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

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02 AUG 2018

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

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	Antidrug antibody
AE	Adverse event
AESI	Adverse event of special interest
AJCC	American Joint Committee on Cancer
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AZDD	AZ drug dictionary
BMI	Body mass index
BoR	Best objective response
BP	Blood pressure
CI	Confidence interval
CR	Complete response
CRF	Case report form
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTC/CTCAE	Common terminology criteria for adverse event
CV	Coefficient of variation
DBL	Database lock
DBP	Diastolic blood pressure
DCO	Data cut-off
DCR	Disease control rate
DLT	Dose-limiting toxicity
DoR	Duration of response
DRM	Data review meeting
EAS	Efficacy analysis set
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group

Abbreviation or special term	Explanation
FAS	Full analysis set
fT3	Free triiodothyronine
fT4	Free thyroxine
IHC	Immunohistochemical
ILD	Interstitial lung disease
IP	Investigational product
irAE	Immune-related adverse events
ITT	Intent-to-treat
LD	Longest diameter
LDH	Lactate dehydrogenase
MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic resonance imaging
NA	Not applicable
NE	Not evaluable
NTL	Non-target lesion
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
OS6	Proportion of patients alive at 6 months from enrollment
OS12	Proportion of patients alive at 12 months from enrollment
PD	Progressive disease
PDAC	Pancreatic ductal adenocarcinoma
PD-L1	Programmed death ligand 1
PDx	Pharmacodynamics
PFS	Progression-free survival
PFS3	Proportion of patients with progression-free survival after 3 months
PFS6	Proportion of patients with progression-free survival after 6 months
PK	Pharmacokinetics
PKS	Pharmacokinetics analysis set
PR	Partial response
PS	Performance status
q6w	Every 6 weeks

Abbreviation or special term	Explanation
q8w	Every 8 weeks
q12w	Every 12 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RDI	Relative dose intensity
RECIST 1.1	Response Evaluation Criteria In Solid Tumours, Version 1.1
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Stable disease
SI	International System
SRC	Safety Review Committee
TEAE	Treatment emergent adverse event
TL	Target lesion
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
WHO	World health organization

AMENDMENT HISTORY

Date	Brief description of change
02Aug2018	N/A

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

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

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

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

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

1.1.2 Secondary objectives

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

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

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

Secondary objectives:	Outcome measures:
To further assess the efficacy of MEDI4736 +AZD5069 in terms of DoR, DCR, PFS, PFS3, PFS6, OS, OS6, and OS12	DoR, DCR, PFS, PFS3, and PFS6 in all patients using Investigator assessments according to RECIST 1.1 OS, OS6, and OS12
To investigate the relationship between PD-L1 expression by IHC and efficacy parameters	ORR, DoR, DCR, and PFS across PD-L1 expression using Investigator assessments according to RECIST 1.1 OS
To investigate the immunogenicity of MEDI4736 in combination with AZD5069	Presence of ADAs for MEDI4736 (confirmatory results: positive or negative; titers)
To assess the PK of MEDI4736 and the combination of MEDI4736 and AZD5069	Concentration of MEDI4736/AZD5069 in blood and noncompartmental PK parameters (such as peak concentration and trough, as data allow; sparse sampling only)

1.1.3 Exploratory objectives

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

Not applicable.

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

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

available	to treatment (where response is defined broadly to include efficacy, tolerability, or safety). In the event that additional tumor molecular profiling is required to understand further any response to treatment, AstraZeneca may request a sample of the most recent tumor biopsy for additional research. Any sample collection can be discontinued or suspended at the discretion of the Sponsor, without need for a protocol amendment.

1.2 Study design

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

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

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

Doses and treatment regimens are described in Section 7.2 of the Clinical study protocol (CSP). Assessments will be conducted as indicated in Table 2 and Table 4 of the CSP.

Figure 1   Cohort 1 (first-line, Phase Ib MEDI4736 + nab-paclitaxel + gemcitabine chemotherapy) design
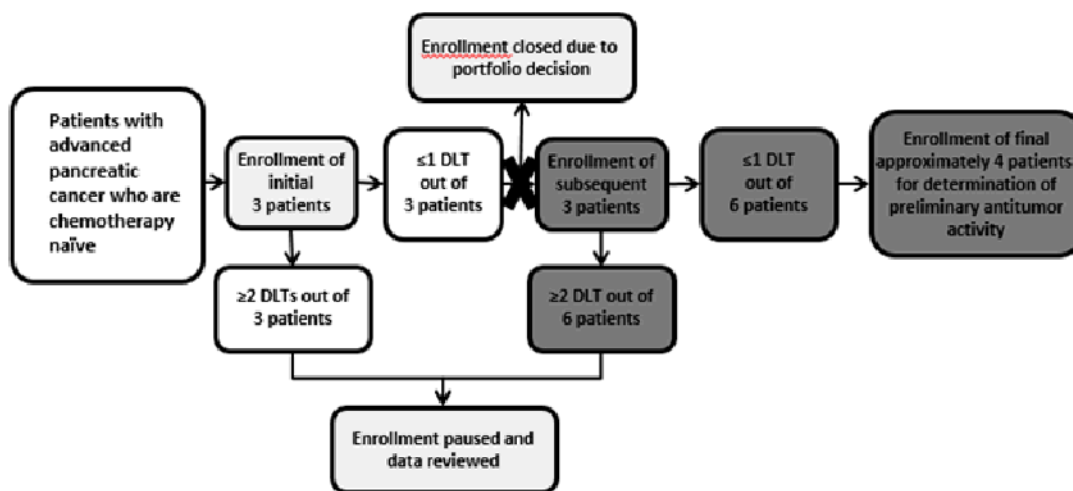
1.2.2   Cohort 2: Second-line, Phase II, MEDI4736 + AZD5069

Cohort 2 is a Phase II, open-label, multicenter assessment of the safety and preliminary antitumor activity of MEDI4736 in combination with AZD5069 in patients with metastatic PDAC whose disease has progressed on a 5-FU-containing or gemcitabine-containing first-line chemotherapy. Cohort 2 will enroll approximately 16 evaluable patients. A schematic diagram of the Cohort 2 design is shown in Figure 2.

Initially, approximately 6 evaluable patients will be enrolled into a safety run-in period to evaluate safety, tolerability, and antitumor activity. After the 6 initial evaluable patients complete 1 treatment cycle, if no unexpected toxicity meet DLT criteria, approximately 10 additional evaluable patients will be enrolled to determine preliminary antitumor activity. All patients in this cohort, including those in the safety run-in, will be included in the preliminary antitumor activity analysis. See Section 7.2.5 of the CSP (version 5.0, 08Feb2018) for details on the definition of DLTs.

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

Figure 2   Cohort 2 (second-line, Phase II MEDI4736 + AZD5069) design
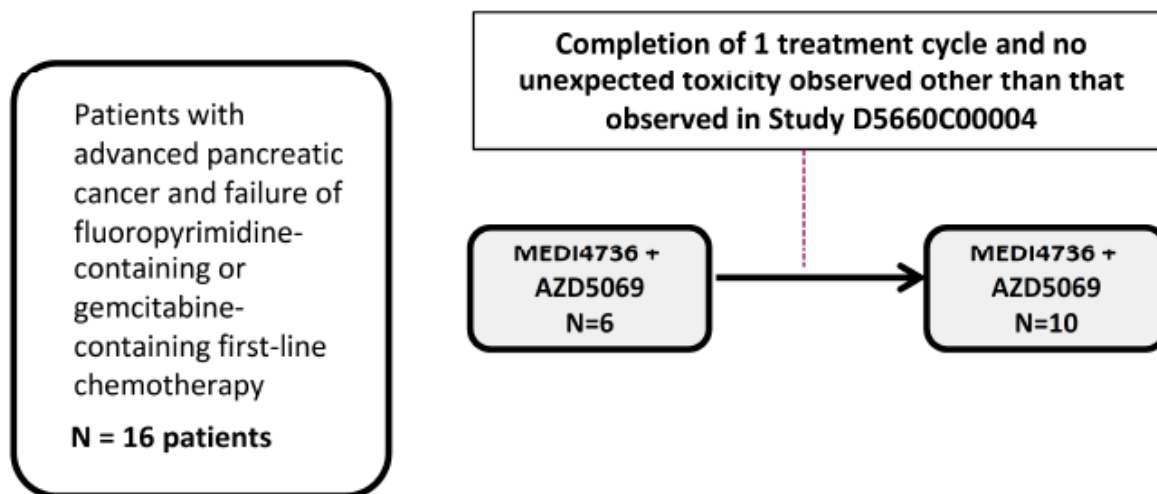
1.3   Number of subjects

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

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

Based on binomial probabilities, the probability of observing 0 or more patients with a toxicity event in 3 patients (6 patients respectively) can be seen in Table 1.

Table 1   Probability of observing toxicity events

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

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

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

the initial 6 evaluable patients, approximately 10 further evaluable patients will be recruited, to target approximately 16 evaluable patients in total.

Based on binomial probabilities, the probability of observing 0 or more patients with a toxicity event in 6 patients (16 patients respectively) can be seen in Table 2.

Table 2 **Probability of observing toxicity events in 6 or 16 patients**

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

2. ANALYSIS SETS

2.1 Definition of analysis sets

Full analysis set

The full analysis set (FAS) will include all patients enrolled to receive treatment and will classify them on the basis of allocated treatment, regardless of the treatment actually received. Patients who were enrolled to receive treatment who did not subsequently go on to receive study treatment are included in the FAS population.

Safety analysis set

All patients who received at least 1 dose of investigational product (IP) and for whom any post-dose data are available will be included in the safety analysis set, according to the treatment they actually received. Study population and demography data description will be produced on the Safety analysis set. When assessing safety and tolerability, summaries will be produced based on the Safety analysis set.

DLT evaluable set

For Cohort 1, the DLT evaluable set will include all patients who completed the DLT evaluation period and/or discontinued study treatment early due to a DLT and who have not missed ≥2 administrations of gemcitabine.

For Cohort 2, the DLT evaluable set will include patients who received 50 % of planned doses of AZD5069 during the DLT period as well as the MEDI4736 infusion and remained active on study at the end of Day 28 of the study Cycle 1.

The DLT evaluation period is defined as the time from the first dose of MEDI4736 for Cohort 1 (resp. MEDI4736 and AZD5069 for Cohort 2) to the end of Cycle 1 (i.e., 28 days in total) or until a patient experiences a DLT or discontinues treatment during Cycle 1, whichever occurs first. Patients will be presented according to the treatment they actually received.

Efficacy Analysis Set

The Efficacy analysis set (EAS) will include patients who received at least 1 dose of IP and with no important protocol deviation that could impact the efficacy evaluation. Patients will be presented according to the treatment they actually received.

These deviations will be discussed and stated during the Data Review Meeting prior to database lock (DBL).

PK analysis set

All patients who received at least 1 dose of IP per protocol for whom any post-dose data are available and who do not violate or deviate from the protocol in ways that would significantly affect the PK analyses will be included in the PK analysis set (PKS). Patients will be presented according to the treatment they actually received.

The population will be defined by the Study Physician, Pharmacokineticist, and Statistician prior to any analyses being performed.

Definitions of the analysis sets for each outcome variable are provided in Table 3.

Table 3   Summary of outcome variables and analysis populations

Outcome variable	Population
Efficacy data	
ORR	Efficacy Analysis Set
DoR*, DCR, PFS, PFS3, PFS6, OS, OS6, OS12	Efficacy Analysis Set
Study population/Demography data	
Patient disposition	All subjects
Demography characteristics	Safety Analysis Set
Baseline and disease characteristics	Safety Analysis Set
Important deviations	Safety Analysis Set
Medical/Surgical history	Safety Analysis Set
Previous anti-cancer therapy	Safety Analysis Set
Concomitant medications/procedures	Safety Analysis Set
Subsequent anti-cancer therapy	Safety Analysis Set
WHO PS	Safety Analysis Set
PK data	
PK data	PK Analysis Set
Immunogenicity	
Immunogenicity data	Safety Analysis Set
Safety data	
Exposure	Safety Analysis Set
AEs	Safety Analysis Set
DLT	Safety Analysis Set
Laboratory measurements	Safety Analysis Set
ECOG PS	Safety Analysis Set
Vital signs	Safety Analysis Set

* *Patients who are evaluable for the analysis of DoR are those identified as responders for the ORR analysis.*

2.2   Deviations

A list of protocol deviations will be reviewed including the impact on the analysis sets and decisions regarding how to handle these deviations will be documented by the study team physician, pharmacokineticist and statistician prior to database lock. Important protocol deviations may include, but are not limited to: not meeting eligibility criteria, non-performance of important assessments, use of prohibited medications, develop discontinuation criteria but not withdrawn from study or discontinued IP as appropriate etc.

Important protocol deviations will be identified from 2 sources: the deviations collected at sites in IMPACT and the deviations programmatically obtained using data collected in the database.

```
┌────────────────────┐       ┌────────────────────┐                ┌────────────────────┐
│ PDs recorded in    │       │ Important PDs      │                │ Important PDs      │
│ IMPACT             │       │ identified using   │                │ reported in        │
│ [Reviewed &        │   +   │ programming        │  ───────────▶  │ listing and        │
│ Important PDs      │       │                    │                │ summary tables     │
│ identified]        │       │                    │                │                    │
└────────────────────┘       └────────────────────┘                └────────────────────┘
```
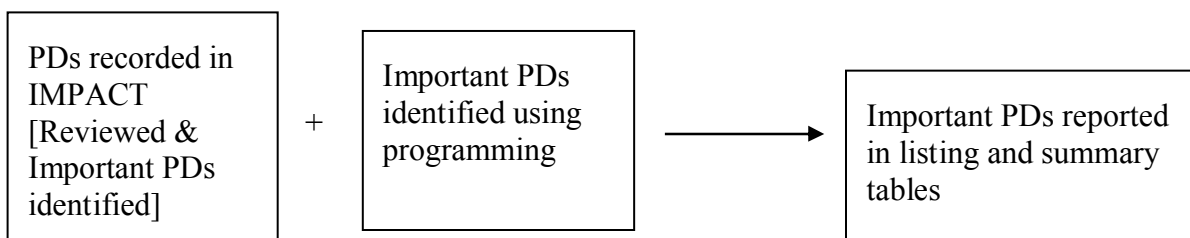
The following programmable general categories will be considered as important deviations and be listed and discussed in the clinical study report (CSR) for both cohorts.

* Deviation 1: Patients enrolled but who did not receive study treatment.

* Deviation 2: Patients who deviate from key entry criteria as per the CSP. These are inclusion criteria 3, 5, 6 and exclusion criteria 1, 3, 4.

* Deviation 3: Baseline RECIST (Response Evaluation Criteria In Solid Tumours) scan > 28 days before the start of study treatment.

* Deviation 4: No baseline RECIST 1.1 assessment on or before the start of study treatment.

* Deviation 5: Received prohibited concomitant medications (including other anti-cancer agents). Please refer to the CSP section 7.7. This will be used as a guiding principle for the physician review of all medications prior to database lock to identify those likely have an impact on efficacy.

In addition to the programmatic determination of the deviations above, monitoring notes or summaries will be reviewed to determine any important post entry deviations that are not identifiable via programming, and to check that those identified via programming are correctly classified. Even the list above is not exhaustive, the final classification of deviations will be made at the data review meeting (DRM) prior to database lock or data freeze. Decisions made at the DRM will be documented and approved by AstraZeneca prior to analysis.

Deviation 1 will lead to exclusion from the Safety analysis set. Any deviation considered to impact upon PK will lead to exclusion from the PKS.

Errors in treatment dispensing will also be summarized and listed separately to the important protocol deviations.

The summary will also include the number of patients who receive no treatment whatsoever for a period of time due to errors in dispensing of medication. Note, this is not due to tolerability issues where patients may stop taking drug.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Derivation of RECIST visit responses

For all subjects, the RECIST tumor response data will be used to determine each subject's visit response according to RECIST version 1.1. It will also be used to determine if and when a subject has progressed in accordance with RECIST and also their best objective response.

Baseline radiological tumor assessments are to be performed no more than 28 days before the start of study treatment and ideally as close as possible to the start of study treatment.

For Cohort 1, tumor assessments are then performed every 8 weeks (q8w) ±7 days for the first 48 weeks (relative to the date of the first infusion) and then every 12 weeks (q12w) ±7 days until confirmed objective disease progression per RECIST 1.1

For Cohort 2, tumor assessments are then performed every 6 weeks (q6w) ±7 days for the first 48 weeks (relative to the date of the first infusion) and then q12w ±7 days until confirmed objective disease progression per RECIST 1.1

If an unscheduled assessment is performed, and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimize any unintentional bias caused by some patients being assessed at a different frequency than other patients.

All RECIST assessments, whether scheduled or unscheduled, will be included in the calculations. This is also regardless of whether a patient discontinues study treatment or receives another anticancer therapy. For patients who discontinue IP due to toxicity in the absence of confirmed objective progression, objective tumor assessments per the scheduled assessments should be continued as planned until confirmed objective disease progression.

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

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

Categorization of objective tumor response assessment will be based on the RECIST 1.1 criteria of response: complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). At each visit, patients will be programmatically assigned a response

based on tumor assessments provided by the investigator for target lesions, non-target lesions and new lesions. Target lesion progression will be calculated in comparison to when the tumor burden was at a minimum (i.e., smallest sum of diameters previously recorded on study). In the absence of progression, tumor response (CR or PR) and SD will be calculated in comparison to the baseline tumor measurements obtained before starting treatment. If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE; unless there is evidence of progression, in which case the response will be assigned as PD). Endpoints of objective response rate (ORR), duration of response (DoR), disease control rate (DCR), progression-free survival (PFS), proportion of patients with progression-free survival after 3 months (PFS3), and proportion of patients with progression-free survival after 6 months (PFS6) will be derived from the overall visit response date and the scan dates.

Note that overall responses as per Investigator opinion will not be used for any endpoint based on RECIST criteria.

Please refer to Appendix D of the CSP for the definitions of CR, PR, SD, NE, and PD and for more details regarding the tumor assessment.

3.1.1 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 (except lymph nodes which must have short axis ≥ 15 mm) with CT or MRI and which is suitable for accurate repeated measurements.

A subject 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 target lesions (TLs). If more than one baseline scan is recorded then measurements from the one that is closest and prior to start of study treatment will be used to define 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 non-target lesions (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. If a patient does not have measurable disease at baseline then the TL visit response will be not applicable (NA).

Table 4   Evaluation of target lesions

Visit Reponses	Description
Complete Response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10mm.
Partial response (PR)	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters as long as criteria for PD are not met
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progression of disease (PD)	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm.
Not Evaluable (NE)	Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. Note: if the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response
Not applicable (NA)	No TLs are recorded at baseline

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; SD Stable disease;
     TL Target lesion.

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 $\geq$ 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 < 10mm 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 < 10mm and all other TLs are 0mm then although the sum may be >0mm the calculation of TL response should be categorized 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. 0mm or < 10mm 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 longest diameter (LD) increases by 20% but remains < 10mm.

- Step 2: If some lesion measurements are missing but all other lesions meet the CR criteria (i.e. 0mm or < 10mm for lymph nodes) then response will be set to NE irrespective of whether, when referencing the sum of TL diameters, the criteria for PD are 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 blinded to treatment assignment. 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 5mm 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 blinded to treatment assignment.

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 / embolization), 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 tumors:

- 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 if ≤ 1/3 of the TLs have missing measurements then scale up as described in the 'Scaling' section below. 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 have missing measurements), treating the lesion with intervention as missing, 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 have a value of 0 recorded. If scaling up is not appropriate due to too few non-missing measurements then the visit response will be set as NE.

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 TLs 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 5   Example of scaling

Lesion	Longest diameter at nadir visit (mm)	Longest diameter at follow-up visit (mm)
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 is missing at the follow-up visit.

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

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

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

CR will not be allowed as a TL response for visits where there is missing data. Only PR, SD or PD (or NE) could be assigned as the TL visit response in these cases. However, for visits with ≤1/3 lesion assessments not recorded, the scaled up sum of TLs diameters will be included when defining the nadir value for the assessment of progression.

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 0cm.

Change in method of assessment of TLs

CT, MRI and clinical examination are the only methods of assessment that can be used within a trial, with CT and MRI being the preferred methods and clinical examination only used in special cases. 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.

3.1.2 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.

NTL response will be derived based on the Investigator's overall assessment of NTLs as follows:

Table 6   Evaluation of non-target lesions

Visit Responses	Description
Complete response (CR)	Disappearance of all NTLs since baseline. All lymph nodes non-pathological in size (<10 mm short axis).
Non CR/Non PD	Persistence of one or more NTL.
Progression (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not Evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: for patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; NTL Non-target
    lesion; TL Target lesion.

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in TLs, the overall tumor 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 tumor.

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.

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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, but should not overtly affect the derivation.

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 tumor assessments where possible until objective disease progression is observed.

3.1.3   Overall visit response

Table 7 defines how the previously defined TL and NTL visit responses will be combined with new lesion information to give an overall visit response.

Table 7   Overall visit response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
NE	Non-PD or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR Complete response, PR Partial response, SD Stable disease, PD Progression of disease, NE Not evaluable, NA Not applicable (only relevant if there were no non-target lesions at baseline).

For each visit, including any unscheduled tumor assessment, the overall response will be programmatically derived from TL/NTL/NL assessments based on Investigator assessments.

3.2 Outcome Variables

Initiation of subsequent anti-cancer therapy includes radiotherapy.

3.2.1   Primary endpoints

3.2.1.1   Objective response rate

ORR will be based on the programmatically derived overall response, using all scans regardless of whether they were scheduled or not.

ORR (per RECIST 1.1) is defined as the number (%) of patients with a confirmed overall response of CR or PR and will be based on the Efficacy Analysis Set. A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat

imaging, preferably at the next regularly scheduled imaging visit and not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. Therefore, data obtained up until confirmed progression, or the last evaluable assessment in the absence of confirmed progression, will be included in the assessment of ORR. Note that the response may be after an unconfirmed progression.

Any patient who discontinues treatment without progression, receives a subsequent therapy and then responds will not be included as responders in the ORR.

The overall responses as per Investigator will be listed only.

3.2.1.2   Safety co-primary endpoints

The safety co-primary endpoints are described in Section 3.3

3.2.2   Secondary endpoints

3.2.2.1   Duration of response

DoR (per RECIST 1.1 as assessed by Investigator assessment) will be defined as the time from the date of first documented response until the first date of documented confirmed progression or death in the absence of disease progression (i.e. date of PFS event or censoring - date of first response + 1). The end of response should coincide with the date of progression, death from any cause or censoring used for the RECIST 1.1 PFS endpoint, based on Investigator assessment.

The time of the initial response will be defined as the latest of the dates contributing toward the first visit response of CR or PR. Note that the time of initial response may be after an unconfirmed progression. 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.

3.2.2.2   Disease control rate

DCR at 6 months is defined as the percentage of patients who have a best objective response (BoR) of CR or PR in the first 6 months (i.e. 24+1=25 weeks to allow for a late assessment within the assessment window) or who have demonstrated SD for a minimum interval of 24 weeks (minus 1 week to allow for an early assessment within the assessment window, i.e. 161 days) following the start of treatment.

DCR at 12 months is defined as the percentage of patients who have a BoR of CR or PR in the first 12 months (i.e. 48+1=49 weeks to allow for a late assessment within the assessment window) or who have demonstrated SD for a minimum interval of 48 weeks (minus 1 week to allow for an early assessment within the assessment window, i.e. 329 days) following the start of treatment.

DCR will be determined based on programmatically derived RECIST 1.1 assessments and all data up until the first progression event.

3.2.2.3   Progression-free survival

PFS (per RECIST 1.1 using Investigator assessments) will be defined as the time from the date of first dose until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from allocated therapy or receives another anticancer therapy prior to progression.

Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment. If the patient has no evaluable visits or does not have baseline data, they will be censored at Day 1 unless they die within 2 visits of baseline.

Given the scheduled visit assessment scheme (i.e. eight-weekly for the first 48 weeks then twelve-weekly thereafter for cohort 1, six-weekly for the first 48 weeks then twelve-weekly thereafter for cohort 2) the definition of 2 missed visits will change as detailed below.

<u>Cohort 1</u>

If the previous RECIST assessment is less than study day 274 (i.e. week 39) then two missing visits will equate to 18 weeks since the previous RECIST assessment, allowing for early and late visits (i.e., 2 x 8 weeks + 1 week for an early assessment + 1 week for a late assessment = 18 weeks). If the two missed visits occur over the period when the scheduled frequency of RECIST assessments changes from eight-weekly to twelve-weekly this will equate to 22 weeks (i.e., take the average of 8 and 12 weeks which gives 10 weeks and then apply same rationale hence 2 x 10 weeks + 1 week for an early assessment + 1 week for a late assessment = 22 weeks). The time period for the previous RECIST assessment will be from study days 274 to 344 (i.e. week 39 to week 49). From week 49 onwards (when the scheduling changes to twelve-weekly assessments), two missing visits will equate to 26 weeks (i.e. 2 x 12 weeks + 1 week for an early assessment + 1 week for a late assessment = 26 weeks).

<u>Cohort 2</u>

If the previous RECIST assessment is less than study day 274 (i.e. week 39) then two missing visits will equate to 14 weeks since the previous RECIST assessment, allowing for early and late visits (i.e., 2 x 6 weeks + 1 week for an early assessment + 1 week for a late assessment = 14 weeks). If the two missed visits occur over the period when the scheduled frequency of RECIST assessments changes from six-weekly to twelve-weekly this will equate to 20 weeks (i.e., take the average of 6 and 12 weeks which gives 9 weeks and then apply same rationale hence 2 x 9 weeks + 1 week for an early assessment + 1 week for a late assessment = 20 weeks). The time period for the previous RECIST assessment will be from study days 274 to 344 (i.e. week 39 to week 49). From week 49 onwards (when the scheduling changes to twelve-weekly assessments), two missing visits will equate to 26 weeks (i.e. 2 x 12 weeks + 1 week for an early assessment + 1 week for a late assessment = 26 weeks).

If the patient has no evaluable visits or does not have baseline data, they will be censored at date of first dose unless they die within 2 visits of first dose (16 weeks plus 1 week allowing for a late assessment within the visit window for Cohort 1, 12 weeks plus 1 week allowing for a late assessment within the visit window for Cohort2).

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

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

- For investigational assessments, the date of progression will be determined based on the earliest of the RECIST assessment/scan dates of the component that indicates progression.

- When censoring a patient for PFS, the patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

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

3.2.2.4 Proportion of patients alive and progression-free after 3 months

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

3.2.2.5 Proportion of patients alive and progression-free after 6 months

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

3.2.2.6 Overall survival

Overall survival (OS) is defined as the time from the date of first dose until death due to any cause (i.e. date of death or censoring – date of first dose + 1). 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 (DCO) for the analysis, and if patients are confirmed to be alive or if the death date is post the DCO date, these patients will be censored at the date of DCO. The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of the final OS analysis should be obtained by the site personnel by checking the patient's notes, hospital records, contacting the patient's general practitioner and checking publicly-available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly-available resources where it is possible to do so under applicable local laws.

Note that for any OS analysis performed prior to the final OS analysis, in the absence of survival calls being made, it may be necessary to use all relevant case report form (CRF) fields to determine the last recorded date on which the patient was known to be alive for those patients still on treatment (since the SURVIVE module is only completed for patients off treatment).

3.2.2.7 Proportion of patients alive at 6 months

The proportion of patients alive at 6 months from enrollment (OS6) will be defined as the Kaplan-Meier estimate of OS at 6 months.

3.2.2.8 Proportion of patients alive at 12 months

The proportion of patients alive at 12 months from enrollment (OS12) will be defined as the Kaplan-Meier estimate of OS at 12 months.

3.2.2.9 Best objective response

BoR is calculated based on the overall visit responses from each RECIST assessment, described in Appendix D of the CSP. It is the best response a patient has had during their time in the study up until RECIST confirmed progression or the last evaluable assessment in the absence of RECIST confirmed progression.

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

CR or PR must be confirmed. For determination of a best response of SD, the earliest of the dates contributing towards a particular overall visit assessment will be used.

SD should be recorded:

- Cohort 1: at least 8 weeks minus 1 week, i.e. at least 49 days (to allow for the assessment window), after first dosing.

- Cohort 2: at least 6 weeks minus 1 week, i.e. at least 35 days (to allow for the assessment window), after first dosing.

For CR/PR, the initial overall visit assessment which showed a response will use the latest of the dates contributing towards a particular overall visit assessment.

BoR will be determined programmatically based on RECIST using all Investigator assessment data up until the first confirmed progression event. This will use all data up until the progression event that is used for the analysis (i.e., unconfirmed progressions are not considered progression events, which means that the BoR may be after an unconfirmed progression for some patients). The denominators for each case will be consistent with those used in the ORR analysis.

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

For patients who die with no evaluable RECIST assessments, if the death occurs ≤17 weeks for cohort 1 and ≤13 weeks for cohort 2 (i.e., 2*8 weeks and 2*6 weeks respectively +1 week to allow for a late assessment within the assessment window) after enrollment, then BoR will be assigned to the PD category. For patients who die with no evaluable RECIST assessments, if the death occurs >17 weeks for cohort 1 and >13 weeks for cohort 2 (i.e., 2*8 weeks and 2*6 weeks respectively +1 week) after the date of enrollment, then BoR will be assigned to the NE category.

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

3.3 Safety variables

3.3.1 Dose-limiting toxicity

DLT criteria for MEDI4736 are defined for Cohort 1 and Cohort 2 in Section 7.2.4 and Section 7.2.5 of the CSP.

DLT criteria for AZD5069 are defined for Cohort in Section 7.2.5 of the CSP.

DLT status, based on a SRC review, are collected in the Adverse events eCRF page.

3.3.2 Adverse events

AEs and SAEs will be collected throughout the study, from the time the informed consent is signed through 90 days after the last dose of IP. Data from all cycles of treatment will be combined in the presentation of safety data. The medical dictionary for regulatory activities (MedDRA) (using the latest or current MedDRA version) will be used to code the AEs. AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE Version 4.03).

A treatment emergent adverse event (TEAE) is an AE with an onset date or a pre-existing AE worsening following the first dose of study treatment through to 90 days after the last dose of IP.

Causally related to treatment events are those assessed by the investigator (as collected in the eCRF) and will also include events with missing responses which default causally related.

If any component of experimental combinations under study is discontinued, then the overall action taken is considered to be "drug discontinued".

Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as serious adverse events (SAEs) and AEs leading to discontinuation. Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the global patient safety physician, be considered other significant adverse events (OAEs) and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious) or significant additional treatment.

AEs of special interest

Some clinical concepts (including some selected individual preferred terms and higher level terms) have been considered "AEs of special interest" (AESI) to the MEDI4736 program. These AESIs have been identified as diarrhea/colitis and intestinal perforation, pneumonitis/ILD (Interstitial lung disease), hepatitis/transaminase increases, endocrinopathies

(i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism, and hypothyroidism and type I diabetes mellitus), rash/dermatitis, nephritis/blood creatinine increases, pancreatitis/serum lipase and amylase increases, myocarditis, myositis/polymyositis, neuropathy/neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis), other inflammatory responses that are rare/less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, haematological and rheumatological events. For AZD5069, an inhibitor of CXCR2, which acts by modulating neutrophil migration, any infections requiring the administration of outpatient oral or IV antibiotics are deemed of special interest, as are ECG abnormalities arising after the beginning of treatment with this agent. Other categories may be added or existing terms may be merged as necessary.

An AstraZeneca medically qualified expert after consultation with the global patient safety physician has reviewed the AEs of interest and identified which preferred terms contribute to each AESI. At the time of the analyses, all AESI categories as present in the most recent version of the AESI identification file for MEDI4736 program will be described; the file might include AESI categories for MEDI4736 and/or AZD5069 molecules. A further review will take place prior to DBL to ensure any further terms not already included are captured within the categories.

3.3.3 Laboratory assessment

Change from baseline in hematology and clinical chemistry variables will be calculated for each post-dose visit on treatment. CTC grades will be defined at each visit according to the CTC grade criteria using project ranges after conversion of lab result to corresponding preferred 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 CTC grades will be calculated.

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

Corrected calcium (mmol/L) = Total calcium (mmol/L) + ([40 − albumin (g/L)] × 0.02)

Creatinine clearance will be derived according to the Cockcroft-Gault formula (Cockcroft and Gault 1976).

Males:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

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 at the local laboratory. Project reference ranges will be used throughout for reporting purposes.

For example:

- If a CTCAE criterion involves a change from Baseline, evaluable patients would have both 1 pre-dose and at least 1 post-dose value recorded

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

3.3.4 Electrocardiograms

Resting 12-lead ECG data at screening and during treatment period 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 3.3.9 below will be used.

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

The variable automatically derived in the database will be used in the analysis.

For triplicate ECGs, the mean of the three ECG assessments will be used to determine the value at that time point. In addition, the worst overall ECG evaluation will be considered at that time point.

3.3.5 Vital signs

Vital signs data obtained up until the 30 days from date of last dose of study treatment or until initiation of the first subsequent therapy following discontinuation of treatment (whichever occurs first), will be used for reporting.

For derivation of post-baseline visit values considering visit window and to handle multiple records, derivation rules as described in Section 3.3.9 below will be used.

3.3.6 Time to first subsequent therapy from discontinuation of study treatment

Time to subsequent therapy from date of last dose is defined as the time from the date of discontinuation of study treatment to the start date of the first subsequent therapy after discontinuation of treatment. Any patient not known to have had a first subsequent therapy will not have this calculation performed.

3.3.7 Treatment exposure

Exposure will be defined separately for each IP as follows:

Total (or intended) exposure of MEDI4736

- Total (or intended) exposure=last dose date +27 days where dose >0 mg or death or DCO date, whichever occurs first – first dose date +1.

Total (or intended) exposure of AZD5069

- Total (or intended) exposure=last dose date where dose >0 mg or death or DCO date, whichever occurs first – first dose date +1.

Actual exposure of study treatment

- Actual exposure = intended exposure – total duration of dose interruptions, where intended exposure will be calculated as above.

A dose interruption is defined as

- any length of time where the patient has not taken any of the planned dose (taking into account the scheduled off treatment period), for MEDI4736,

- any length of time where the patient has not taken any of the planned daily dose, for AZD5069.

Doses interruptions as collected in the eCRF (Action taken <molecule>=Dose interrupted in each Exposure form) will be used for analysis.

For actual exposure on MEDI4736, only valid doses will be considered when identifying the dose interruptions. A dose will be considered as valid when the dose is non null and the volume after and before infusion are not equal.

Dose reductions of MEDI4736 are not permitted per Section 6.7 of the CSP. The actual exposure calculation makes no adjustment for any dose reductions that may have occurred.

Exposure will also be measured by the number of cycles initiated. For both cohorts, a cycle corresponds to a period of 28 days. If a cycle is prolonged for any reason, this should still be counted as one cycle. A cycle will be counted if treatment is started even if the full dose is not delivered.

3.3.8 Dose intensity

Relative dose intensity (RDI) is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation.

Relative dose intensity (RDI) 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. 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 window for dosing.

As per CSP, the initial intended doses are described in Table 8 below:

Table 8 **Initial intended doses**

	MEDI4736	**Nab-paclitaxel**	**Gemcitabine**	**AZD5069**
Cohort 1	1.5g	125 mg/m²	1 000 mg/m²	-
Cohort 2	1.5 g	-	-	20 mg or 40 mg or 80 mg

For AZD5069, the recommended dose of 80mg bid was approved as initial dose.

Dose modifications are described in CSP Appendix E for MEDI4736, and Sections 6.7.2 and 6.7.3 for nab-paclitaxel+gemcitabine and AZD5069 respectively. They will not affect the RDI derivation.

3.3.9 General considerations for safety assessments

Time windows will need to be defined 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.

The following formula can be considered:

- Upper bound (Visit_x)= Day(Visit_x)+integer part of ((Day(Visit_x+1) – Day(Visit_x))/2)

- Lower bound (Visit_x)=2 for first post-baseline visit

  =Upper bound (Day(Visit_x-1)) +1 otherwise

An example is displayed in the appendix (Section 8).

Note: Due to the differing assessment schedules the visit windows will be different for the different study treatments and endpoints.

- Data collected between the start of treatment and the relevant follow-up period (including the permitted time-window for a late assessment) following the last dose of study treatment will be considered as on treatment

- 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 to the scheduled visit date should be summarized, or the earlier in the event the values are equidistant from the nominal visit date. The listings will highlight the value for that patient that went into the summary table, wherever feasible. Note: in summaries of extreme values all post baseline values collected are used including those collected at unscheduled visits regardless of whether or not the value is closest to the scheduled visit date.

  - When several timepoints are planned within the same visit (for instance vital signs are planned pre-, during and post-infusion), data from all timepoints will be summarized. In case of unscheduled assessments, the same algorithm as above will be applied.

- 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 will be defined as the last non-missing measurement prior to dosing with study treatment. For laboratory data and weight assessments, any assessments made on day 1 will be considered pre-dose. For ECOG, data collected on Day 1 will be considered as baseline. 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 will be taken as a baseline value. For non-numeric laboratory tests (i.e. some of the urinalysis parameters) where taking an average is not possible then the closest pre-dose value will be taken as baseline. In the scenario where there are two assessments on day 1, one with time recorded and the other without time recorded, the one with time recorded would be selected as baseline. Study day will be calculated in relation to date of first 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.

3.4 Pharmacokinetic and Immunogenicity variables

Analyses to evaluate the pharmacokinetics and immunogenicity of MEDI4736/AZD5069 will be performed by AstraZeneca/MedImmune Clinical Pharmacology group or designee.

3.4.1 Pharmacokinetic noncompartmental analysis

Calculation of PK parameters will be performed at Covance. The actual sampling times will be used in the PK calculations. The peak and trough concentration PK parameters only will be determined after the first and steady-state doses (as data allow). Samples below the lower limit of quantification will be treated as missing in the analyses.

3.4.2 Immunogenicity analysis

The immunogenicity titer and presence of neutralizing ADAs will be reported for samples confirmed positive for the presence of ADAs.

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

3.5 Biomarker variables

Programmed cell death ligand 1 (PD-L1) expression status (positive, negative) will be retrieved from the item "Total Positive Cells (%)" available in the raw database.

4. ANALYSIS METHODS

Enrollment of Cohort 1 is currently closed due to portfolio decisions that are not related to safety or observed efficacy. Data from Cohort 1 will be listed only (including derived variables).

For the analyses described during Section 4, where applicable and data allow, listings will be generated for Cohort 1 and Cohort 2. Associated Tables and Figures will be produced for Cohort 2 only.

4.1 General principles

The general principles as mentioned below will be followed throughout the study:

- Descriptive statistics will be used for all variables, as appropriate, and will be presented by cohort. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category.

- Unless otherwise stated, percentages will be calculated out of the population total for the corresponding cohort.

- For continuous data the mean and median will be rounded to 1 additional decimal place compared to the original data. The standard deviation will be rounded to 2

additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data.

- For PK data the geometric mean and coefficient of variation (CV) will be presented to 4 significant figures (sf), minimum and maximum will be presented to 3 sf and n will be presented as an integer.

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

- SAS® version 9.4 will be used for all analyses.

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

Concomitant medications will be medications taken at least once from the first dosing date until 90 days after the last dose of the study treatment. Medications with missing start or end dates will also be assumed to be concomitant (whatever is the ongoing status).

Age will be derived for analysis purpose as: year(<reference date>) - year(date of birth), -1 if "day and month" of the reference date is before "day and month" of the date of birth, with inform consent date as reference date.

Handling of missing/incomplete dates

The original incomplete or missing dates will be presented in the listings also.
- Adverse events: all AEs will be considered as treatment-emergent unless the opposite can be clearly stated. Imputation will be done only in the context of identifying TEAEs.

- Concomitant medications: all medications will be considered as concomitant unless the opposite can be clearly stated.

No other imputation will be made.

In practice, original incomplete or missing dates for adverse events and medications will be imputed as below:
- Missing day: Impute the 1st of the month unless year and month is same as year and month of first dose of study drug then impute first dose date

- Missing day and month: impute 1st January unless year is the same as first dose date then impute first dose date

- Completely missing – impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date.

When imputing a start date ensure that the new imputed date is sensible i.e. is prior to the end date of the AE or med.

The following other general principles will also apply:

- All data collected will be listed.

- Efficacy data will be summarized and analyzed based on the Efficacy Analysis Set. PK data will be summarized and analyzed based on the PKS. Safety and treatment exposure data will be summarized on the Safety analysis set. Study population and demography data will be summarized based upon the Safety analysis set.

4.2 Analysis methods

Results of all statistical analysis will be presented using a 80% confidence interval (CI) unless otherwise stated.

Populations to be considered for each endpoint are detailed in Table 3.

The following table (Table 9) details which endpoints are to be subjected to formal statistical analysis.

Table 9   Pre-planned statistical to be conducted

		Type of endpoint
Endpoints analyzed	**Notes**	**Cohort 2**
Objective response rate	Exact 80% CI using Investigator RECIST 1.1 assessments	Primary
	Exact 60% CI using Investigator RECIST 1.1 assessments	
Duration of response	Descriptive data including Kaplan-Meier curves using Investigator RECIST 1.1 assessments	Secondary
Disease Control Rate	Summarized n (%) and 80% CI	Secondary
Progression-free survival	Kaplan-Meier estimates and plots Median PFS Events summary	Secondary
PFS3	PFS estimate at 3 months with 80%CI	Secondary
PFS6	PFS estimate at 6 months with 80%CI	Secondary
Overall survival	Kaplan-Meier estimates and plot Median OS Events summary	Secondary
Proportion of patients alive at 6 months	OS estimate at 6 months with 80%CI	Secondary
Proportion of patients alive at 12 months	OS estimate at 12 months with 80%CI	Secondary

Target lesion size	Descriptive data on percent change from baseline	Secondary
	Waterfall plot on best percentage change	
	Spider plot on percentage change	

4.2.1   Multiplicity (Not Applicable)

4.2.2   Primary endpoints

4.2.2.1   Objective response rate

The efficacy co-primary endpoint for Cohort 2 (ORR) will be estimated with 80% exact Clopper-Pearson CIs.

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

For internal decision-making support, the primary analysis will be repeated with 60% exact Clopper-Pearson CIs.

4.2.2.2   Safety co-primary endpoints

Analysis methods for the safety co-primary endpoints are described in Section 4.2.4

4.2.3   Secondary endpoints

4.2.3.1   Objective response rate

ORR is a secondary endpoint for Cohort 1. This endpoint is described in Section 4.2.2.

4.2.3.2   Duration of response

Descriptive data will be provided for the DoR in responding patients, including the associated Kaplan-Meier curve if data allow.

4.2.3.3   Disease control rate

The DCR will be summarized (i.e., number of patients) with 80% CI. Summary statistics (i.e., number of patients [%] and 80% CIs) on DCR at 6 and 12 months will be produced.

4.2.3.4   Progression-free survival

Kaplan-Meier plot of PFS will be presented. Summaries of the number and percentage of patients experiencing a PFS event and the type of event (RECIST 1.1 or death), are still in survival follow-up, are lost to follow-up and have withdrawn consent will be provided along with median PFS (if calculable). Median progression-free survival will also be presented, based on the Kaplan-Meier estimates.

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

The PFS3 and PFS6 will be calculated using Kaplan-Meier estimates, as the cumulative probability of progression-free survival to each of those time periods. Estimates of PFS3 and PFS6 will each be presented with 80% CIs.

4.2.3.6 Overall survival

Kaplan-Meier plot of OS will be presented. 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 (if calculable).

4.2.3.7 Proportion of patients alive at 6 and 12 months

The OS6, and OS12, will be calculated using Kaplan-Meier estimates of the cumulative probability of survival at each of those time periods. The survival estimates of OS6 and OS12 will be presented with 80% CIs.

4.2.3.8 Best objective response

For each treatment arm, best objective response (BoR) will be summarized by n (%) for each category (CR, PR, SD, PD and NE). No formal statistical analyses are planned for BoR.

4.2.3.9 Change in tumor size

The absolute values and percentage change in target lesion tumor size from baseline will be summarized using descriptive statistics and presented at each timepoint. The best change in target lesion tumor size from baseline, (where best change in target lesion size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction) will also be summarized.

Tumor size will also be presented graphically using waterfall plots, to present each patient's best percentage change in tumor 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 tumor size levels will be added to the plots, which correspond with the definitions of progression and 'partial' response respectively. 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.

Additionally, 'spider' plots will be produced. This depicts each patient's percentage change in tumor size as a line over time.

4.2.4 Safety data

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.

Data from all cycles of treatment will be combined in the presentation of safety data. AEs (both in terms of MedDRA preferred terms and CTCAE grade) will be listed individually by patient. The number of patients experiencing each AE will be summarized by CTCAE grade. Other safety data will be assessed in terms of physical examination, clinical chemistry, hematology, vital signs, and ECGs. Exposure to MEDI4736, nab-paclitaxel + gemcitabine, and AZD5069 will be summarized. Time on study and MEDI4736, nab-paclitaxel + gemcitabine, and AZD5069 combination therapy dose interruptions will also be summarized.

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

DLTs

The proportion of patients with at least one DLT will be displayed considering the tick box of the AE page.

AEs

All AEs, both in terms of current MedDRA preferred term and CTCAE grade, will be summarized descriptively by count (n) and percentage (%). The majority of the AE summaries, unless otherwise stated, will be based on treatment-emergent AEs. Any AE occurring before study treatment (i.e. before the administration of the first dose on Study Day 1) 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'.

AEs observed up until 90 days following discontinuation of the IP (i.e., the last dose of MEDI4736 or nab-paclitaxel or gemcitabine or AZD5069) or until the initiation of the first subsequent anticancer therapy following discontinuation of treatment (whichever occurs first) will be used for reporting of all of the AE summary tables.

However, to assess the longer term toxicity profile, all of the AE summaries will also be produced containing AEs observed up until 90 days following discontinuation of the IP (i.e. without taking subsequent therapy into account).

A small selection of AE summaries may also be produced containing AEs observed from initiation of the first subsequent therapy following discontinuation of study treatment until 90 days following discontinuation of IPs (i.e. summarizing those AEs experienced by patients taking subsequent therapy during the AE collection follow-up window post discontinuation of study treatment). These outputs will only be produced if the number of AEs observed warrant the inclusion of such outputs for interpretational purposes. Any data post 90 days last dose for IPs will be presented in a separate summary that presents any events that occur prior to dosing or starting more than 90 days after discontinuing treatment.

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. Any event that occurs after a patient has received further therapy for cancer will be flagged. A separate data listing of AEs occurring more than 90 days after discontinuation of IP will be produced.

Frequencies and percentages of patients reporting each preferred term will be presented (i.e. multiple events per patient will not be accounted for apart from on the episode level summaries).

Summary information (the number and percent of patients by system organ class and preferred term) will be tabulated for:

- All AEs

- All AEs causally related to study treatment (as determined by the reporting investigator)

- AEs by maximum CTCAE grade

- AEs with CTCAE grade 3 or higher

- AEs with CTCAE grade 3 or higher, causally related to study treatment (as determined by the reporting investigator)

- AEs with outcome of death

- AEs with outcome of death causally related to study treatment (as determined by the reporting investigator)

- AEs by outcome

- All SAEs

- All SAEs causally related to study treatment (as determined by the reporting investigator)

- SAEs leading to discontinuation of study treatment

- AEs leading to discontinuation of study treatment

- AEs leading to discontinuation of study treatment, causally related to study treatment (as determined by the reporting investigator)

- AEs leading to hospitalization

- Other significant AEs

- Other significant AEs causally related to study treatment (as determined by the reporting investigator)

- Immune mediated AEs (as determined by the reporting investigator)

- Infusion reaction AEs (as determined by the reporting investigator)

An overall summary of the number and percentage of patients in each category will be presented. 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 (i.e., x %), 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 time to onset and the duration of the first AE will also be presented.

Deaths

A listing of all deaths will be provided, on the FAS.

Adverse events of special interest

Preferred terms used to identify adverse events of special interest (as defined in Section 3.3.2) will be listed before DBL and documented in the study master file. Grouped summary tables will be produced and may also show the individual preferred terms which constitute each AESI grouping. For each 'grouped' term, the number (%) of patients experiencing any of the specified terms will be presented by maximum CTCAE grade. 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 the above-mentioned grouped AE categories will include number (%) of patients who have:

- At least one adverse event of special interest presented by outcome

- At least one adverse event of special interest causally related to study treatment

- At least one adverse event of special interest leading to discontinuation of study treatment

A summary of total duration (days) of AESI will be provided for events which have an end date and this will be supported by summaries of ongoing AESIs at death and, separately, at DCO.

Additionally, there will be several summaries of AESIs requiring concomitant treatment, and particularly the relationship of AESIs to the use of immunosuppressive agents (i.e., depicting which AESI triggered immunosuppressive use) and, separately, to the use of immunosuppressive agents at high doses.

Laboratory assessment

Data obtained up until the last assessment during follow-up, as detailed in Appendix 2, following discontinuation of the IP or until the initiation of the first subsequent therapy following discontinuation of treatment (whichever occurs first) will be used for reporting. Data summaries will be provided in International System (SI) of units. 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.

Scatter plots (shift plots) of baseline to maximum value on treatment will be produced for lab parameters where data is available, including for example but not exclusive to: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, corrected calcium, lactate dehydrogenase (LDH), magnesium, sodium, potassium, glucose, creatinine, urea or blood urea nitrogen (depending on local practice), and thyroid-stimulating hormone (TSH), free triiodothyronine (fT3) and free thyroxine (fT4).

Scatter plots (shift plots) of baseline to minimum value on treatment will be produced for: hemoglobin, lymphocyte (count, absolute); neutrophils (count, absolute); platelet count; albumin, total protein, corrected calcium, magnesium, sodium, potassium, glucose and TSH, fT3 and fT4.

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:

- Hematology: hemoglobin, total white cell count, lymphocytes (absolute count), neutrophils (absolute count), platelets

- Clinical chemistry: ALT, AST, ALP, total bilirubin, albumin, magnesium – hypo and – hyper, sodium – hypo and – hyper, potassium – hypo and – hyper, corrected calcium – hypo and – hyper, glucose – hypo and hyper, creatinine

For the parameters with no CTCAE grading that are listed in the CSP, shift tables from baseline to maximum, and baseline to minimum value on-treatment will be provided.

All shift plots will be produced with appropriate reference lines.

Liver Enzyme Elevations and Hy's law

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

- Elevated ALT, AST, and total bilirubin at any point during the study following the start of study treatment

    - ALT ≥ 3x –≤ 5x, > 5x –≤ 8x, > 8x –≤10x, > 10x–≤20x, and > 20x ULN

    - AST ≥ 3x –≤ 5x, > 5x –≤ 8x, > 8x –≤10x, > 10x–≤20x, and > 20x ULN

    - Total bilirubin ≥2x–≤ 3x, > 3x –≤ 5x, > 5x ULN

    - ALT or AST ≥3x - ≤5x, >5x - ≤8x, >8x - ≤ 10x, >10x - ≤ 20x and >20x ULN

    - ALT or AST ≥3x ULN and Total bilirubin ≥2x ULN (Potential Hy's law). Note: The onset date of ALT or AST elevation should be prior to or on the date of Total Bilirubin elevation.

Liver biochemistry test results over time for patients with elevated ALT or AST (i.e. ≥ 3x ULN), and elevated total bilirubin (i.e. ≥ 2x ULN) (at any time) will be plotted. Individual patient data where ALT or AST (i.e. ≥ 3x ULN) plus total bilirubin (i.e. ≥ 2x ULN) are elevated at any time will be listed also.

Plots of ALT and AST vs. total bilirubin will also be produced with reference lines at 3×ULN for ALT, AST, and 2×ULN for total bilirubin. In each plot, the maximum values on treatment will be reported, ALT/AST will be on the horizontal axis and total bilirubin will be in the vertical axis.

ECG assessment

Shift plots to minimum and maximum observation on treatment will be produced for each of the ECG parameters presenting mean QT duration, mean RR duration, and QTcF. The

reviewing physician will determine what is worth further consideration, for example ECG data at screening and during treatment period may be included in the summary tables for RR, QT and QTcF. Overall evaluation of ECG is collected in terms of normal or abnormal, and the relevance of the abnormality is termed as "clinically significant" or "not clinically significant". QTcF changes (values of >450, >480, and >500; increase/decrease of >30, >60, and >90 from baseline to any time; and value >450 and increase of > 30 and value >500 and increase of >60) during treatment will be summarized.

Vital signs

Summary tables will include data up to the 30-day follow-up period or until the initiation of the first subsequent anticancer therapy following discontinuation of treatment (whichever occurs first).

Vital signs parameters (systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, temperature, respiratory rate and weight) will be summarized over time in terms of absolute values and changes from baseline at each scheduled visit.

Box plots for absolute values and change from baseline in SBP, DBP, pulse rate, temperature, respiratory rate and weight will be presented, if warranted after data review

Time to Subsequent Therapy from discontinuation of study treatment

This will be listed only.

4.2.5   Pharmacokinetic data

Pharmacokinetic concentration data will be listed for each patient and each dosing day, and a summary provided by nominal visit/time point for all evaluable patients in the PKS. In addition, a box plot for different cycles of trough and peak will be produced.

4.2.5.1   Immunogenicity analysis

Immunogenicity results will be listed by patient and a summary will be provided of the number and percentage of patients who develop detectable anti-MEDI4736, anti-nab-paclitaxel, anti-gemcitabine and ADZ5069 antibodies, if applicable, based on the Safety analysis set. If available, the immunogenicity titer and neutralizing ADA data will be listed for samples confirmed positive for the presence of anti-MEDI4736 antibodies.

The effect of immunogenicity on PK, PDx, efficacy and safety will be evaluated if data allow. These outputs will be produced by AstraZeneca/MedImmune Clinical Pharmacology group or designee.

4.2.6   Biomarker data

If sufficient data are available, the relationship of PD-L1 expression and of exploratory biomarkers to ORR, DoR, DCR, OS, and PFS will be presented for a subset of patients in the EAS population who are evaluable for each biomarker.

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

PD-L1 expression determined by immunohistochemistry will be reported in the CSR. Summaries and analyses for exploratory biomarkers will be documented in a separate analysis

plan and will be reported outside the CSR in a separate report. These outputs will be produced by AstraZeneca/MedImmune Biomarker group or designee.

4.2.7 Demographic and baseline characteristics data

The following will be summarized for all patients in the Safety analysis set (unless otherwise specified):

- Patient disposition (including screening failures and reason for screening failure)- All subjects

- Patient recruitment by country and center – All subjects

- Important protocol deviations

- Inclusion in analysis sets (FAS, Safety analysis set, PKS, DLT evaluable set, EAS) - FAS

- Demographics (derived age, age group [<50, ≥50-< 65, ≥65-<75 and ≥ 75 years], sex, race, ethnicity)

- Patient characteristics at baseline (height, weight, weight group [<70, ≥70 - ≤90 and > 90 kg], body mass index (BMI) and body mass index group [<18.5, ≥18.5 - <25.0, ≥25.0 - <30, ≥30.0)

- Previous disease-related treatment modalities

- Number of regimens of previous chemotherapy at baseline

- Disease characteristics at baseline (ECOG Performance status (PS), primary tumor location, histology type, tumor grade, American Joint Committee on Cancer (AJCC) stage, pancreas cancer location and overall disease classification, best response to previous therapy, time from informed consent to first dose [≤ 14 days, 14 days < to ≤ 21 days, 21 days < to ≤ 42 days, > 42 days])

- Extent of disease at baseline

- Disease related medical history (past and current combined)

- Relevant surgical history

- Time from most recent disease progression to start of study treatment

- Disallowed concomitant medications

- Allowed concomitant medications

- Nicotine use, categorized (never, current, former) and descriptive statistics by type of substance use

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

4.2.8 Treatment exposure

The following summaries related to study treatment will be produced for the Safety analysis set:

- Total exposure (weeks) of each molecule.

- Actual exposure (weeks) of each molecule.

- Total number of cycles received (i.e. at least some drug administered).

- Number of dose reductions of AZD5069 along with reasons, and number of dose interruptions of MEDI4736 and AZD5069. Dose interruptions will be based on investigator initiated dosing decisions. In addition, interruptions due to AEs and due to reasons other than AEs will be summarized separately.

- Number of infusions received (MEDI4736).

- Number of cycles with AZD5069 administration

- Number of administrations (AZD5069)

- RDI of MEDI4736 and AZD5069.

- Exposure over time will be plotted.

The total and actual exposures will also be expressed as total treatment years, defined as the total across all patients in the analysis set.

4.2.9 ECOG PS

ECOG PS will be summarized over time.

4.2.10 Subsequent Therapy

Subsequent therapies received after discontinuation of study treatment will have summaries produced, together with number of regimens received.

5. TIMING OF ANALYSES

No interim analysis is planned.

5.1   Cohort 1

The timing for Cohort 1 will follow the Cohort 2 Primary and Follow-up analyses timing (see Section 5.2).

5.2   Cohort 2

A safety review will occur when the 6 initial patients complete 1 treatment cycle, before the decision to expand to 10 additional patients, in order to observe if any unexpected toxicity has occurred other than that observed in Study D5660C0004. Medics/safety will review the data collected from RAVE; Safety TLFs will be produced for that purpose with Safety listings as a minimum.

A decision was made not to perform a Primary analysis (6 months after the last 10 additional subjects recruited have Cycle 2 Day 15 assessments).

The full TLF package will be produced at the time of the final DBL (planned 12 months after the last of the 10 additional subjects is recruited).

Patient listings will be produced for patients still on study at the time of the follow-up analysis. These listings will be produced from RAVE.

6.   CHANGES OF ANALYSIS FROM PROTOCOL

Table 10   Details of changes from the clinical study protocol

Protocol	SAP	Explanation
Section 5.2.3	Section 3.3.4	*For Cohort 1, ECGs will be recorded at screening and as clinically indicated.* *For Cohort 2, 12-Lead ECGs will be recorded in triplicate at screening and day 1 of each treatment cycle.* Triplicates are collected at screening for both cohorts, as mentioned in CSP Tables 2 and 3 footnote [c]
Section 8.2.2	Section 1.3.2	*Based on binomial probabilities, the probability of observing 0 or more patients with a toxicity event in 6 patients (6 patients respectively) can be seen in Table 2.* Sentence updated in the SAP with the right number of patients: "… with a toxicity event in 6 patients (16 patients respectively)…".
Section 8	Section 4.2	95%CI replaced with 80%CI due to small sample size
Section 8.5.1.1	Section 4.2.3.2	Descriptive statistics produced for Cohort 2 only since only listings to be produced as mentioned in CSP Section 8.5
Section 8.5.1.3	Section 4.2.3.4	Only for Cohort 2 since only listings to be produced as mentioned in CSP Section 8.5
Section	Section 4.2.3.5	Only for Cohort 2 since only listings to be produced as

8.5.1.4		mentioned in CSP Section 8.5
Section 8.5.1.5	Section 4.2.3.6	Only for Cohort 2 since only listings to be produced as mentioned in CSP Section 8.5
Section 8.5.1.6	Section 4.2.3.7	Only for Cohort 2 since only listings to be produced as mentioned in CSP Section 8.5
Section 8.4.2.4, Section 8.5.1	Section 3.2.2.1 Section 4.2.3.2	DoR: CSP Section 8.4.2.4 mentions "until the first date of documented progression" for the main analysis and "with confirmation of progression" for the sensitivity analysis SAP sections are updated to perform the main analysis considering the requirement for a confirmed progression. No analysis modified for unconfirmed progression will be conducted due to lack of meaningful contribution to the interpretation of the data.
Section 8.4.2.4, Section 8.5.1	Section 3.2.2.3 Section 4.2.3.4	PFS: CSP Section 8.4.2.4 mentions "until the date of objective disease progression" for the main analysis and "with confirmation of progression" for the sensitivity analysis SAP sections are updated to perform the main analysis considering the absence of requirement for a confirmed progression. No analysis modified for confirmed progression will be conducted.
Section 8.4.2.4, Section 8.5.1	Section 3.2.2.9 Section 4.2.3.8	BOR: CSP Section 8.4.2.4 mentions "until the first progression event" for the main analysis and "with confirmation of progression" for the sensitivity analysis SAP sections are updated to perform the main analysis considering the requirement for a confirmed progression. No analysis modified for unconfirmed progression will be conducted due to lack of meaningful contribution to the interpretation of the data.

7. REFERENCES

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CTCAE v4.03

A copy of CTCAE, Version 4.03 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

8. APPENDIX

Appendix 1: Visit windows

For example, the visit windows for vital signs data for Cohort 1 (visits on Day 1, 8, 15 of each cycle):

Cycle	Day cycle	Day	Lower	Upper
1	8	8	2	11
1	15	15	12	22
2	1	29	23	32
2	8	36	33	39
2	15	43	40	50
3	1	57	51	60
3	8	64	61	67
3	15	71	68	78
4	1	85	79	88
4	8	92	89	95
4	15	99	96	106
5	1	113	107	116
5	8	120	117	123
5	15	127	124	134
6	1	141	135	144
6	8	148	145	151
6	15	155	152	162
7	1	169	…	

Appendix 2: Follow-up period for laboratory parameters

	Cohort 1	Cohort 2
Urine hCG or serum β-hCG	30 days (±3)	30 days (±3)

Hematology	90 days (±7)	90 days (±7)
Serum or plasma chemistry	90 days (±7)	90 days (±7)
Thyroid function tests (TSH, fT3, and fT4)	30 days (±3)	30 days (±3)