up to 12 months or until disease progression, whichever comes sooner.

Schematic diagrams of the overall study design are shown in Figure 1, Figure 2, and Figure 3, and a flowchart of the study is presented in Figure 4.

Figure 1 Overall study design for tremelimumab monotherapy

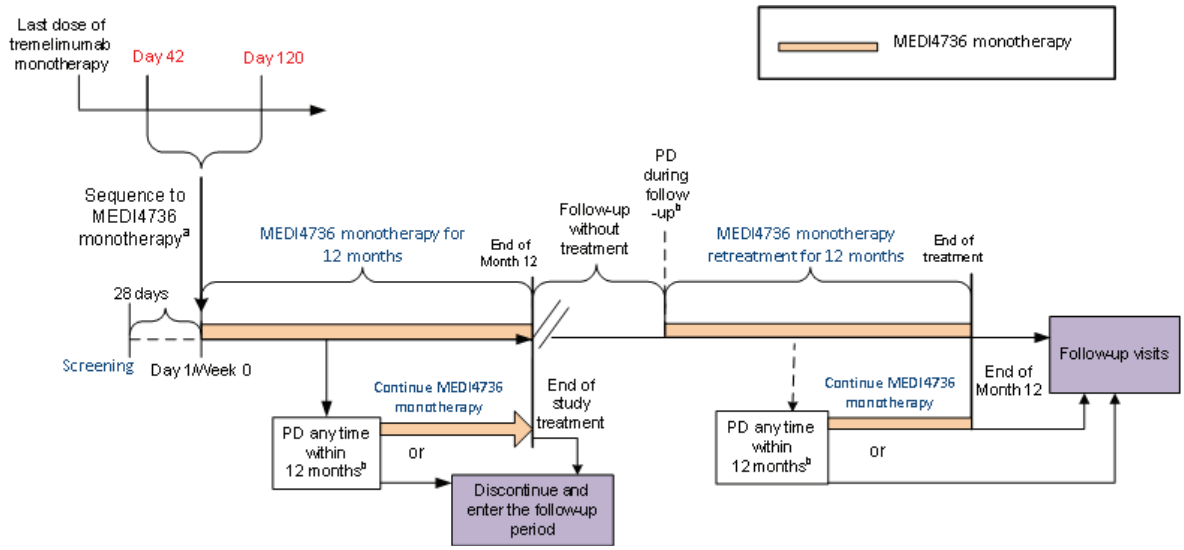


[a] PD will be according to RECIST 1.1. The decision to retreat with tremelimumab monotherapy or sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy is at the discretion of the Investigator. A confirmatory scan is required for patients who sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy. In cases of unequivocal PD/symptomatic PD, the Investigator may elect not to confirm PD depending on the status of the patient before sequencing.

Note: Using a minimax Simon 2-Stage design, the first 20 evaluable patients for each tumor type will be assessed for ORR, and recruitment will be stopped early if no response is observed. (Ongoing patients will still be eligible to sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy as previously described.) If 1 or more responses are observed out of the first 20 treated patients with the selected tumor type, an additional 12 patients will be enrolled, for a total of 32 evaluable patients. If no responses are observed, the DCR data will also be evaluated to make a final decision before discontinuing the tumor cohort. If at least 10 out of the first 20 patients achieve DCR (≥50% DCR) after 2 tumor assessments, then an additional 12 patients may be enrolled, for a total of 32 evaluable patients. Patients' tumor response and DCR will be monitored on an ongoing basis to minimize the time between Stages 1 and 2.

Abbr: DCR Disease control rate; ORR Objective response rate; PD Progressive disease; RECIST 1.1 Response Evaluation Criteria In Solid Tumors, Version 1.1.

Figure 2 Overall study design for MEDI4736 monotherapy

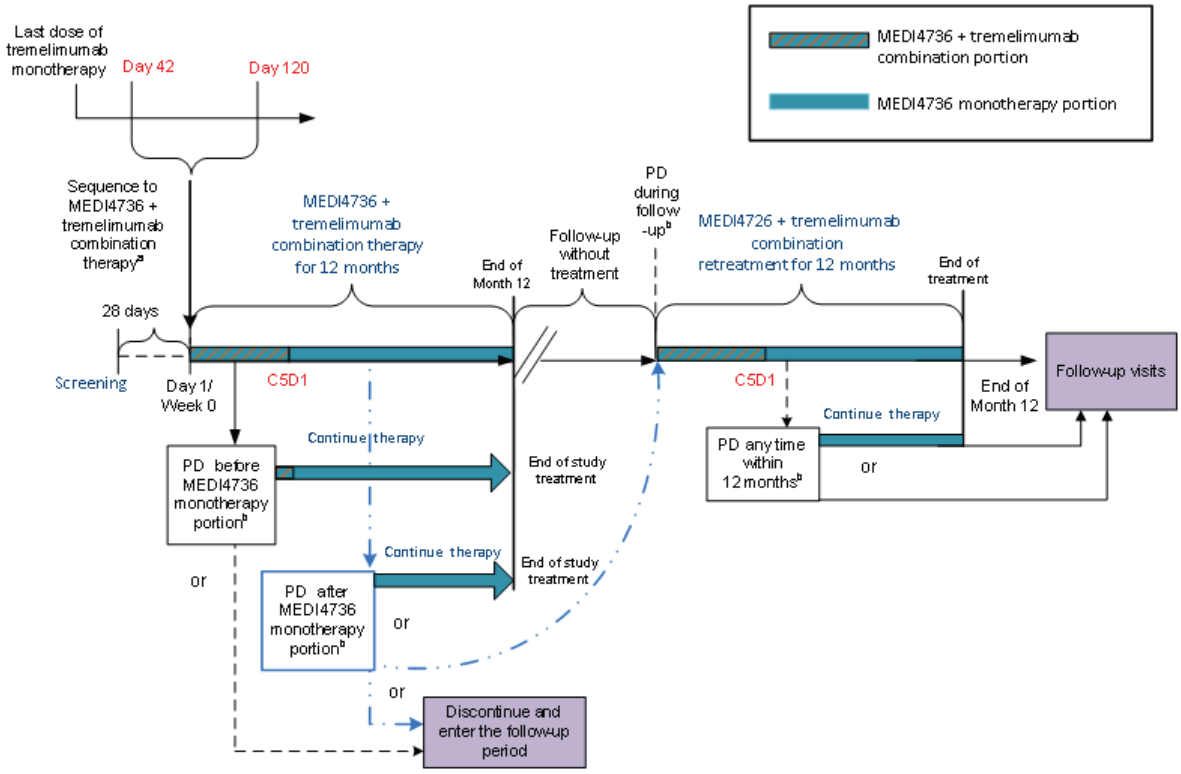


[a] For patients who have confirmed PD during the tremelimumab monotherapy follow-up period, treatment with sequenced therapy will not be more than 60 days after confirmed progression.

[b] PD will be according to RECIST 1.1. All patients who are eligible to restart treatment after screening will receive a maximum of 12 months of further treatment.

Abbr: PD Progressive disease; RECIST 1.1 Response Evaluation Criteria In Solid Tumors, Version 1.1.

Figure 3 Overall study design for MEDI4736 + tremelimumab combination therapy

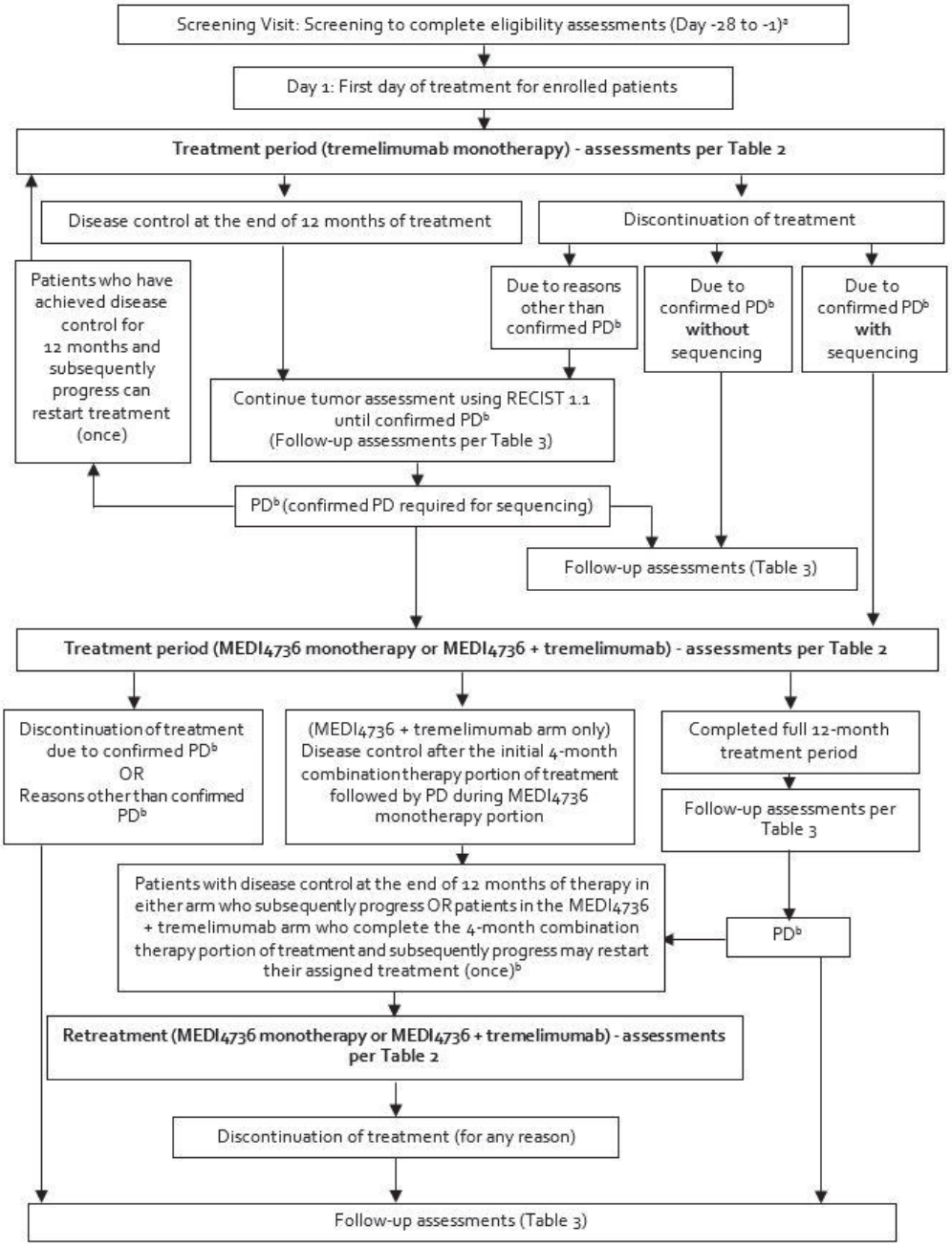


[a] For patients who have confirmed PD during the tremelimumab monotherapy follow-up period, treatment with sequenced therapy will not be more than 60 days after confirmed progression.

[b] PD will be according to RECIST 1.1. Patients receiving combination therapy who complete the 4 dosing cycles with the combination of MEDI4736 + tremelimumab (with clinical benefit per Investigator judgment), but subsequently experience progression (according to RECIST 1.1) during treatment with MEDI4736 alone, will be given the option to restart MEDI4736 + tremelimumab combination therapy (once). All patients who restart treatment will receive a maximum of 12 months of further treatment.

Abbr: PD Progressive disease; RECIST 1.1 Response Evaluation Criteria In Solid Tumors, Version 1.1.

Figure 4 Study flowchart for patients enrolled in the study



[a] Screening assessments can be performed in a step-wise process. The baseline tumor assessment should be performed within 28 days prior to enrollment. Fresh tumor biopsy samples, if necessary, should be obtained as the last step in the screening process, after the patient has been confirmed to meet all other inclusion criteria and confirmed not to meet any exclusion criteria.

[b] In addition to PR and CR, a confirmatory scan is required following the initial demonstration of PD. (See protocol section 5.1 for more information.) Patients must have confirmed PD on tremelimumab monotherapy or during follow-up prior to sequencing to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy, which is at the Investigator's discretion. In cases of unequivocal

PD/symptomatic PD, the Investigator may elect not to confirm PD depending on the status of the patient before sequencing.
Abbr: CR Complete response; PD Progressive disease; PR Partial response; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, Version 1.1.

For each tumor cohort, a minimax Simon 2-Stage design (Simon 1989) will be used to stop recruitment early if no response is observed in the first stage and thus reduce patient exposure to non-active treatment. If 1 or more responses are observed in the first 20 treated patients with the selected tumor type, an additional 12 patients will be enrolled, for a total of 32 evaluable patients. If no responses are observed, the DCR data will also be evaluated to make a final decision before discontinuing the tumor cohort. If at least 10 out of the first 20 patients achieve DCR (≥50% DCR) after 2 tumor assessments, then an additional 12 patients may be enrolled, for a total of 32 evaluable patients. Patients' tumor response and DCR will be monitored on an ongoing basis in order to minimize the time between Stage 1 and Stage 2.

Tumor assessments will be performed as follows for each tumor type (additional tumor types may be added at the discretion of the Sponsor), with categorization of objective tumor response by Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1):

- Urothelial bladder cancer (UBC) and triple-negative breast cancer (TNBC): Every 8 weeks relative to the date of first infusion of investigational product (IP) until confirmed progression

- Pancreatic ductal adenocarcinoma (PDAC): Every 6 weeks for the first 48 weeks relative to the date of first infusion of IP and then q12w thereafter until confirmed progression

1.3 Number of subjects

This study will screen approximately 38 patients with each selected advanced solid tumor type globally to enroll approximately 32 evaluable patients (ie, patients eligible to be included in the Evaluable analysis set).

The study is sized to allow the use of a minimax Simon 2-Stage design within each of the tumor types according to the following assumptions and algorithms. The minimax Simon 2-Stage design as well as DCR after 2 tumor assessments will be evaluated to reduce exposure of a large number of patients to ineffective treatment, according to the algorithm below:

- H0: p0=0.02 (p0: proportion of responders under the null hypothesis)

- H1: p1=0.14 (p1: proportion of responders under the alternate hypothesis)

Algorithm:

N=32 evaluable patients, with N1=20 and N2=12

- If no response is observed out of the first 20 patients, the DCR data will also be evaluated to make a final decision before discontinuing the tumor cohort. (Ongoing patients will still be eligible to sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy as previously described.) If ≥10 out of the first 20 patients achieve DCR (≥50% DCR) after 2 tumor assessments, then an additional 12 patients may be enrolled. A final decision to continue enrollment will be made by the Sponsor after evaluating all of the available clinical data at that time.

- If 1 or more responses are observed out of the first 20 patients, enroll 12 additional patients, for a total of 32 evaluable patients for each tumor type.

- If ≤2 responses are observed out of the 32 patients, then no further investigation of that tumor type will be done.

- If >2 responses are observed out of the 32 patients, the null hypothesis will be rejected, and further investigation of that tumor type is warranted.

The assessment of response after the first 20 evaluable patients in the tumor types will be based on Investigator/site tumor data RECIST 1.1 assessment. This design will ensure a type I error of no more than 5% (1-sided) and an 83% power for each of the tumor types.

2. ANALYSIS SETS

2.1 Definition of analysis sets

Definitions of the analysis sets for each outcome variable are provided in Table 1.

Table 1 Summary of outcome variables and analysis populations

Outcome variable	Populations
Efficacy data	
ORR, DoR, DCR, BoR, PFS, OS	FAS[a], MEDI[b] & COMBO[c] analysis sets
Demography	FAS[d]
PK data	PK Analysis Set
Safety data	
Exposure	Safety Analysis Set[e]
AEs	Safety Analysis Set[e]
Laboratory measurements	Safety Analysis Set[e]
Vital signs	Safety Analysis Set[e]

[a] The FAS will be used for the efficacy analysis of patients who received tremelimumab monotherapy.
[b] The MEDI analysis set will be used for patients who sequence to MEDI4736 monotherapy.
c The COMBO analysis set will be used for patients who sequence to MEDI4736 + tremelimumab combination therapy.
[d] Separate summaries will be performed for tremelimumab monotherapy, MEDI4736 monotherapy, and MEDI4736 + tremelimumab combination therapy
Abbr: AE Adverse event; BoR Best objective response; DCR Disease control rate; DoR Duration of response; FAS Full Analysis Set; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; PK Pharmacokinetic.

2.1.1 Full Analysis Set

The statistical analysis with the full analysis set (FAS) will include all treated patients (i.e., received at least 1 dose of tremelimumab monotherapy).

2.1.2 MEDI Analysis Set

This analysis set is a subset of the full analysis set, and it will include all patients who are treated with tremelimumab, receive at least 1 dose of MEDI4736 monotherapy, and have a baseline tumor assessment prior to MEDI4736 monotherapy dosing.

2.1.3 COMBO Analysis Set

This analysis set is subset of the full analysis set, and it will include all patients who are treated with tremelimumab, receive at least 1 dose of MEDI4736 + tremelimumab

combination therapy, and have a baseline tumor assessment prior to MEDI4736 + tremelimumab combination therapy dosing.

2.1.4 Safety Analysis Set

All patients who received at least 1 dose of IP (tremelimumab monotherapy, MEDI4736 monotherapy, or MEDI4736 + tremelimumab combination therapy) will be included in the Safety Analysis Set. When assessing safety and tolerability, summaries will be produced based on the Safety Analysis Set. Separate safety tables and figures will be produced for tremelimumab monotherapy, MEDI4736 monotherapy, and MEDI4736 + tremelimumab combination therapy.

2.1.5 Pharmacokinetic Analysis Set

All patients who receive at least 1 dose of IP per the protocol for whom any post-dose data are available will be included in the PK analysis set.

2.2 Violations and deviations

The pharmacokineticist will determine the strategy for dealing with data affected by protocol deviations with input from AstraZeneca (AZ) study physician as needed before any formal statistical analysis is performed.

All important deviations related to the study inclusion or exclusion criteria and study conduct will be listed and summarized by treatment group. None of the deviations will lead to any patients being excluded from any of the analysis sets described in Section 2.1 (with the exception of the PK and PD analysis set, if the deviation is considered to impact upon PK or PD respectively).

If the deviations are important enough to have the potential to impact the primary analysis, additional sensitivity analyses may be performed.

The following general categories will be considered important deviations. This list is not exhaustive and additional important deviations may be added prior to database lock. A full list is provided within the study Protocol Deviations documentation.

· Informed consent procedure deviation (e.g., no informed consent signed prior to any screening procedure)

· Eligibility criteria deviation (e.g., any inclusion criteria not met or exclusion criteria met)

..Prohibited medication deviation (e.g., patient received other anticancer agents, investigational agents, or radiotherapy while on study treatment)

The categorization of these as important deviations is not automatic and will depend on duration and the perceived effect on efficacy. In addition to the programmatic determination of the deviations above, monitoring notes or summaries will be reviewed by the clinical team

to determine any important post-entry deviations that are not identifiable via programming, and to check that those identified via programming are correctly classified. The final classification will be made prior to database lock.

A summary will be produced showing any patients who received a treatment different to that assigned to them for any duration of treatment (for example if a patient was prescribed MEDI4736 monotherapy but did receive at least one dose of tremelimumab).

Patients who receive the wrong treatment (e.g. at least one dose of tremelimumab, when intended treatment was MEDI4736 monotherapy) at any time will be included in the safety analysis set as described in Section 2.1.4. During the study, decisions on how to handle these situations will be made on an individual basis with written instruction from the study team leader/physician and/or statistician.

3. PRIMARY AND SECONDARY VARIABLES

3.1 General considerations

Baseline will be the last non-missing assessment, within 28 days of first dose date, of the variable under consideration prior to the intake of first dose of study treatment. For patients who sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy following confirmed PD on tremelimumab monotherapy or during follow-up, baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy within 28 days prior to sequencing.

In all summaries change from baseline variables will be calculated as the post treatment value minus the value at baseline. Percentage change from baseline will be calculated as follows:

[(Post baseline value – Baseline value)/Baseline value] ×100

Study day is calculated from first dose for safety data:

Study day = date of assessment – date of first dose +1

3.2 Demography and baseline variables

1. Age (years) will be grouped in to the following categories:

   >=18 - <50
   >=50 - <65
   >=65 - <88

2. Weight (kg) will be grouped into the following categories:

   < 50
   >= 50

3. Body mass Index (BMI) will be calculated as weight (kg) / height $(m)^2$ and grouped into the following categories:

   Normal (<25)
   Overweight (25-30)
   Obesity (>30)

4. Time from most recent disease progression (months) until date of first dose will be calculated for all patients using (FAS).

3.3 Derivation of RECIST visit responses

For all patients, the RECIST version 1.1 (see further Appendix E of the Clinical Study Protocol (CSP)) tumour response data will be used to determine each patient's visit response. It will also be used to determine if and when a patient has progressed in accordance with RECIST 1.1 and also their BoR. The baseline assessment should be performed no more than 28 days before the start of study therapy, and ideally as close as possible to the start of IP. Follow-up tumor assessments will be performed every 6 (PDAC) or 8 (UBC/TNBA) weeks for the first 48 weeks (relative to the date of the first infusion of tremelimumab or MEDI4736) and then every 12 weeks thereafter until confirmed progression, with categorization of objective tumor response by RECIST 1.1. If an unscheduled assessment is performed and the patient has not progressed, every attempt will be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

Disease progression requires confirmation; the confirmatory scans should be performed to preferably occur at the next scheduled visit and no less than 4 weeks after the initial assessment of progressive disease (PD) in the absence of significant clinical 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 IP start). This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients. For all patients who are treated through progression, the Investigator should ensure patients do not have any significant, unacceptable or irreversible toxicities that indicate continuing treatment will not further benefit the patient, and that the patient still meets all of the inclusion criteria and none of the exclusion criteria for this study including re-consenting to continue treatment. Progression will be considered confirmed if the following criteria are met

- ≥20% increase in the sum of diameters of target lesions (TL) compared with the nadir at 2 consecutive visits with an absolute increase of 5 mm[a]

- and/or significant progression (worsening) of non-target lesions (NTL) 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.

[a] The assessment of progression requires a ≥20% increase in the sum diameters of target lesions at the first progression time point 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.

RECIST version 1.1 will be regarded as primary in terms of the efficacy analyses and RECIST 1.1 modified for confirmation of progression is supportive. At each visit for the site investigator data, an overall visit response will be determined programmatically - using the information from TLs, NTLs and new lesions.

RECIST outcomes will be calculated using a computer program for the site investigator data.

3.3.1 Site Investigator Assessment Using RECIST 1.1 Target lesions (TLs)

Measurable disease is defined as having at least one measurable lesion, not previously irradiated, which is ≥ 10 mm in the longest diameter (LD) (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 patient can have a maximum of 5 measurable lesions recorded at baseline with a maximum of 2 lesions per organ (representative of all lesions involved suitable for accurate repeated measurement) and these are referred to as TLs. If more than one baseline scan is recorded then measurements that is closest before the first dose of IP will be used as the baseline sum of TLs. 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.

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.

Measurable disease (i.e., at least one TL) is one of the entry criteria for the study. However, if a patient with non-measurable disease is enrolled in the study, the evaluation of overall visit responses will be based on the overall NTL assessment and the absence/presence of new lesions (see Section 3.3.2 for further details). If a patient does not have measurable disease at baseline then the TL visit response will be not applicable (NA).

Table 2 TL Visit Responses

Visit Responses	Description
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to <10mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters as long as criteria for PD are not met.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Not Evaluable (NE)	Only relevant in certain situations (i.e. if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit; and scaling up could not be performed for lesions with interventions). Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response
Not Applicable (NA)	No target lesions are recorded at baseline

Rounding of TL data

For calculation of PD and PR for TLs, percentage changes from baseline and previous minimum should be rounded to 1 decimal place before assigning a TL response. For example 19.95% should be rounded to 20.0% but 19.94% should be rounded to 19.9%.

Missing TL data

For a visit to be evaluable, all TL measurements should be recorded. However, a visit response of PD should still be assigned if any of the following occurred:

- A new lesion is recorded.
- A NTL visit response of PD is recorded.
- The sum of TLs is sufficiently increased to result in a 20% increase, and an absolute increase of ≥ 5mm, from nadir even assuming the non-recorded TLs have disappeared.

Note: the nadir can only be taken from assessments where all the TLs had a lesion diameter recorded.

Lymph nodes

For lymph nodes, if the size reduces to < 10 mm then these are considered non-pathological. However, a size will still be given and this size should still be used to determine the TL visit response as normal. In the special case where all lymph nodes are < 10 mm and all other TLs are 0 mm then although the sum may be >0 mm the calculation of TL response should be over-written as a CR.

TL visit responses subsequent to CR

A CR can only be followed by CR, PD or NE. If a CR has occurred then the following rules at the subsequent visits must be applied:

- Step 1: If all lesions meet the CR criteria (i.e. 0 mm or < 10 mm for lymph nodes) then response will be set to CR irrespective of whether the criteria for PD of TL is also met i.e. if a lymph node LD increases by 20% but remains < 10 mm.

- Step 2: If some lesion measurements are missing but all other lesions meet the CR criteria (i.e. 0 mm or < 10 mm for lymph nodes) then response will be set to NE irrespective of whether when referencing the sum of TL diameters the criteria for PD is also met.

- Step 3: If not all lesions meet the CR criteria and the sum of lesions meets the criteria for PD then response will be set to PD

- Step 4: If after steps 1 – 3 a response can still not be determined the response will be set to remain as CR

TL too big to measure

If a TL becomes too big to measure this should be indicated in the database and a size ('x') above which it cannot be accurately measured should be recorded. If using a value of x in the calculation of TL response would not give an overall visit response of PD, then this will be flagged and reviewed by the study team. It is expected that a visit response of PD will remain in the vast majority of cases.

TL too small to measure

If a TL becomes too small to measure a value of 5 mm will be entered into the database and used in TL calculations, unless the radiologist has indicated and entered a smaller value that can be reliably measured. If a TL response of PD results then this will be reviewed by the study team.

Irradiated lesions/lesion intervention

Previously irradiated lesions (i.e. lesion irradiated prior to entry into the study) should be recorded as NTLs and should not form part of the TL assessment.

Any TL (including lymph nodes), which has had intervention during the study (for example, irradiation / palliative surgery / embolisation), should be handled in the following way and once a lesion has had intervention then it should be treated as having intervention for the remainder of the study noting that an intervention will most likely shrink the size of tumours:

- Step 1: the diameters of the TLs (including the lesions that have had intervention) will be summed and the calculation will be performed in the usual manner. If the visit response is PD this will remain as a valid response category.

- Step 2: If there was no evidence of progression after step 1, treat the lesion diameter (for those lesions with intervention) as missing and scale up as described below, as long as there remain ≤ 1/3 of the TLs with missing measurements. If the scaling results in a visit response of PD then the patient would be assigned a TL response of PD.

- Step 3: If after both steps PD has not been assigned, then if appropriate, a scaled sum of diameters will be calculated (as long as ≤ 1/3 of the TLs with interventions), and PR or SD then assigned as the visit response. Patients with intervention are evaluable for CR as long as all non-intervened lesions are 0 (or <10mm for lymph nodes) and the lesions that have been subject to intervention also has a value of 0 recorded.

At subsequent visits the above steps will be repeated to determine the TL and overall visit response. When calculating the previous minimum, lesions with intervention should be treated as missing and scaled up where appropriate (as per step 2 above).

Scaling (applicable only for irradiated lesions/lesion intervention)

If > 1/3 of TL measurements are treated as missing (because of intervention) then TL response will be NE, unless the sum of diameters of non-missing TL would result in PD (i.e. if using a value of 0 for missing lesions, the sum of diameters has still increased by > 20% or more compared to nadir and the sum of TL has increased by 5mm from nadir).

If ≤ 1/3 of the TL measurements are treated as missing (because of intervention) then the results will be scaled up (based on the sizes at the nadir visit 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 non-missing lesions to the nadir sum of diameters excluding the lesions with missing measurements.

Table 3 Example of scaling

Lesion	Longest diameter at nadir visit	Longest diameter at follow-up visit
1	7.2	7.1
2	6.7	6.4
3	4.3	4.0
4	8.6	8.5
5	2.5	Intervention
Sum	**29.3**	**26**

Lesion 5 has had an intervention at the follow-up visit.

The sum of lesions 1-4 at the follow-up is 26 cm. The sum of the corresponding lesions at baseline visit is 26.8 cm.

Scale up as follows to give an estimated TL sum of 28.4cm:

$$\frac{26}{26.8} \times 29.3 = 28.4cm$$

Lesions that split in two

If a TL splits in two, then the LDs of the split lesions should be summed and reported as the LD for the lesion that split.

Lesions that merge

If two TLs merge, then the LD of the merged lesion should be recorded for one of the TL sizes and the other TL size should be recorded as 0 mm.

Change in method of assessment of TLs

CT and MRI are the only methods of assessment that can be used within the trial. If a change in method of assessment occurs between CT and MRI, this will be considered acceptable and no adjustment within the programming is needed.

If a change in method involves clinical examination (e.g., CT changes to clinical examination or vice versa), any affected lesions should be treated as missing.

3.3.2 Site Investigator Assessment Using RECIST: Non-target lesions (NTLs) and new lesions.

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.

Response for NTLs will be derived based on the investigator's overall assessment of NTLs as follows:

Table 4 NTL Visit Responses

Visit Responses	Description
Complete Response (CR)	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10 mm short axis).
Progressive Disease (PD)	Unequivocal progression of existing NTL. 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.
Non-CR/Non-PD	Persistence of one or more NTLs with no evidence of progression.
Not Evaluable (NE)	Only relevant when one or some of the NTL 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 TL at baseline, this is relevant if any of the NTL were not assessed at this visit and the progression criteria have not been met.
Not Applicable (NA)	Only relevant if there are no NTLs at baseline

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 the presence of SD or PR in TLs, the overall tumour burden has increased sufficiently to merit a determination of disease progression. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

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: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

New lesions will be identified via a Yes/No tick box. The absence and presence of new lesions at each visit should be listed alongside the TL and NTL visit responses.

A new lesion indicates progression so the overall visit response will be PD irrespective of the TL and NTL response.

If the question 'Any new lesions since baseline' has not been answered with Yes or No and the new lesion details are blank this is not evidence that no new lesions are present and should be treated as NE in the derivation of overall visit response.

Symptomatic progression is not a descriptor for progression of NTLs: it is a reason for stopping study therapy and will not be included in any assessment of NTLs.

Patients with 'symptomatic progression' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

3.3.3 Site Investigator Assessment Using RECIST 1.1: Overall visit response

Table 5 defines how the previously defined TL and NTL visit responses will be combined with new lesion information to give an overall visit response.

Table 5 Overall Visit Responses

Target Lesions	Non-target lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No (or NE)	PR
SD	Non PD or NE	No (or NE)	SD
NA	Non CR/Non PD	No	SD
NA	Non PD	NE	SD
NE	Non PD or NE	No (or NE)	NE
NA	NE	No (or NE)	NE
PD	Any	Any	PD
Any	PD	Any	PD
Any	Any	Yes	PD
NA	NA	No	NED

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NED = no evidence of disease, NA = not applicable (only relevant if there were no TL/NTL at baseline).

3.4 RECIST 1.1 based variables

All RECIST 1.1 assessments, whether scheduled or unscheduled, will be included in the calculations. This is also regardless of whether a patient discontinues study treatment or receives another anticancer therapy.

At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, or PD depending on the status of their disease compared with baseline and previous assessments. Baseline will be assessed within the 28 days prior to enrollment. For patients who sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy following confirmed progression on tremelimumab monotherapy or during follow-up, a new baseline assessment will be recorded prior to the first dose of sequenced therapy. If the scan confirming PD on tremelimumab monotherapy occurs within 28 days of the first dose of sequenced therapy, this scan may be used as the baseline scan for sequencing to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy. If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE) (unless there is evidence of progression in which case the response will be assigned as PD).

Please refer to Appendix E of the CSP for the definitions of CR, PR, SD, and PD.

3.4.1 Primary variable - Objective response rate

Main analysis

The primary endpoint is objective response rate (ORR per RECIST 1.1 as assessed by the site Investigator), defined as the number (%) of patients with a confirmed overall response of CR or PR and will be based on all treated patients who have measurable disease at baseline per the site Investigator. Therefore, if the site Investigator finds any patient who does not have measurable disease at baseline, then the analysis of ORR using site Investigator data will exclude that patient and the denominator will be all treated patients who have measurable disease at baseline per the site Investigator.

A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging 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.

Supplemental analysis

The above derivation of ORR will be repeated for patients who sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy. This derivation of ORR will also be repeated for patients who sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy, this time covering the entire study period.

3.4.2 Secondary variables

3.4.2.1 Duration of response

Main analysis

Duration of response (per RECIST 1.1 as assessed by the site Investigator) 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.

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.

If patients do not progress within 3 months (PDAC patients) or 4 months (UBC/TNBC patients) of the last evaluable assessment, the last evaluable RECIST assessment will be used. Where

3 months is defined as 12 weeks -7 days = 77 days

4 months is defined as 16 weeks -7 days = 105 days

12 months is defined as 52 weeks -7 days = 357 days

following the start of study treatment.

Supplemental analysis

The above derivation of DoR will be repeated for patients who sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy.

3.4.2.2 Disease control rate

Main analysis

Disease control rate at 3 months (PDAC patients) or 4 months (UBC/TNBC patients) and 12 months (all patients) is defined as the percentage of patients who have a best objective response (BoR) of CR or PR in the first 3 or 4 months and 12 months, respectively, or who have demonstrated SD for a minimum interval of 3 months or 4 months and 12 months, following the start of study treatment. Where 3,4 and 12 months are defined in Section 3.4.2.1. DCR will be determined programmatically based on RECIST 1.1 using site Investigator data and all data up until the first progression event.

Supplemental analysis

The above derivation of DCR may be repeated for patients who sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy for 3 months (PDAC patients) or 4 months (UBC/TNBC patients) only.

3.4.2.3 Progression-free survival

Main analysis

PFS (per RECIST 1.1 as assessed by the site Investigator) will be defined as the time from the date of enrollment until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to progression. The confirmatory scan must be no sooner than 4 weeks after the initial suspected progression and preferably at the next scheduled visit in the absence of clinically significant deterioration.
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 + window of 1 week (i.e. 2 x q8w +7

days for UBC/TNBC patients, or 2 x q6w +7 days for PDAC patients), 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 1 day 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:

- Date of progression will be determined based on the earliest of the dates of the component that triggered the progression on the first set of scans 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.

In the absence of clinically significant deterioration, the investigational site is advised to continue the patients on their respective treatments until progression has been confirmed.

Supplemental analysis

The above derivation of PFS may be repeated for patients who sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy. PFS (per RECIST 1.1 as assessed by the site Investigator) for these patients will be defined as the time from the date of initial treatment with sequenced therapy (ie, either MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy) until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to progression.

3.4.2.4 Overall survival

Main analysis

Overall survival is defined as the time from the date of first dose of IP 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 based on local laws.

Supplemental analysis

Overall survival for patients who sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy is defined as the time from the date of initial treatment

with sequenced therapy (ie, either MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy) until death due to any cause.

Sensitivity analysis

No sensitivity analysis is planned for OS.

3.4.2.5 Best objective response

Main analysis

Best objective response is calculated based on the overall visit responses from each RECIST 1.1 assessment, described in Appendix E in the CSP. It is the best response a patient has had during their time in the study up until RECIST 1.1 progression (or confirmed progression where applicable) or the last evaluable assessment in the absence of RECIST 1.1 progression.

Categorization of BoR will be based on RECIST 1.1 (Appendix D of the CSP) using the following response categories: CR, PR, SD, PD, and NE.

CR or PR must be confirmed. BoR will be determined programmatically based on RECIST 1.1 using site Investigator data using all data up until the first progression event.

For patients whose progression event is death, BoR will be calculated based upon all evaluable RECIST 1.1 assessments prior to death.

For patients who die with no evaluable RECIST 1.1 assessments, if the death occurs ≤17 weeks after enrollment (ie, 2 x q8w +7 days) for UBC/TNBC patients, or ≤13 weeks (i.e. 2 x q6w +7 days) for PDAC patients, then BoR will be assigned to the progression (PD) category. For patients who die with no evaluable RECIST assessments, if the death occurs >17 weeks or >13 weeks, respectively, after the date of enrollment then BoR will be assigned to the NE category. For patients to have a best overall response of SD, the response of SD must be observed for >15 weeks (UBC/TNBC patients) or >11 weeks (PDAC), respectively, after the date of enrolment, otherwise the BoR will be assigned to the NE category.

Progression events that have been censored due to them being >17 or >13 weeks, respectively for UBC/TNBC or PDAC patients, after the last evaluable assessment will not contribute to the BoR derivation.

Supplemental analysis

For patients who have confirmed progression on tremelimumab monotherapy or during follow-up and sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy, the above analyses for BoR may be repeated.

3.4.2.6 Time to Response

Time to response (TTR) (per RECIST 1.1 as assessed by the site investigator) is defined as the time from the date of first dose until the date of first documented response (which is

subsequently confirmed). The date of first documented response should coincide with that used for the RECIST 1.1 DoR endpoint.

Time to response will not be defined for those patients who do not have documented confirmed response and will be derived for the full analysis set, tremelimumab monotherapy patients only.

3.5 Safety variables

3.5.1 General considerations for safety assessments

Time windows will need defining for any presentations that summarize values by visit. The following conventions should also apply:

The time windows should be exhaustive so that data recorded at any time point has the potential to be summarized. Inclusion within the time window should be based on the actual date and not the intended date of the visit.

All unscheduled visit data should have the potential to be included in the summaries.

The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls half way between the two visits (the lower limit of the first post-baseline visit will be Day 2). If an even number of days exists between two consecutive visits then the upper limit will be taken as the midpoint value minus 1 day.

For example, the visit windows for vital signs data are:

- Day 29, visit window 2 – 43
- Day 57, visit window 44 – 71
- Day 85, visit window 72 – 99
- Day 113, visit window 100 – 127
- Day 141, visit window 128 – 155
- Day 169, visit window 156 – 183 (where the subsequent visit is Day 197)

For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used (regardless of where it falls in an interval).

Listings should display all values contributing to a time point for a patient.

For visit based summaries:

- If there is more than one value per patient within a time window then the closest value should be summarized, or the earlier in the event the values are equidistant from the nominal visit date. The listings should highlight the value for that patient that went into the summary table, wherever feasible.

— To prevent very large tables or plots being produced that contain many cells with meaningless data, for each cohort visit data should only be summarized if the number of observations is greater than the minimum of 11 and > 1/3 of patients dosed.

For summaries at a patient level, all values should be included, regardless of whether they appear in a corresponding visit based summary, when deriving a patient level statistic such as a maximum.

Baseline is defined in Section 4.1. For laboratory data, any assessments made on day 1 will be considered pre-dose. Alternatively, if two visits are equally eligible to assess patient status at baseline (e.g., screening and baseline assessments both on the same date prior to first dose with no washout or other intervention in the screening period), the average should be taken as a baseline value. Where safety data are summarized over time, study day will be calculated in relation to date of first study treatment

Missing safety data will generally not be imputed. However, safety assessment values of the form of "< x" (i.e., below the lower limit of quantification) or > x (i.e., above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "< x" or "> x" in the listings.

1. For missing diagnostic dates, if day and/or month are missing use 01 and/or Jan. If year is missing, put the complete date to missing.

2. For missing start AE dates, if day and/or month are missing, use day and/or month of first dose.

3. For missing end AE dates, the following will be applied:

    1. Missing day - Impute the last day of the month unless month is the same as month of the first dose of study drug then impute last dose date.

    2. Missing day and month – impute 31st December unless year is the same as first dose date then impute last dose date.

    3. Completely missing date – need to look at whether the AE/medication is still ongoing before imputing a date and also when it started in relation to study drug. If the ongoing flag is missing then assume that AE is still present / medication is still being taken (i.e. do not impute a date). If the AE/medication has stopped and start date is prior to first dose date then impute the 1st dose date, if it started on or after first dose date then impute a date that is after the last dose date.

Precision of derived variables, such as conversion from conventional units to System International (SI) units, mean value across Electrocardiogram (ECG) replicates, and change from baseline, should be reported consistently with the source data, with respect to both the

type of precision (decimal places or significant figures) and the number of digits/decimals retained.

Source data are generally stored/delivered with fixed decimal places (e.g. height of 183 cm with zero decimal places) or in significant figures (e.g. concentration of 90.0 ng/mL with three significant digits). The precision of individual results may not be directly specified in the source data or corresponding documentation, and in such cases must be inferred from the data itself.

The minimum precision across all data of each input variable (excluding values of lower apparent precision, due ending in zeros) will be used for determining the precision of derived variables.

Note the following standard scientific rules for retaining precision are applicable. Scientific or conversion constants will not contribute to the precision of calculated values.

For data recorded in fixed decimals:

- Addition or subtraction: Results will be reported to the same decimal precision of the number with least number of decimal places. For example: 5.01+5.01=10.02 (two decimal places); 10.1 + 1.01 = 11.1 (one decimal place).
- Multiplication or division: Results will be reported to the least number of decimal places. For example, 9.5 x 1.11 = 10.5 (one decimal place).

For data recorded in significant digits:

- Addition or subtraction: Results will be reported to the same decimal precision of the number with least number of decimal places. For example: 10.213 – 10.1 = 0.1 (one decimal place).
- Multiplication or division: Results will be reported to the least number of significant figures. For example, 9.5 x 1.11 = 11 (two significant figures).

Exception: Derived percentages will by default be calculated to one decimal place if source data contains three or more significant figures; otherwise zero decimals will be used.

Uncommon Exception: Values may instead be rounded to match conventions or standards that independent of source data and may not be addressed in the SAP; e.g. laboratory data standard such as LOINC or LIMS.

Rounded values for derived data shall be used for all reporting. Unrounded values may be used for interim statistical analyses.

3.5.2 Adverse events

All AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

Any adverse events (AE) occurring before treatment with IP will be included in the data listings but will not be included in the summary tables of AEs. For AEs, on treatment (or treatment emergent AEs) will be defined as any AE that started after dosing or prior to dosing and that worsens following exposure to the treatment.

Any AE occurring within 90 days of discontinuation of IP (ie, the last dose of tremelimumab monotherapy, MEDI4736 monotherapy, or MEDI4736 + tremelimumab combination therapy) will be included in the AE summaries.

Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of tremelimumab monotherapy, MEDI4736 monotherapy, or MEDI4736 + tremelimumab combination therapy) will be flagged in the data listings. AEs occurring more than 90 days after discontinuation of tremelimumab monotherapy, MEDI4736monotherapy, or MEDI4736 + tremelimumab combination therapy will be flagged in the data listings. These events will not be included in AE summaries.

Serious AEs

Adverse Events will be assigned as serious by the investigator (as defined in section 6.2 of the CSP).

Severity of AEs

The Common Terminology Criteria for Adverse Events (CTCAE) grade will be assigned by the investigator. Severity of all AEs will be graded according to the CTCAE, Version 4.03:

1. Grade 1 - Mild AE
2. Grade 2 - Moderate AE
3. Grade 3 - Severe AE
4. Grade 4 - Life-threatening or disabling AE
5. Grade 5 - Death related to AE

AEs leading to discontinuation

Discontinuation of IP due to adverse event (DAE) will be considered separately for MEDI4736 and tremelimumab, and in the combination group, AEs resulting on both IPs discontinuing are also of interest.

AEs of special interest

Adverse Events of special interest are events of scientific and medical interest specific to the further understanding of the tremelimumab and MEDI4736 safety profile and require close monitoring and rapid communication by the Investigator to the Sponsor. Tremelimumab and 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 these IPs.For tremelimumab and MEDI4736, AESIs will comprise of (see CSP section 6.5):

1. Diarrhea / Colitis and intestinal perforation
2. Pneumonitis / ILD
3. hepatitis / transaminase increases
4. Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
5. Rash / Dermatitis
6. Nephritis / Blood creatinine increases
7. Pancreatitis / serum lipase and amylase increases
8. Myocarditis
9. Myositis / Polymyositis
10. Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
11. 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.

3.5.3 Treatment exposure

Exposure will be defined separately for tremelimumab monotherapy, MEDI4736 monotherapy, MEDI4736 on the MEDI4736+ tremelimumab combination arm, tremelimumab on the MEDI4736+ tremelimumab combination arm.

Total (intended) exposure (months) =

$$\frac{\text{last dose date where dose} > 0 \text{ mg} - \text{first dose date} + 1}{}$$

365.25 / 12

For patients who sequence onto MEDI4736 + tremelimumab, exposure to tremelimumab will be calculated separately for the monotherapy phase, and the combination treatment.

Total (or intended) exposure of tremelimumab (monotherapy)

1. Total (or intended) exposure is defined as the total treatment period from first dose date of study drug to the earliest of "last dose date of study drug + (27 days or 83 days)" or death date or DCO. Twenty seven days will be added in the numerator of above formulae if the patient stopped dosing before week 24 and 83 days will be added if the patient stopped dosing at week 24 or later.

Total (or intended) exposure of MEDI4736 (monotherapy)

2. Total (or intended) exposure is defined as the total treatment period from first dose date of study drug to the earliest of "last dose date of study drug + 27 days" or death date or DCO.

Total (or intended) exposure of MEDI4736 (combination)

3. Total (or intended) exposure is defined as the total treatment period from first dose date of study drug to the earliest of "last dose date of study drug + (27 days)" or death date or DCO or start of re-treatment.

Total (or intended) exposure of tremelimumab (combination)

4. Total (or intended) exposure is defined as the total treatment period from first dose date of study drug to the earliest of "last dose date of study drug + 27 days" or death date or DCO.

Actual exposure of tremelimumab (separately for monotherapy and combination phases) or MEDI4736 =

Actual exposure (months) = intended exposure – total duration of dose missed, where intended exposure will be calculated as above.

Doses may be missed by mistake, or be planned, e.g. a delay due to AE. The actual exposure calculation makes no adjustment for any dose reductions that may have occurred.

For patients on study treatment at the time of the ORR analysis, the data cut-off (DCO) date will be used to calculate exposure.

Patients who permanently discontinue Tremelimumab or MEDI4736 during a dose interruption

If a patient permanently discontinues IP during a dose interruption, then the date of last administration recorded on DOSDISC will be used in the programming. The reason for

permanent discontinuation of treatment recorded on DOSDISC will be the reason for the dose interruption that they were currently on when they permanently discontinued treatment. The dose interruption will not be included as a dose interruption in the summary tables but will be recorded on the DOSE module and consequently appear in the listing for dosing. Dose interruption summaries will be provided for tremelimumab monotherapy only.

3.5.4 Dose intensity

Relative dose intensity (RDI) is the percentage of the actual dose intensity delivered relative to the intended dose intensity through to treatment discontinuation. Percentage intended dose (PID) is the percentage of the actual dose delivered relative to the intended dose through to progression or treatment completion. Both will be derived using study treatment data up to twelve months or until the date of objective disease progression (if this is earlier) as defined by RECIST 1.1 using the investigator site assessments. If the investigator considered that it was in the patient's best interest to continue study treatment past this time, this was not included in the derivation of dose intensity.

For each cohort and for MEDI4736 alone RDI and PID will be defined as follows:

- RDI = 100% * d/D, where d is the actual cumulative dose delivered up to the actual last day of dosing and D is the intended cumulative dose up to the actual last day of dosing. D is the total dose that would be delivered, if there were no modification to dose or schedule. When accounting for the calculation of intended cumulative dose 3 days should be added to the date of last dose to reflect the protocol allowed

- PID = 100% * d_2/D_2, where d_2 is the actual cumulative dose delivered up to progression (or a censoring event) and D_2 is the intended cumulative dose up to progression (or a censoring event). D_2 is the total dose that would be delivered, if there were no modification to dose or schedule.

3.5.5 Vital signs

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

Vital signs data obtained up until the 30 days from the date of last dose of MEDI4736 treatment will be used for reporting. Change from baseline in vital signs variables will be calculated for each post-dose visit on treatment. For derivation of post baseline visit values considering visit window and to handle multiple records, derivation rules as described in Section 3.5.1 will be used.

3.5.6 Laboratory data

Laboratory data will be collected throughout the study, from screening to the follow-up visits as described in Table 2, 3, 4, 5, 6 and 7 of the CSP. Blood and urine samples for determination of haematology, clinical chemistry, and urinalysis will be collected as described in Section 5.2.1 of the CSP. For derivation of post-baseline visit values considering visit window and how to handle multiple records, derivation rules as described in Section 3.5.1 will be used.

Change from baseline in haematology and clinical chemistry variables will be calculated for each post-dose visit on treatment. Common Terminology Criteria (CTC) grades will be defined at each visit according to the CTC grade criteria using local or project ranges as required, after conversion of lab result to corresponding SI units. The following parameters have CTC grades defined for both high and low values: Potassium, Sodium, Magnesium, Glucose and Corrected calcium so high and low CTCAE grades will be calculated.

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

Corrected calcium (mmol/L) = Total calcium (mmol/L) + ([40 – albumin (G/L)] × 0.02).

Absolute values will be compared to the project reference range and classified as low (below range), normal (within range or on limits of range) and high (above range).

The maximum or minimum on-treatment value (depending on the direction of an adverse effect) will be defined for each laboratory parameter as the maximum (or minimum) post-dose value at any time.

Local reference ranges will be used for the primary interpretation of laboratory data. The denominator used in laboratory summaries of CTC grades 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 a pre-dose and at least 1 post-dose value recorded.

- If a CTCAE criterion does not consider changes from to be evaluable the patient need only have 1 post dose-value recorded.

3.5.7 ECGs

ECG data obtained up until the 30 days from date of last dose of IP will be used for reporting. For derivation of post baseline visit values considering visit window and to handle multiple records present in any visit window, derivation rules as described in Section 3.5.1 will be used.

At each time point the Investigator's assessment of the ECG will be collected locally. Heart rate, duration of QRS complex, RR, PR and QT intervals will be collected centrally via a digital read.

For triplicate ECGs, the mean of the three ECG assessments will be used to determine the value at that time point.

QT interval corrected for heart rate using Fridericia's formula (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.

3.5.8 Pharmacokinetics variables

Pharmacokinetic analysis of the serum concentration data for tremelimumab and MEDI4736 will be performed by MedImmune clinical pharmacology department or a third-party designee.

Summary statistics of serum concentration data will be tabulated by treatment arm and visit, including geometric mean, geometric CV, range, and number of samples. PK parameters, such as peak and trough concentration of MEDI4736 and tremelimumab, will be derived from raw data measurements as data allow. No formal non-compartmental (NCA) PK analysis will be conducted due to the sparse PK sampling scheme for MEDI4736 and tremelimumab that would not allow meaningful determination of PK parameters.

The LLOQ of MEDI4736 in serum is 0.050 μg/mL. The LLOQ of tremelimumab in serum is 0.156 μg/mL.

3.5.9 Immunogenicity variables

Serum samples for ADA (anti-drug antibody) assessments will be conducted utilizing a tiered approach (screen, confirm, titer), and ADA data will be collected at scheduled visits shown in the CSP. ADA result from each sample will be reported as either positive or negative. If the sample is positive, the ADA titer will be reported as well. In addition, the presence of neutralizing antibody (nAb) may be tested for all ADA-positive samples using a ligand-binding assay. The nAb results will be reported as positive or negative.

For each subject, following responses variables will be evaluated:

- ADA prevalence, defined as the proportion of study population having drug reactive antibodies at any point in time, baseline or post-baseline.
- ADA incidence (treatment-emergent ADA), defined as the sum of both treatment-induced and treatment-boosted ADA.
- ADA positive post-baseline and positive at baseline.
- ADA positive post-baseline and not detected at baseline (treatment-induced ADA).
- ADA not detected post-baseline and positive at baseline.
- Treatment-boosted ADA, defined as a baseline positive ADA titer that was boosted to a 4-fold or higher level (greater than the analytical variance of the assay) following drug administration.
- Persistently positive ADA, defined as having at least 2 post-baseline ADA positive measurements with at least 16 weeks (112 days) between the first and last positive measurement. or an ADA positive result at the last available assessment. The category includes patients meeting these criteria who are ADA positive at baseline.

- Transiently positive ADA, defined as having at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive. The category includes patients meeting these criteria who are ADA positive at baseline.
- nAb positive at any visit, defined as the proportion of study population having neutralizing ADA at any point in time.

3.5.10 Biomarker variables

Exploratory biomarker variables will be derived by AstraZeneca/MedImmune Biomarker group or designee.

4. ANALYSIS METHODS

Analyses will be conducted at multiple timepoints during the study as follows:

— The primary statistical analyses will be based on a minimax Simon 2-Stage design (Simon 1989) algorithm described under Section 1.3. Objective response rate and DCR will be evaluated on an ongoing basis for the first 20 evaluable patients within each tumor type to complete Stage 1 of the minimax Simon 2-Stage design, as described in Section 1.3.

— The initial analysis of all endpoints, including OS, will take place following sponsor approval of this SAP and database lock after the last evaluable patient has completed approximately 6 months of MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy after sequencing, or the last patient has withdrawn from the study, or the study is discontinued by the Sponsor.

— A final analysis of OS and safety may be conducted approximately 18 months after the last patient is dosed in the sequencing therapies.

4.1 General principles

Efficacy analyses will be reported separately for treatment with tremelimumab monotherapy and also for patients treated with MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy. Similarly, safety summaries will be undertaken for the individual treatments (ie, safety analyses for tremelimumab monotherapy only, MEDI4736 monotherapy only, MEDI4736 + tremelimumab combination therapy only), and for the joined tremelimumab monotherapy and MEDI4736 monotherapy/ MEDI4736 + tremelimumab combination therapy.

Efficacy data will be summarized and analyzed based on the full analysis set, MEDI and COMBO analysis sets (see Table 1). PK data will be summarized and analyzed based on the PK Analysis Set. Safety data will be summarized based on the Safety Analysis Set.

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 based on the number of patients in each cohort corresponding to the efficacy or safety populations, or in limited cases treated patients with measureable disease (e.g. ORR, DoR).

SAS® version 9.1.3 or higher will be used for all analyses.

For continuous data the mean and median will be rounded to 1 additional decimal place compared to the original data. The standard deviation (SD) and standard error of the mean (SEM) will be rounded to 2 additional decimal places compared to the original data. Coefficient of variation (CV) shall always be reported as a percent with one decimal. Minimum and maximum will be displayed with the same accuracy as the original data.

For categorical data, percentages will be rounded to 1 decimal place.

For PK data, an extra digit of precision will be added (typically four significant digits in total) for reporting of the geometric least-squares (LS) means and bounds of all confidence intervals (CI) within inferential analyses. Ratios and any corresponding CI which are obtained during inferential statistical analysis shall be reported as a percent with at least two decimal places (e.g., 99.88). P-values shall be reported to four decimal places or as <0.0001. If a result is to be compared to a reference value, e.g. 0.80 or 1.25, meaning for example that a value within [0.80, 1.25] limits included, the result should be given with such precision that there are no misunderstandings. For example, 0.79999 is normally rounded to 0.800 but when compared to 0.80 it is misleading.

Modifications to the above described rounding conventions may be made as scientifically appropriate. In rare cases where there is insufficient precision for meaningful scientific interpretation, the means, SD, SEM, and CI may be presented with one additional decimal place. For example, the SD or SEM may round down to zero, which would not be scientifically appropriate. Also when the precision changes across the reported source data range, the most common precision may be used for summarization.

AE and concomitant medication missing (partial) start/stop dates will appear as missing (partial) in the patient data listings, but will be imputed to permit the proper tabulation of AE and medication data. The imputation of missing AE and concomitant medication onset/start and end/stop dates will be used to determine the status of each AE and the previous/concomitant status of each medication. Please refer to Section 3.5.1 for the method of imputation of missing AE and concomitant medication onset/start and end/stop dates.

4.2 Analysis methods

Results of all statistical analysis will be presented using a 95% exact (Clopper-Pearson) CI, unless otherwise stated. All analyses are descriptive and no statistical testing will be performed, hence no p-values will be calculated.

The following table (Table 6) details the endpoints main and pre-planned supplementary analyses, making it clear which analysis is regarded as primary for that endpoint. All endpoints will be reported separately for treatment with tremelimumab monotherapy and also for patients treated with MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy, unless otherwise indicated.

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

Table 6 Formal statistical analyses to be conducted and pre-planned sensitivity analyses

Endpoints analyzed	Notes
Objective response rate	Primary analysis using site Investigator RECIST 1.1 assessments (Full analysis set) 1. N(%) ORR (CR or PR) and 95% Clopper-Pearson CI Supplementary analysis 2. N(%) ORR and 95% Clopper-Pearson CI (MEDI analysis set) 3. N(%) ORR and 95% Clopper-Pearson CI (COMBO analysis set)
Duration of response	Secondary analysis using site Investigator RECIST 1.1 assessments (Full analysis set) 4. Kaplan-Meier plots 5. Median DoR, for patients who have a response Supplementary analysis 6. Kaplan-Meier plots, and median DoR (MEDI analysis set) 7. Kaplan-Meier plots, and median DoR (COMBO analysis set)
Disease Control Rate	Secondary analysis using site Investigator RECIST 1.1 assessments (Full analysis set) 8. N(%) DCR at 3 or 4 months and 95% Clopper-Pearson CI 9. N(%) DCR at 12 months and 95% Clopper-Pearson CI Supplementary analysis 10. N(%) DCR at 3 or 4 months and 95% Clopper-Pearson CI (MEDI analysis set) 11. N(%) DCR at 3 or 4 months and 95% Clopper-Pearson CI (COMBO analysis set) 12.

Endpoints analyzed	Notes
Progression-free survival	Secondary analysis using site Investigator RECIST 1.1 assessments (Full analysis set) 13. Kaplan-Meier plots 14. N(%) patients experiencing a PFS event 15. N(%) type of event (RECIST 1.1 or death) 16. Median PFS Supplementary analyses using site Investigator RECSIT 1.1 assessments 17. Kaplan-Meier plots, N(%) patients experiencing a PFS event, type of event and median PFS (MEDI analysis set) 18. Kaplan-Meier plots, N(%) patients experiencing a PFS event, type of event and median PFS (COMBI analysis set) Sensitivity analyses using site Investigator RECIST 1.1 assessments modified for confirmation of progression (Full analysis set) 19. Kaplan-Meier plots
Overall survival	Secondary analyses (Full analysis set) 20. Kaplan-Meier plots 21. N(%) died, alive, lost to follow-up, withdrawn consent 22. Median OS 23. Proportion alive at 12 months (using Kaplan-Meier methods) Supplementary analysis 24. Kaplan-Meier plots, N(%) died etc, median OS, and proportion alive at 12 months (MEDI analysis set) 25. Kaplan-Meier plots, N(%) died etc, median OS, and proportion alive at 12 months (COMBI analysis set)
Best Objective response	Secondary analyses using site Investigator RECIST 1.1 assessments (Full analysis set) 26. N (%) BoR (CR, PR, SD, PD and NE) Supplementary analysis 27. N (%) BoR (MEDI analysis set) 28. N (%) BoR (COMBO analysis set)

Abbr: CI confidence interval.

4.2.1 Demography and baseline variables

The following information from the beginning of the study will be summarized for all patients in the study and the data will be listed if indicated below:

1. Patient disposition (including screening failures and reason for screening failure) (data to be listed also)

2. Analysis sets (data to be listed also)

The following information from the beginning of the study will be listed and summarized for all patients in the FAS, and for other analysis sets where indicated:

3. Important protocol deviations (data to be listed also)

4. Demographics (age, age group, sex, race and ethnic group) (data to be listed also)

5. Patient characteristics (height, weight, weight group, body mass index (BMI) and BMI group)

6. Number of cycles of previous chemotherapy at baseline

7. Previous disease-related cancer treatment

8. Disease related medical history

9. Relevant surgical history

10. Disease characteristics at baseline (Eastern Cooperative Oncology Group [ECOG] performance status, AJCC staging, primary tumour location [bladder], histology type, TNM staging, time from diagnosis and overall disease classification)

11. Extent of disease at baseline

12. Time from most recent disease progression to start of treatment

13. Allowed concomitant medications (for COMBO and MEDI analysis sets also)

14. Post-discontinuation disease-related anticancer therapy (for COMBO and MEDI analysis sets also)

15. Steroids taken by patients with adverse events of special interest (AESIs) (for COMBO and MEDI analysis sets also).

The AZ drug dictionary (AZDD) will be used for concomitant medication coding.

Medications with start/stop dates that are partially/completely missing will be analyzed as described in section 3.5.1.

4.2.2 RECIST 1.1 based variables

4.2.2.1 Primary endpoint - Objective response rate

Primary analysis

The primary objective of assessing the efficacy of tremelimumab monotherapy in terms of ORR will be evaluated by summarizing the number and percentage of patients with a tumor

response (CR/PR), along with a 2-sided 95% exact Clopper-Pearson CI. The primary summary will be produced using the full analysis set, with all patients treated with tremelimumab monotherapy alone who have measurable disease at baseline as the denominator.

The number (%) of patients with a confirmed response (as defined in Section 3.4.1) and the number (%) of patients with an unconfirmed response (a single visit or a confirmed response) will also be presented.

Supplemental analysis

Additional analyses of ORR may be undertaken, repeating the above primary analysis using the patients who sequence to MEDI4736 monotherapy (MEDI analysis set).

A separate supplementary analysis using the patients who sequence to MEDI4736 + tremelimumab combination therapy (COMBO analysis sets) will also be undertaken.

Combined analyses

Exploratory analysis of ORR, calculating the number/percentage of patients with a tumour response (CR/PR) for the time period starting from the baseline assessment scan prior to treatment of tremelimumab monotherapy until the end of the study including the MEDI period. This may be summarized for:

1. patients who received tremelimumab monotherapy together with those who went on to receive MEDI4736 monotherapy (full analysis set and MEDI analysis set),

Likewise, calculating from baseline assessment scan prior to treatment of tremelimumab monotherapy until the end of the study including the COMBO period

2. patients who received tremelimumab monotherapy together with those who received MEDI4736 + tremelimumab combination therapy (full analysis set and COMBO analysis sets),

4.2.2.2 Secondary endpoints

Duration of response

Secondary analysis

Kaplan-Meier summary statistics of DoR as well will be presented for the FAS. Median DoR from onset of response, percentage remaining in response at 3 months (PDAC patients), 4 months (UBC/TNBC patients) and 12 months (all patients) and time of response from date of first dose will also be presented in a separate summary table. Duration of response, and time to onset of response from date of first dose, will be reported in months. Only patients who have a response will be included in this summary table, and the denominator will be all patients treated with tremelimumab monotherapy who have measurable disease at baseline (see Section 3.4.1).

A Kaplan-Meier plot of the proportion of patients in response over time will also be produced.

Supplemental analysis

The Kaplan-Meier summaries and plots may be undertaken separately for patients in the MEDI and COMBO analysis sets.

Swimmer plots may be produced for FAS, MEDI and COMBO analysis sets. This depicts each duration of response for each patient as a separate bar (horizontally) over time. Each cohort will appear on a separate plot.

Disease control rate

Secondary analysis

The number of patients and percent (%) with 95% exact CIs for DCR (as defined in section 3.4.2.2) at 3 or 4 and 12 months will be summarized using the FAS.

Supplemental analysis

For patients who sequenced to MEDI4736 monotherapy (MEDI) or MEDI4736 + tremelimumab combination therapy (COMBI), the above summary statistics for DCR may be repeated for DCR at 3 or 4 months.

Progression-free survival

Secondary analysis

Kaplan-Meier plots of PFS will be presented. Summaries of the type of event (RECIST 1.1 or death) will be provided along with 25%, 50% and 75% PFS, will also be summarized.

Days between the progression censor date and DCO for patients censored at 6 weeks (PDAC patients) or 8 weeks (UBC/TNBC patients) prior to DCO will be summarized for FAS analysis sets.

Days between the progression censor date and DCO for patients censored at 13 weeks (PDAC patients) or 17 weeks (UBC/TNBC patients) prior to DCO will be summarized for MEDI and COMBO analysis sets.

Treatment status at progression will be summarized for FAS analysis set.

The number of patients censored for progression at more than x weeks before the DCO will also be reported. Where x is gap between visits (plus acceptable tolerance) as follows:

UBC and TNBC: visits are scheduled q8w ±1 week, therefore x = 63 days

PDAC: visits are scheduled q6w ±1 week, therefore x = 49 days

Supplemental analysis

For patients who sequence onto tremelimumab monotherapy or MEDI4736 + tremelimumab combination therapy, the above summaries for PFS may be repeated, separately for the COMBO and MEDI analysis sets.

Sensitivity analysis

As a sensitivity analysis, summaries and Kaplan-Meier plots of PFS may be provided for the FAS, using both confirmed and unconfirmed progression.

Overall survival

Secondary analysis

Kaplan-Meier plots of OS will be presented for the tremelimumab monotherapy treatment group, using the FAS. 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.

The proportion of patients alive at 12 months after starting treatment with tremelimumab monotherapy will be summarized (using Kaplan-Meier techniques).

Supplemental analysis

For patients who sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy, the above summaries for OS may be repeated.

Sensitivity analysis

No sensitivity analysis is planned for OS.

Best objective response

Secondary analysis

Best objective response will be summarized by n (%) for each category (CR, PR, SD, PD, and NE).

Supplemental analysis

For patients who sequence to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy, the above summary of BoR may be repeated.

Additional summaries

Subsequent cancer therapy

The number (and percentage) of patients receiving one or more further cancer therapies will be summarized before progression, after progression, no progression, as well as patients not taking any further cancer therapy. This summary will be produced separately for FAS, MEDI and COMBO analysis sets.

Change in target lesion size

Change in target lesion size will be presented graphically using waterfall plots for FAS, MEDI and COMBO analysis sets separately, to present each patient's best percentage change in tumour size as a separate bar, with the bars ordered from the largest increase to the largest decrease. Reference lines at the +20% and -30% change in tumour size levels will be added to the plots, which correspond with the definitions of progression and 'partial' response respectively.

Additionally, 'spider' plots will be produced for FAS, MEDI and COMBO analysis sets. This depicts each patient's percentage change in tumor size as a line over time. Additional waterfall plots showing percentage change in tumor size at specific timepoints may be produced if it is felt that these are warranted to provide greater clarity.

Time to response

The TTR, based upon the site investigator assessment of RECIST 1.1, will be summarized (ie, number of patients [%] based upon the number of responders) by the scheduled assessment timepoint that the response was first observed. Additionally, descriptive summary statistics (ie, minimum, maximum, median, Q1 and Q3) will also be presented in the same table.

4.2.3 Safety variables

Safety and tolerability data will be presented using the safety analysis set. Safety data will be summarized only. No formal statistical analyses will be performed on the safety data.

Safety summaries will be produced separately for safety analyses for tremelimumab monotherapy, MEDI4736 monotherapy, and MEDI4736 + tremelimumab combination therapy, and for the joined tremelimumab monotherapy and MEDI4736 monotherapy/ MEDI4736 + tremelimumab combination therapy.

Data from all cycles of treatment will be combined in the presentation of safety data.

The following sections describe the planned safety summaries. However, additional safety tables may be required to aid interpretation of the safety data.

4.2.3.1 Adverse events

Adverse events (both in terms of MedDRA system organ class [SOC], preferred terms [PT] and CTCAE grade) will be summarized descriptively by count (n) and percentage (%) for the safety analysis set.

The current MedDRA dictionary will be used for coding.

Any AE occurring before the administration of the first dose of tremelimumab monotherapy will be included in the AE listings, but will not be included in the summary tables (unless otherwise stated). These will be referred to as 'pre-treatment'. Any AE occurring or worsening on or after the first day of dosing of tremelimumab monotherapy will be included in tremelimumab monotherapy safety tables, until the cut-off points described below and in Table7.

For patients who do not have confirmed disease progression or do not meet the criteria for sequencing, AEs observed up until 90 days following discontinuation of tremelimumab monotherapy, or until the initiation of the first subsequent therapy following discontinuation of treatment (whichever occurs first) will be reported in the tremelimumab monotherapy AE summary tables. Any AEs starting after 90 days following discontinuation of tremelimumab monotherapy treatment will be listed only.

For patients with confirmed disease progression and who meet the criteria for sequencing, the window for beginning MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy is not less than 42 days and not more than 120 days after the last dose of tremelimumab monotherapy. Adverse events occurring after the last dose of tremelimumab monotherapy will be included in outputs as described.

Adverse events starting before the first dose of sequenced treatment, but <90 days after the last dose of tremelimumab will be summarized in the tremelimumab monotherapy AE table.

Adverse events starting on or after the first dose of sequenced treatment, but < 90 days after the last dose of tremelimumab will be summarized in the sequenced treatment table.

Adverse events starting before the first dose of sequenced treatment, but ≥90 days after the last dose of tremelimumab will appear in data listings.

Adverse events starting on or after the first dose of sequenced treatment, but ≥90 days after the last dose of tremelimumab will be summarized as MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy AEs.

Sequenced treatment starting <42 days or > 120 days after the last dose of tremelimumab will be considered a protocol deviation

Adverse events observed up until 90 days following discontinuation of MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy, or until the initiation of the first subsequent therapy following discontinuation of treatment (whichever occurs first) will be reported in the AE summary tables. Any AEs starting after 90 days following discontinuation of treatment will be listed only.

All reported AEs will be listed along with the date of onset, date of resolution (if AE is resolved) and investigator's assessment of severity and relationship to study drug. Frequencies and percentages of patients reporting each PT will be presented (i.e. multiple events per patient will not be accounted for apart from on the episode level summaries).

Missing (partial) start/stop dates will appear as missing (partial) in the patient data listings, but will be imputed to permit proper tabulation of AE data. (see Section 3.5.1)

Adverse Events will be categorized into one or more of the following categories depending on the type of events reported:

- All AEs
- All AEs with causality related to MEDI4736 and/or tremelimumab
- AEs with CTCAE grade 3 or higher
- AEs with CTCAE grade 3 or higher, causally related to MEDI4736 and/or tremelimumab
- AEs with an outcome of death
- AEs with an outcome of death causality related to MEDI4736 and/or tremelimumab
- AE leading to discontinuation of MEDI4736 and/or tremelimumab
- AE leading to discontinuation of MEDI4736 and/or tremelimumab, causally related
- All serious adverse events (SAEs)
- All SAEs with causality related to MEDI4736 and/or tremelimumab
- All AEs with leading to discontinuation of MEDI4736 and/or tremelimumab
- All AESI

An overall summary of the number and percentage of patients in each category will be presented. This table will be produced for patients who received:

- Tremelimumab monotherapy
- MEDI4736 monotherapy
- MEDI4736 + tremelimumab combination therapy
- Tremelimumab monotherapy, and MEDI4736 monotherapy/ MEDI4736 + tremelimumab combination therapy.

The number and percentage of patients reporting adverse events will be summarized by MedDRA System organ class (SOC) and PT, by treatment group. Each AE event rate (per 100 patient years) will also be summarized by preferred term within each SOC for the output summarizing all AEs. For each preferred term, the event rate is defined as the number of

patients with that AE divided by the total drug exposure of patients at risk of AE. The denominator is calculated as the total over each patient of days from first dose to the earlier of the date of onset of the event or the last day of study medication.

In addition, a truncated AE table of most common AEs and another table showing most common AEs with CTCAE grade 3 or higher, showing all events that occur in at least 5% of patients overall will be summarized by preferred term, by decreasing frequency. This cut-off may be modified after review of the data. When applying a cut-off, the raw percentage should be compared to the cut-off, no rounding should be applied first (i.e., an AE with frequency of 4.9% will not appear if a cut-off is 5%). Summary statistics showing the duration of the first AE will also be presented as appropriate.

Summaries of the number and percentage of patients will be provided by maximum reported CTCAE grade, SOC, PT and treatment group.

Adverse events causally related to tremelimumab will be summarized for the patients receiving Tremelimumab monotherapy and MEDI4736 + tremelimumab combination therapy. Adverse events causally related to MEDI4736 will be summarized for the patients receiving MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy. Only combination patients will be summarized in a table of causally related to either treatment.

All AE data will be listed for all patients. Investigator terms with their PT will be listed for each patient. These listings will include the last dose for the patient along with the number of days since last dose. Adverse events that occur within 90 days after the last dose will be attributed to the visit in which the last dose was given. A summary of total duration (days) of AE will be provided for events which have an end date.

Deaths

Five summaries of deaths (for patients on each treatment) will be provided by number and percentage of patients by treatment group, if a sufficient number occur for the following categories:

- Death related to disease under investigation only
- Adverse Events with outcome of death only
- Adverse Events with outcome of death only (AE start date falling after 90 day follow up period)[a]
- Number of patients with death related to disease and an AE with outcome of death
- Other deaths[b]

a Patients who sequenced within 90 days of the last dose of tremelimumab monotherapy, will have AE/death attributed to the sequenced treatment.

b Patients who died and are not captured in the earlier categories.

Other summaries of deaths will include AEs with outcome of death by SOC and PT, AEs with outcome of death causally related to treatment by SOC and PT, and key patient information for AEs with outcome of death.

Details of any deaths will be listed for all patients.

Serious Adverse Events

Serious AEs will be summarized for patients who received:

- Tremelimumab monotherapy
- MEDI4736 monotherapy
- MEDI4736 + tremelimumab combination therapy
- Tremelimumab monotherapy, and MEDI4736 monotherapy/ MEDI4736 + tremelimumab combination therapy

SAEs causally related to treatment will be summarized by SOC and PT, for patients who received:

- Tremelimumab monotherapy
- MEDI4736 monotherapy
- MEDI4736 + tremelimumab combination therapy
- Tremelimumab monotherapy, and MEDI4736 monotherapy/ MEDI4736 + tremelimumab combination therapy

and key information will be listed for the main three treatment groups only.

Discontinuations due to Adverse Events

Adverse events leading to discontinuation of IP, as well as causally related DAEs will be summarized by SOC and PT, and key information will be listed

Adverse events of special interest

Preferred terms used to identify AESI (as defined in section 3.5.2) will be listed before DBL and documented in the Study Master File. Grouped summary tables of certain MedDRA preferred terms will be produced. For each ‘grouped’ term, the number (%) of patients experiencing any of the specified terms will be presented by maximum CTCAE grade. Time to onset of first AESI for each grouped term and preferred term within it will also be produced. Groupings will be based on preferred terms provided by the medical team prior to

DBL, and a listing of the preferred terms in each grouping will be provided. Additional summaries of time to onset of first AESI will be provided. A summary of total duration (days) of AESI will be provided for events which have an end date.

Other significant adverse events

Immune-related AEs may be summarized, by category, as well as listing key information.

4.2.3.2 Treatment exposure

The following tables will be produced for the safety analysis set, for tremelimumab monotherapy, MEDI4736 and tremelimumab combination therapy, separately:

Total exposure and actual exposure

Dose interruptions

Dose intensity

Subsequent Therapy

Subsequent disease-related anticancer therapies received, after discontinuation of study treatment, will be tabulated for each treatment group.

4.2.3.3 Vital signs

Box plots for change from baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, temperature, respiratory rate and weight will be presented. Change from baseline at each visit for these variables will be tabulated for each treatment group.

4.2.3.4 Laboratory data

Data obtained up until the 90 days following discontinuation of IP treatment or until the initiation of the first subsequent therapy following discontinuation of IP treatment (whichever occurs first) will be used for reporting the laboratory results. This will more accurately depict laboratory toxicities attributable to IP only as the number of toxicities between 30 and 90 days following discontinuation of IP are likely to be attributable to subsequent therapy. Any data post 90 days of the last dose will only be listed.

All data summaries will be provided in SI units.

Flags will be applied to values falling outside the reference ranges (which will be explicitly noted on these listings, where applicable), and to values for which CTC grading applies.

Box plots of change from baseline will be presented for haematology and clinical chemistry variables, for each treatment.

Shift tables for laboratory values by worst CTC grade will be produced, and for specific parameters separate shift tables indicating hyper- and hypo- directionality of change will be produced. The laboratory parameters for which CTC grade shift outputs will be produced are:

1. Haematology: Haemoglobin, Lymphocytes, Neutrophils, Platelets

2. Clinical chemistry: Albumin, Alkaline Phosphatase (ALP), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Corrected calcium – hypo and – hyper, Creatinine, Gamma-Glutamyl Transferase (GGT), Glucose – hypo and – hyper, Magnesium – hypo and – hyper, Potassium – hypo and – hyper, Sodium – hypo and – hyper, Total bilirubin.

For urinalysis, shift tables from baseline to maximum value will be produced, except for pH and specifc gravity (continuous variables), who will be summarized as a change from baseline.

Hy's law

The following summaries will include the number (%) of patients who have:

Elevated ALT, AST, and Total bilirubin during the study

Liver biochemistry test results over time for patients with elevated ALT or AST, and elevated total bilirubin (at any time) will be plotted. Individual patient data where ALT or AST plus Total bilirubin are elevated at any time will be listed also.

Plots of ALT and AST vs. Total bilirubin by cohort will also be produced with reference lines at 3×ULN for ALT, AST, and 2×ULN for Total bilirubin. In each plot, Total bilirubin will be in the vertical axis.

4.2.3.5 ECGs

ECGs are to be performed at screening, and only if clinically indicated post-screening.

ECG data obtained up until the 30 day safety follow-up visit will be included in the summary tables.

Overall evaluation of ECG is collected at visit in terms of normal or abnormal, and the relevance of the abnormality is termed as “clinically significant” or “not clinically significant”. This information will be summarized per scheduled timepoint at which an ECG was actually performed.

4.2.3.6 Physical examination

Physical examination data will not be summarized or listed.

4.2.4 Pharmacokinetics

PK data summaries are not within the remit of this SAP.

4.2.4.1 Population pharmacokinetics and exposure-response/safety analysis

A population PK model will be developed by AstraZeneca/MedImmune Clinical Pharmacology group or designee.

4.2.4.2 Pharmacokinetic non-compartmental analysis

No formal non-compartmental PK analysis will be conducted due to the sparse PK sampling scheme of tremelimumab and MEDI4736.

4.2.4.3 Immunogenicity

ADA and nAb results to MEDI4736 and to tremelimumab will be listed for each patient in the safety analysis set.

All analyses will be conducted on the ADA evaluable population of patients in the safety analysis set. The ADA evaluable population is defined as those patients who have a non-missing baseline ADA and at least 1 non-missing post-baseline ADA result.

A summary of the number and percentage of patients who develop detectable ADA to MEDI4736 and to tremelimumab by ADA categories (Section 3.5.9) in different treatment arms will be presented. Median and range of titer for each category will be provided. The effect of ADA on PK, will be evaluated, if the data allow.

4.2.4.4 Biomarkers

Summary statistics of exploratory biomarkers will be produced by AstraZeneca/MedImmune Biomarker group or designee.

Pooling of biomarker results with other tremelimumab and MEDI4736 studies is outside of the scope of this SAP.

5. INTERIM ANALYSES

No interim analysis for efficacy is planned for this study. However, ORR and DCR will be evaluated on an ongoing basis for the first 20 evaluable patients within a given selected solid tumor type to complete Stage 1 of the minimax Simon 2-Stage design

5.1 Changes of Analysis from Protocol

Table 7 Details of changes from protocol

Original CSP text	Updated SAP text	Justification
Section 8.3 Table 11 ORR, DoR, DCR, BoR, PFS, OS To be evaluated on the Evaluable,	Section 2.1 Table 1 ORR, DoR, DCR, BoR, PFS, OS	To be consistent across the IO project how FAS is defined for non-randomized ph II studies. The

MEDI and COMBO analysis sets	To be evaluated on the FAS, MEDI and COMBO analysis sets	new definition of FAS is the same as that of the Evaluable set, hence there was no need to use Evaluable set
Section 8.3.1 Full Analysis Set The statistical analysis with the full analysis set (FAS) will include all enrolled patients. This analysis set will be used to summarize demography, disease characteristics and other baseline variables	Section 2.1.1. Full Analysis Set The statistical analysis with the full analysis set (FAS) will include all treated patients (i.e., received at least 1 dose of tremelimumab monotherapy) who have measurable disease at baseline.	To be consistent across the IO project how FAS is defined for non-randomized ph II studies.
Section 8.3.2 Evaluable Analysis Set A subset of the FAS will include all treated patients (ie, received at least 1 dose of tremelimumab monotherapy) who have measurable disease at baseline.	Definition of Evaluable Analysis Set not in SAP.	To be consistent across the IO project how FAS is defined for non-randomized ph II studies. The new definition of FAS is the same as that of the Evaluable set, hence there was no need to use Evaluable set
Section 8.3.4 Pharmacokinetic analysis set All patients who receive at least 1 dose of IP per the protocol for whom have at least 1 measurable PK concentration post-dose 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.	Section 2.1.5 Pharmacokinetic Analysis Set All patients who receive at least 1 dose of IP per the protocol for whom any post-dose data are available will be included in the PK analysis set.	To be consistent across the IO project how PK analysis set is defined

Section 8.4.1.2 For sensitivity analysis in the tremelimumab monotherapy group only, ORR may be assessed using the RECIST 1.1 site Investigator tumor data following a modification where any objective progression requires confirmation. Therefore, data obtained up until confirmed progression, or the last evaluable assessment in the absence of a confirmed progression, may be included in the assessment of ORR. Note that the response may be after an unconfirmed progression.	This sensitivity analysis is no longer being performed	ORR results is not impacted by having a modification where any objective progression requires confirmation. Hence no need to do it
Section 8.4.1.3 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.	Section 3.4.2.1 If patients do not progress within 3 months (PDAC patients) or 4 months (UBC/TNBC patients) of the last evaluable assessment, the last evaluable RECIST assessment will be used. Where 3 months is defined as 12 weeks -7 days = 77 days 4 months is defined as 16 weeks -7 days = 105 12 months is defined as 52 weeks -7 days = 357 days following the start of study treatment.	Consistent with other analyses
Section 8.4.1.3 5.2 Sensitivity analyses of DoR may be performed in the	This sensitivity analysis is no longer being performed	The impact on DoR by having a modification where any objective

tremelimumab monotherapy group only based on Investigator assessment according to RECIST 1.1 modified for confirmation of progression.		progression requires confirmation will not be significant
Section 8.4.1.3 DCR at 4 or 12 months is defined as the percentage of patients who have a best objective response (BoR) of CR or PR in the first 4 or 12 months, respectively, or who have demonstrated SD for a minimum interval of 16 or 52 weeks, respectively (-7 days, ie, 105 or 357 days, respectively), following the start of study treatment.	Section 3.4.2.2 Disease control rate at 3 months (PDAC patients) or 4 months (UBC/TNBC patients) is defined as the percentage of patients who have a best objective response (BoR) of CR or PR in the first 3 or 4 or 12 months, or who have demonstrated SD for a minimum interval of 3 or 4 months and 12 months, respectively, or who have demonstrated SD for a minimum interval of 3 months or 4 months and 12 months, respectively, following the start of study treatment. Where 3, 4 and 12 months are defined in Section 3.4.2.1.	Consistent with 2 q6w visits for PDAC as well as q8w visits for UBC/TNBC patients
Section 8.4.1.3 Sensitivity analyses of DCR may be performed in the tremelimumab monotherapy group only based on Investigator assessment according to RECIST 1.1 modified for confirmation of progression.	This sensitivity analysis is no longer being performed	The impact on DCR by having a modification where any objective progression requires confirmation will not be significant
Section 8.4.1.3 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.	Section 0 If the patient progresses or dies after 2 or more missed visits plus a window of 1 week (i.e. 2 x q8w +7 days for UBC/TNBC patients, or 2 x q6w +7 days for PDAC	Consistent with the allowable window (±7 days) around scheduled visits

	patients), the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment	
Section 8.4.1.3 For patients who die with no evaluable RECIST 1.1 assessments, if the death occurs ≤17 weeks (ie, 16 weeks ±7 days) after enrollment, then BoR will be assigned to the progression (PD) category. For patients who die with no evaluable RECIST assessments, if the death occurs >17 weeks (ie, 16 weeks ±7 days) after the date of enrollment then BoR will be assigned to the NE category. Progression events that have been censored due to them being >17 weeks after the last evaluable assessment will not contribute to the BoR derivation.	Section 3.4.2.5 For patients who die with no evaluable RECIST 1.1 assessments, if the death occurs ≤17 weeks after enrollment (ie, 2 x q8w +7 days) for UBC/TNBC patients, or ≤13 weeks (i.e. 2 x q6w +7 days) for PDAC patients, then BoR will be assigned to the progression (PD) category. For patients who die with no evaluable RECIST assessments, if the death occurs >17 weeks or >13 weeks, respectively, 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 or >13 weeks, respectively for UBC/TNBC or PDAC patients, after the last evaluable assessment will not contribute to the BoR derivation.	Consistent with 2 q6w visits + 7 days for PDAC patients, as well as q8w visits for UBC/TNBC patients.
Section 8.4.1.3 Sensitivity analyses of BoR may be performed in the tremelimumab monotherapy group only based on Investigator assessment according to RECIST 1.1 modified for confirmation of progression.	This sensitivity analysis is no longer being performed	The impact on BoR by having a modification where any objective progression requires confirmation will not be significant
Section 8.4.1.3	Section 3.4.2.7 **Time to**	Since the primary objective of this study

No equivalent text	**Response** Time to response (TTR) (per RECIST 1.1 as assessed by the site investigator) is defined as the time from the date of first dose until the date of first documented response (which is subsequently confirmed). The date of first documented response should coincide with that used for the RECIST 1.1 DoR endpoint. Time to response will not be defined for those patients who do not have documented confirmed response.	is ORR, it is important to know how long it takes before patients have a response to the study treatment. Hence TTR was added
Section 8.5.1 – not included	Section 4.2.2.1 <u>Combined analyses</u> Exploratory analysis of ORR, calculating the number/percentage of patients with a tumour response (CR/PR) for the time period starting from the baseline assessment scan prior to treatment of tremelimumab monotherapy until the end of the study including the MEDI period.	Of clinical interest after CSP sign-off
Section 8.5.2 – not included	Section 4.2.2.2 <u>Combined analyses</u> Exploratory analysis of PFS, calculated for the time period starting from the baseline assessment scan prior to treatment of tremelimumab monotherapy until the end of the study including the MEDI	Of clinical interest after CSP sign-off

	period.	
Section 8.5.2 No equivalent text	Section 4.2.2.2 **Time to response** The TTR, based upon the site investigator assessment of RECIST 1.1, will be summarized (ie, number of patients [%] based upon the number of responders) by the scheduled assessment timepoint that the response was first observed. Additionally, descriptive summary statistics (ie, minimum, maximum, median, Q1 and Q3) will also be presented in the same table.	Since the primary objective of this study is ORR, it is important to know how long it takes before patients have a response to the study treatment. Hence TTR was added
Section 8.4.2.1 – not explicitly included. Implicit that all summaries would be produced for patients who received: • Tremelimumab monotherapy • MEDI4736 monotherapy • MEDI4736 + tremelimumab combination therapy	Section 4.2.3.1 An overall summary of the number and percentage of patients in each category will be presented. This table will be produced for patients who received: • Tremelimumab monotherapy • MEDI4736 monotherapy • MEDI4736 + tremelimumab combination therapy • tremelimumab monotherapy and MEDI4736 monotherapy • tremelimumab monotherapy and MEDI4736 +	Of clinical interest after CSP sign-off

	tremelimumab combination therapy.	
Section 8.4.2.1 – not explicitly included. Implicit that all summaries would be produced for patients who received: • Tremelimumab monotherapy • MEDI4736 monotherapy • MEDI4736 + tremelimumab combination therapy	Section 4.2.3.1 Serious AEs will be summarized for patients who received: • Tremelimumab monotherapy • MEDI4736 monotherapy • MEDI4736 + tremelimumab combination therapy • tremelimumab monotherapy and MEDI4736 monotherapy • tremelimumab monotherapy and MEDI4736 + tremelimumab combination therapy.	Of clinical interest after CSP sign-off
Section 8.5.1 Sensitivity analysis may be performed in the tremelimumab monotherapy group only on programmatically derived ORR using site Investigator data (RECIST 1.1 modified for confirmation of progression) to determine if there is any difference when using progression confirmation rules.	This sensitivity analysis is no longer being performed	ORR results is not impacted by having a modification where any objective progression requires confirmation. Hence no need to do it
Section 8.5.2 In addition, a sensitivity analysis using DoR from the site Investigator tumor data may be done in the tremelimumab monotherapy group only (RECIST 1.1 modified for confirmation of progression) to determine the effect of confirmation of progression.	This sensitivity analysis is no longer being performed	The impact on DoR by having a modification where any objective progression requires confirmation will not be significant

Section 8.5.2 In addition, a sensitivity analysis of DCR may also be summarized in the tremelimumab monotherapy group only based upon the site Investigator tumor data (for RECIST 1.1 modified for confirmation of progression).	This sensitivity analysis is no longer being performed	The impact on DCR by having a modification where any objective progression requires confirmation will not be significant
Section 8.5.2 In addition, a sensitivity analysis of BoR in the tremelimumab monotherapy group only may also be summarized based upon the site Investigator tumor data (for RECIST 1.1 modified for confirmation of progression).	This sensitivity analysis is no longer being performed	The impact on BoR by having a modification where any objective progression requires confirmation will not be significant

6. REFERENCES

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