Statistical Analysis Plan

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Sponsor Name:	AstraZeneca
Protocol Number and Title:	**D5660C0004** **A Phase 1b/2, Open-Label, Multicentre Study Assessing the Safety, Tolerability, Pharmacokinetics, and Preliminary Anti-tumour Activity of MEDI4736 in Combination With AZD9150 or AZD5069 in Patients With Advanced Solid Malignancies and Subsequently Comparing AZD9150 and AZD5069 Both as Monotherapy and in Combination with MEDI4736 as Second Line Treatment in Patients with Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck**
Protocol Version and Date:	**Final Version 1.0, 23 April 2015** **Amendment 1, v2.0, 18 August 2015** **Amendment 2, v3.0, 14 December 2015** **Amendment 3, v4.0, 22 March 2016** **Amendment 4, v5.0, 31 July 2016** **Amendment 5, v6.0, 10 May 2017** **Amendment 6, v7.0, 12 February 2018** **Amendment 7, v8.0, 31 July 2018** **Amendment 8, v9.0, 12 August 2018** **Amendment 9, v10.0, 24 August 2018** **Amendment 10, v11,0, 18 June 2019** **Amendment 11, v12,0, 20 November 2019** **Amendment 11, v12,1, 13 November 2019 (Germany only)**
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SAP Version:	Final Version 4.0
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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
ADA(s)	Antidrug antibody(ies)
AE(s)	Adverse event(s)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ASO	Antisense oligonucleotide
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{(ss)}$	Area under the plasma concentration-time curve at steady state
$AUC_{(0-24)}$	Area under the plasma concentration-time curve from zero to 24 hours
$AUC_{(0-48)}$	Area under the plasma concentration-time curve from zero to 48 hours
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from zero to the time of the last measurable concentration
BID	Bis in die (ie, twice daily)
BICR	Best Independent Central Review
BOR	Best Overall Response
BP	Blood pressure
CBR	Clinical benefit rate
cEt	Constrained ethyl
cfDNA	Circulating- Free Deoxyribonucleic Acid
CI	Confidence interval
CL	Clearance
CL/F	Apparent plasma clearance
CL_R	Renal clearance

Abbreviation	Description
CL_{ss}/F	Apparent plasma clearance at steady state
C_{max}	Maximum plasma concentration
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CRF	Case report form (electronic/paper)
CRM	Continuous reassessment method
CRP	C-reactive protein
CSR	Clinical study report
$C_{ss\ max}$	Maximum plasma concentration at steady state
$C_{ss\ min}$	Minimum plasma concentration at steady state
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Concentration at the end of a dosing interval
CXCR2	CXC chemokine receptor-2
D	Day
DCR	Disease control rate
DLT(s)	Dose-limiting toxicity(ies)
DNA	Deoxyribonucleic acid
DOR	Duration of overall response
ECG	Electrocardiogram
ECL	Electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of treatment
ESMO	European Society for Medical Oncology
%Fe	Fraction of dose excreted (%)

Abbreviation	Description
GGT	Gamma-glutamyl transpeptidase
GLP	Good Laboratory Practice
gmean	Geometric mean
GRO-α	Growth regulated oncogene-alpha
h	Hour(s)
HIV	Human immunodeficiency virus
HPF	High-power field
HPV	Human papilloma virus
IB	Investigator's Brochure
IBW	Ideal body weight
IC_{50}	Half maximal inhibitory concentration
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICR	Independent Central Review
IEC(s)	Independent Ethics Committee(s)
Ig	Immunoglobulin
IgG1κ	Immunoglobulin G1 kappa
IL	Interleukin
IM	Immunogenicity
IRB(s)	Institutional Review Board(s)
IV	Intravenous(ly)
IWRS	Interactive web-based randomisation system
kg	Kilogram(s)
Km	Michaelis constant
KM	Kaplan-Meier
L	Litre(s)

Abbreviation	Description
LDH	Lactate dehydrogenase
MDSC(s)	Myeloid-derived suppressor cell(s)
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute(s)
mL	Millilitre
MR	Metabolite-to-parent ratio
MRI	Magnetic resonance imaging
mRNA	Messinger ribonucleic acid
MRT	Mean residence time
MTD(s)	Maximum tolerated dose(s)
NC	Not calculated
NE	Not evaluable
NOAEL	No observed adverse effect level
NSCLC	Non-small cell lung cancer
NTL	Nontarget lesion
OAE(s)	Other significant adverse event(s)
ORR	Objective response rate
OS	Overall survival
OS-12	Overall survival at 12 months after allocation to treatment
P-gp	P-glycoprotein 1 (also known as multidrug resistance protein 1)
PD	Progression of disease
PD-1	Programmed cell death 1 (CD279)
PD-L1	Programmed cell death-ligand 1 (also known as B7 homolog 1, CD274)
PD-(L)1	Programmed cell death 1 (CD279) and/or programmed cell death-ligand 1 (also known as B7 homolog 1, CD274)

Abbreviation	Description
PDN	Pharmacodynamics
PFS	Progression-free survival
PID	Percentage intended dose
PK	Pharmacokinetic(s)
PO	Per os (ie, by mouth)
PR	Partial response
PS	Performance status
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q4W	Every 4 weeks
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	Corrected QT interval
QTcF	Calculated QTc using Fridericia's formula
QW	Every week
R_{ac}	Extent of accumulation on multiple dosing
RBC	Red blood cell(s)
RECIST	Response Evaluation Criteria in Solid Tumours
RM	Recurrent and/or metastatic
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
SAE(s)	Serious adverse event(s)
SC	Subcutaneous
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable disease
StD	Standard deviation
sPD-L1	Soluble programmed cell death-ligand 1

Abbreviation	Description
SRC	Safety Review Committee
STAT3	Signal transducer and activator of transcription 3
$t_{1/2}$	Concentration half-life
$t_{½\lambda z}$	Terminal (elimination) half-life
T3	triiodothyronine
T4	thyroxine
TBD	To be determined
TEAE(s)	Treatment-emergent adverse event(s)
TL	Tumour lesion
T_{max}	Time to reach C_{max}
Treme	Tremelimumab
TSH	Thyroid stimulating hormone
$T_{ss\ max}$	Time to reach C_{max} at steady state
ULN	Upper limit of normal
V_1	Central volume of distribution
V_d/F	Apparent volume of distribution
V_{ss}	Apparent volume of distribution after intravenous distribution
V_{ss}/F	Apparent volume of distribution after oral administration
V_z	Apparent volume of distribution during terminal phase after intravenous administration
V_z/F	Apparent volume of distribution during terminal phase after oral administration
WBC	white blood cell(s)
WBDC	Web-based data capture
wk	Week

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to outline the planned analyses to support the completion of the Clinical Study Report (CSR) for protocol D5660C00004. The planned analyses identified in the SAP will be included in regulatory submissions and/or future manuscripts. Exploratory analyses not identified or defined in this SAP may be performed to support the clinical development program. Any post-hoc or unplanned analyses performed and not identified in this SAP will be documented in the respective CSR.

Throughout this SAP, the references MEDI4736 and AZD9150 are used to refer to "Durvalumab" and "Danvatirsen" respectively.

2.1. RESPONSIBILITIES

[redacted] will perform the statistical analyses and is responsible for the production and quality control of all tables, listings, and figures (TLFs) under the direction of AstraZeneca Early Clinical Biometrics. [redacted]

2.2. TIMINGS OF ANALYSES

The primary analysis of safety and efficacy for Part A (dose-escalation and safety cohorts) is planned after all patients complete the final study visit or terminate early from Part A of the study.

A Safety Review Committee (SRC) will review accumulating safety data from Part A to assess the occurrence of dose-limiting toxicities (DLTs) and to recommend the dose to be used in each cohort following the first cohort.

In Part B (dose-expansion phase), within each combination arm in the anti-PD-(L)1 naïve patients (Arms B3 and B4), after 12 evaluable patients have been followed for efficacy, a predictive probability will be calculated to assess the chance of observing at least 8 of 35 responses (either partial response [PR] or complete response [CR]) following each patient up to and including the 19th evaluable patient. If the predictive probability falls below 20% within an arm, then any arm in which this happens will be stopped. If the predictive probability remains above 20% following the 19th evaluable patient, then an interim analysis in each arm will be performed once 20 evaluable patients have been assessed for efficacy in that arm. Each of the combination arms will continue to enroll patients up to a

maximum of 35 efficacy evaluable patients following the interim analysis if at least 5 of 20 patients have responded with at least a PR.

For each combination arm in the anti-PD-(L)1 pretreated patients (Arms B1 and B2); a predictive probability will be calculated to assess the chance of observing at least 3 of 20 responses (either PR or CR) following 10 efficacy evaluable patients in each arm. If the predictive probability falls below 20% within an arm, then the corresponding arm will be stopped. However, no formal interim analysis will be conducted for the combination arms in the anti-PD-(L)1 pretreated patients.

Recruitment will continue while predictive power is measured. If an arm is to be stopped, no new patients will be recruited but patients who are already on study will continue in accordance with study guidelines outlined in Section 4 of the protocol Amendment 9.

If at least 2 CRs or PRs are observed in the first 20 patients in either of the 2 pretreated expansion arms, an additional 25 to 32 patients may be enrolled to that particular pretreated combination arm.

Predictive power monitoring will not be performed for the 2 monotherapy groups (B5 and B6) in dose-expansion Part B. The 2 monotherapy arms will continue recruiting until 12 efficacy evaluable patients have been enrolled in each arm.

In addition, Arms B7 and B8 will enroll patients who have not received prior systemic treatment for recurrent and/or metastatic squamous cell cancer of the head and neck (RM-SCCHN) and will receive combination treatment of AZD9150 in combination with MEDI4736. With approximately 48 patients in each arm, the probability of observing ≤ 12 responses (CR or PR) out of 48 patients is 9%; given the true probability of responses is 35%. . The probability of observing ≥ 15 responses (CR or PR) out of 48 patients is 20%, given the true probability of responses is 25%. In addition, B8 will incorporate predictive power monitoring for futility beginning with the 15th patient. If at any time from the 15th patient through to the 48th patient, the chance to observe 13 responses in 48 patients falls below 20%, then the arm will be stopped.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

3.1.1. Dose-escalation and safety cohorts: Part A

The primary objective of the Part A is to determine the maximum-tolerated doses (MTDs) or recommended doses for dose-expansion and to determine the safety profiles of either AZD9150 or AZD5069 in combination with MEDI4736 and/or MEDI4736/ tremelimumab (treme) in patients with advanced solid malignancies refractory to standard therapy or for which no standard of care regimen currently exists.

3.1.2. Dose-expansion Part B

The primary objectives of the dose-expansion phase are to:

- Evaluate the objective response rate (ORR) of AZD9150 and AZD5069 both as monotherapy and in combination with MEDI4736 in the second-line treatment of patients with RM-SCCHN and in patients with no prior exposure to anti-PD-(L)1 therapies and also in patients who have not received prior systemic treatment for RM-SCCHN (1L RM SCCHN)

- Evaluate ORR of AZD9150 as a fixed dosed Q2W in patients with no prior exposure to anti-PD-(L)1 therapies and who have not received prior systemic treatment for recurrent or metastatic SCCHN (1L RM SCCHN).

3.2. SECONDARY OBJECTIVES

3.2.1. Dose-escalation and Safety cohorts Part A

The secondary objectives of the dose-escalation phase are to:

- Assess the pharmacokinetics (PK) of AZD9150, AZD5069, and MEDI4736 and/or MEDI4736/treme in the selected dose combinations

- Determine the immunogenicity (IM) of MEDI4736 and/or MEDI4736/treme in combination with AZD9150 or AZD5069

- Determine the IM of AZD9150 in combination with MEDI4736 and/or MEDI4736/treme

- Assess pharmacodynamic response in blood for AZD9150 (signal transducer and activator of transcription 3 [STAT3] knockdown)

3.2.2. Dose-expansion Part B

The secondary objectives of the dose-expansion phase are to:

- Evaluate the safety and tolerability of AZD9150 and AZD5069 both as monotherapy and in combination with MEDI4736
- Assess secondary measures of efficacy (disease control rate [DCR] at 12 weeks; duration of overall response [DOR]; progression-free survival [PFS]; overall survival [OS]; and proportion of patients alive at 12 months)
- Assess the PK of AZD9150 and AZD5069 both as monotherapy and in combination with MEDI4736
- Assess the urinary pharmacokinetics of AZD9150 alone or in combination with MEDI4736
- Determine the IM of MEDI4736 in combination with AZD9150 or AZD5069
- Determine the IM of AZD9150 alone or in combination with MEDI4736
- Assess pharmacodynamic response in blood for AZD9150 and MEDI4736 (soluble PD-L1 will not be evaluated for Arms B1, B2, and B4 post the first 20 patients and for Arms B7 and B8)
- Assess tumour cell pharmacodynamics (STAT3 knockdown)
- Assess baseline circulating myeloid-derived suppressor cell (MDSC) and effect of treatment on circulating MDSCs (will not be evaluated for Arms B1, B2, and B4 post the first 20 patients and for Arms B7 and B8)
- Evaluate baseline tumour PD-L1 expression for potential correlation with drug activity or the ability to prospectively identify patients likely to respond to treatment

3.3. EXPLORATORY OBJECTIVES

The exploratory objectives of the study (in both parts of the study) are to:

- Evaluate baseline levels of and changes in blood-borne biomarkers that may correlate with treatment or clinical response, that may include but are not limited to gene expression, immunogenomics (genetics associated with immune responses such as homozygosity/heterozygosity of MHC-I genes), T-cell activation or proliferation markers, T-cell repertoire, and cytokines or other soluble factors

- Assess serum samples for pharmacodynamic response to AZD5069 (transient increase in CXC chemokine receptor-2 [CXCR2] ligands interleukin 8 [IL-8] and growth regulated oncogene-alpha, [GRO-α])

- Evaluate tumour-based biomarkers in archival tumour samples that may correlate with treatment or prospectively identify patients likely to respond to treatment with AZD9150 or AZD5069 in combination with MEDI4736 and/or MEDI4736/treme (may include but not limited to PD-L1 expression, phospho- or total STAT3 expression, tumour genetics, immunogenomics [genetics associated with immune responses -such as homozygosity/heterozygosity of MHC-I genes], characterization of immune infiltrates, gene expression or other stratification markers)

- Evaluate circulating-free deoxyribonucleic acid (cfDNA: including circulating tumour deoxyribonucleic acid [DNA] as well as non-tumour cell free DNA) measures at baseline or on-treatment or changes upon treatment or changes upon treatment that may correlate with treatment or response. (Note: only cfDNA required to be obtained for new patients consented under protocol amendment 5, dated 10 May 2017 and onwards [B3, B7, B8 and Part A]).

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

- Explore the relationship between pharmacokinetics and selected endpoints (which may include pharmacodynamics, efficacy, and/or safety), where deemed appropriate

- To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (i.e., distribution, safety, tolerability, and

efficacy) to treatment with AZD9150 and AZD5069 both as monotherapy and in combination with MEDI4736 (and/or MEDI4736/treme) and/or development of cancer

An additional exploratory objective for the dose-expansion phase (Part B) only is to evaluate changes in tumour-based biomarkers that may correlate to treatment or response, including but not limited to, immune cell infiltrate, gene expression changes, cell activation or proliferation markers, and cytokines.

3.4. BRIEF DESCRIPTION

This multi-centre, open-label, Phase 1b/2 study is designed as a 2-part study consisting of a dose-escalation and safety run-in cohorts in Part A and a dose-expansion in Part B at the recommended Phase 2 dose (RP2D)/maximum tolerated dose (MTD). An overview of the design for both Part A and Part B is shown in Figure 1.

3.4.1. Dose-escalation and Safety cohorts Part A

The dose-escalation and safety run-in cohorts in Part A of this study initially involves patients with advanced solid malignancies refractory to standard therapy or for which no standard of care regimen currently exists. Subsequently, there is further confirmation of dose, safety, and tolerability assessments done in specific solid tumour types that are refractory to standard therapy or for which no standard of care regimen currently exists. Further, there is also a tolerability safety run-in with the RP2D/MTD for AZD9150 and AZD5069 in combination with fixed dose of MEDI4736/treme. Approximately 30 evaluable patients per treatment arm are planned to be enrolled in dose-escalation cohorts; approximately 18 patients will be enrolled in each of the safety run-in cohorts (in combination with MEDI4736/treme), and approximately 20 patients per tumour type are planned to be enrolled in the solid malignancy safety cohorts. For the dose-escalation cohorts, considering the patient's history of taking any drugs, herbal supplements, and/or foods prohibited with concurrent administration of AZD5069 or within 14 days of the first dose of AZD5069 as well as the patient's anticipated need or likelihood to consume such products at any time throughout the study, patients were allocated sequentially to treatment arm A1 (AZD9150/MEDI4736) or treatment arm A2 (AZD5069/MEDI4736). A continuous reassessment method–based approach is used to identify the set of AZD9150/MEDI4736 and AZD5069/MEDI4736 dose combinations where the incidence of dose-limiting toxicity (DLT) is no larger than 33%.

At the time of this protocol amendment 5 dated 10 May 2017, the MTDs/RP2D for each of the 2 agents in combination with MEDI4736 (durvalumab) were identified from the dose-escalation arms A1 and A2 [AstraZeneca 2016 (a), AstraZeneca 2016 (b)]. The RP2D for

AZD5069 was established at 40 mg twice daily (BID). Also, based on clinical review of maturing data from patients treated with AZD5069 in combination with MEDI4736 in arm A2, it was determined that the DLT of neutropenia occurring in patients treated with AZD5069 were due to a mechanism of AZD5069 (myelokathexis, which was inhibition of mature neutrophil release from the bone marrow) and were likely to confer much lower risk of infection than neutropenia associated with cytoreductive therapies (reduced numbers of early through late stage developing myeloid cells). Therefore, the SRC decided to enrol an additional cohort of at least 6-12 evaluable patients under an alternative dose schedule of AZD5069 (80 mg BID with scheduled dose holds and titration) designed to enable optimal efficacy and safety for individual patients. This cohort was labelled as arm A3. At the time of amendment 5, the SRC reviewed the outcome of 6 evaluable patients from Arm A3 and determined that 80 mg BID (using the alternate dosing schedule for managing neutropenic toxicity) was safe, tolerable, and thus declared as RP2D.

For the safety run-in cohorts (Arm A4) that include treme, patients with solid tumour were planned to be allocated to AZD9150/MEDI4736/treme or AZD5069/MEDI4736/treme with consideration of the patient's history of taking any drugs, herbal supplements, and/or foods prohibited with concurrent administration of AZD5069 or within 14 days of the first dose of AZD5069.

For the dose and safety confirmation cohorts (Arm A6 and Arm A7) in solid tumour indications, patients were planned to be allocated sequentially to AZD9150/MEDI4736 or AZD5069/MEDI4736 with considerations of other medication usage identical to that for the safety run-in cohorts described above. Based on preliminary data from arms A1 and A2, metastatic prostate tumour and metastatic breast cancer patients were planned to be treated.

In addition, it was initially planned to demonstrate the absence of a food effect on AZD5069 absorption enrolling approximately 10 patients either in a fasted or following a high fat meal. Sponsor decision was not to open the cohort for enrolment based on data analyzed for combination of AZD5069 and MEDI4736. At the time of protocol amendment 7, the Sponsor made a decision not to open treatment Arms A5 and A7 that were originally planned for enrolment based on data analyzed for the combination of AZD5069 and MEDI4736.

In summary, all Part A arms conducted at study sites at the time of the protocol amendment 9 are as follows:

- Treatment arm A1: enrolled two cohorts of AZD9150 (2 mg/kg and 3 mg/kg) every week (QW) respectively in combination with MEDI4736 (20 mg/kg every 4 weeks [Q4W]). Cohort is closed to enrolment.

- Treatment arm A2: enrolled two cohorts of AZD5069 (40mg BID capsules/tablet and 80mg tablet BID) respectively in combination with MEDI4736 (20mg/kg Q4W). Cohort is closed to enrolment.

- Treatment arm A3: AZD5069 (80mg BID tablet) in combination with MEDI4736 (20mg/kg Q4W). Cohort is closed to enrolment.

- Treatment arm A4: enrolled into 3 cohorts AZD9150 3mg/kg QW + treme 1 mg/kg Q4W +MEDI4736 20mg/kg Q4W, AZD9150 2mg/kg QW + tremetreme 1mg/kg Q4W+MEDI4736 20mg/kg Q4W and AZD9150 3mg/kg every 2 weeks (Q2W) + treme 1mg/kg Q4W +MEDI4736 20 mg/kg Q4W. These cohorts are now closed to enrolment.

- Treatment arm A6: AZD9150 3 mg/kg QW + MEDI4736 20mg/kg Q4W was originally planned to enroll prostate and breast cancer patients. Enrolment occurred in patients with prostate cancer. Cohort is closed to enrolment.

3.4.2. Dose-expansion Part B

When the maximum or recommended doses for dose-expansion was established in Part A from arms A1 and A2, in parallel with the other arms of Part A, Part B of the study commenced in patients with RM SCCHN). If the RP2D combination is established earlier in one arm of Part A than the other, the Sponsor may manually assign patients to the pretreated arms (B1/B2) for the determined RP2D combination to obtain safety data (for US sites only). These manually randomized patients will not be included in any efficacy analyses and could be replaced with actual randomized patients when the RP2D for both arms is achieved.

The primary objective of the dose-expansion phase is to evaluate the objective response rate (ORR) of AZD9150 and AZD5069 both as monotherapy and in combination with MEDI4736 for treatment of patients with RM-SCCHN.

In the dose-expansion Part B (B1-B6), 10-55 eligible and efficacy evaluable second line+ patients with RM SCCHN patients were planned to be enrolled and randomized depending on the treatment Arms. In addition, non randomized Arms B7 and B8 will each enroll 48 efficacy evaluable first line SCCHN patients (no prior systemic treatment for RM SCCHN). Based on the patient's history of treatment with an anti-PD-(L)1 antibody, the

patient will be assigned to either treatment arms B1 or B2 or treatment arms B3, B4, B5, B6, B7 or B8.

Anti-PD-(L)1 Pretreated Population

Patients with prior anti-PD-(L)1 antibody exposure who have also been excluded by the Investigator for treatment with AZD5069 will be assigned to the following treatment arm:

- Treatment arm B1: AZD9150 3 mg/kg QW in combination with MEDI4736 20mg/kg Q4W (anti-PD-(L)1 pretreated population)

Patients with prior anti-PD-(L)1 antibody exposure who have **not** been excluded by the Investigator for treatment with AZD5069 will be assigned via an interactive web-based randomization system (IWRS) in a 1:1 ratio to 1 of the following 2 treatment arms:

- Treatment arm B1: AZD9150 3 mg/kg QW in combination with MEDI4736 20mg/kg Q4W (anti-PD-(L)1 pretreated population)

- Treatment arm B2: AZD5069 80 mg BID in combination with MEDI4736 20mg/kg Q4W (anti-PD-(L)1 pretreated population)

Anti-PD-(L)1 Naive Population

Patients with **no** prior anti-PD-(L)1 antibody exposure who have been excluded by the Investigator for treatment with AZD5069 will be assigned via an IWRS in a 2:1 ratio to 1 of the following 2 treatment arms:

- Treatment arm B3: AZD9150 3 mg/kg QW in combination with MEDI4736 20mg/kg Q4W (anti-PD-(L)1 naïve population)

- Treatment arm B5: AZD9150 alone (anti-PD-(L)1 naïve population)

Patients with **no** prior anti-PD-(L)1 antibody exposure who have **not** been excluded by the Investigator for treatment with AZD5069 will be assigned via an IWRs in a 2:2:1:1 ratio to 1 of the following 4 treatment arms:

- Treatment arm B3: AZD9150 3 mg/kg QW in combination with MEDI4736 20mg/kg Q4W (anti-PD-(L)1 naïve population)

- Treatment arm B4: AZD5069 40 mg BID in combination with MEDI4736 20mg/kg Q4W (anti-PD-(L)1 naïve population)

- Treatment arm B5: AZD9150 3 mg/kg QW alone (anti-PD-(L)1 naïve population)
- Treatment arm B6: AZD5069 40 mg BID alone (anti-PD-(L)1 naïve population)

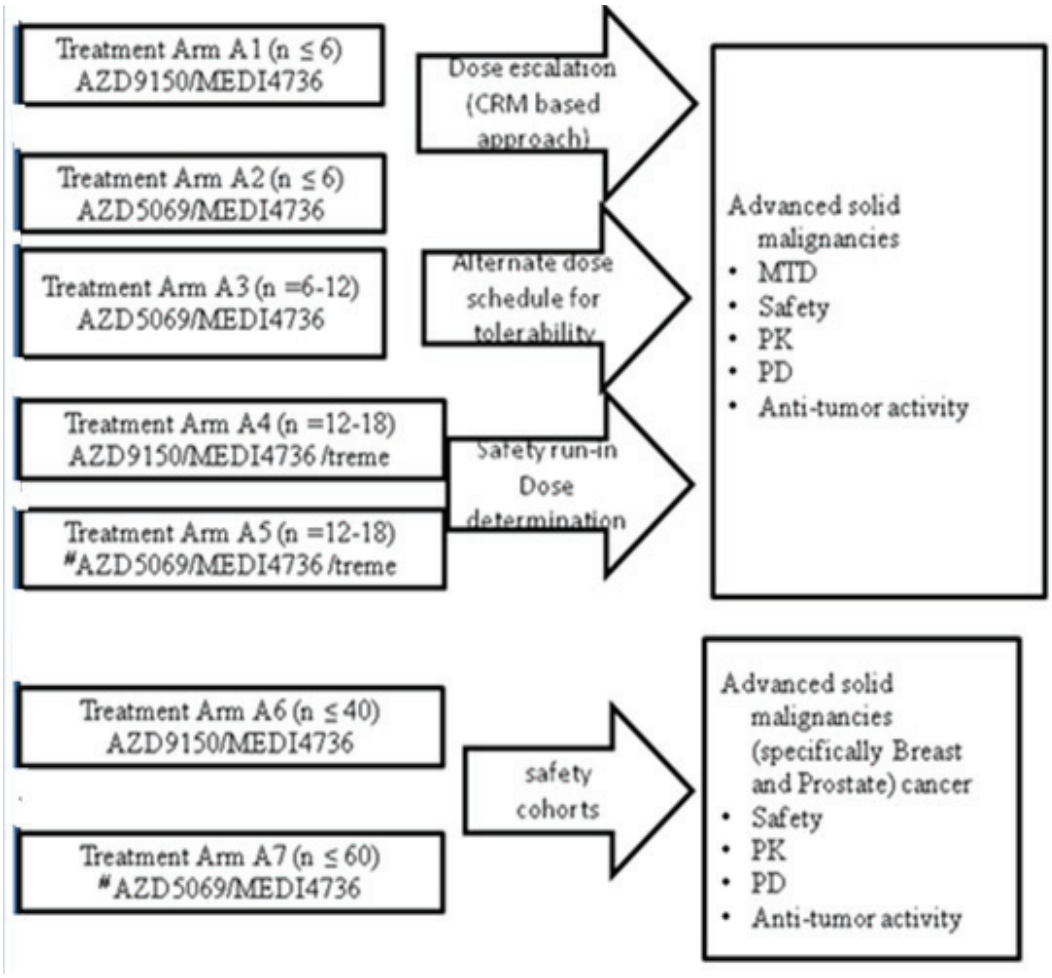
In addition, the following non randomized Arms will enroll patients with no prior exposure to anti-PD-(L)1 therapies and patients who have not received prior systemic treatment for RM disease.

- Treatment arm B7: AZD9150 3mg/kg QW in combination with MEDI4736 20 mg/kg Q4W (anti-PD-(L)1 naïve population)
- Treatment arm B8: AZD9150 400mg Q2W (200 mg in lead-in period) in combination with MEDI4736 1.5g Q4W (anti-PD-(L)1 naïve population)

The doses for the monotherapy treatments will be determined by the SRC based on the experience with the 2 agents gained in other trials and available at that time. The dose-expansion Part B will use an adaptive approach to sample size based on Bayesian statistical methodology, so the number of actively enrolling treatment arms may decrease as the study continues. The dose-expansion Part B is based on efficacy evaluable patients. Patients identified as not efficacy evaluable will be replaced.

Figure 1 - Study flow chart

Part A: Dose escalation & Safety Cohorts



Abbreviations: MTD=maximum tolerated dose; PK=pharmacokinetics; PD=pharmacodynamics; treme= tremelimumab.
Note: Treatment arms A1, A2, A3, A4, and A6 are closed to enrolment. Treatment arms A5 and A7 will not open.

Part B: Dose Expansion

See Protocol Amendment 9, Section 1.4, pages 54 and 55 for design details for Part B.

3.5. PATIENT SELECTION

Dose-escalation and safety cohorts in Part A

The study population in Part A will consist of patients with histologically confirmed solid malignancies (other than hepatocellular carcinoma) that are refractory to standard therapy or for which no standard of care regimen currently exists.

Dose-expansion Part B

The study population in Part B (B1 to B8) will consist of patients with histologically and/or cytologically confirmed SCCHN that is recurrent and/or metastatic (RM), and not amenable to curative therapy by surgery or radiation. Patients may have failed 0 to 3 previous cytoreductive chemotherapeutic (B1 to B6) or patients who have not received any prior systemic treatment for RMSCCHN (B7 and B8) as described in more detail in protocol amendment 9 Section 3 dated 24 August 2018. Patients must have at least 1 tumour lesion amenable to biopsy and must be medically fit and willing to undergo a biopsy during screening and, unless clinically contraindicated, at the end of Cycle 1. (In the event of disease progression, biopsies at the end of treatment are optional but encouraged.)

In amendment 10 section 6 dated 18Jun2019, a discussion regarding serious bleeding events with combination drug MEDI4736 (Durvalumab) in squamous cell carcinoma of the head and neck patients. This section was then removed in amendment 11.1-Germany section 6 dated 13 Nov 2019 but remains part of amendment 11 section 6 dated 3 Nov 201920.

3.6. DETERMINATION OF SAMPLE SIZE

3.6.1. Dose-escalation and Safety cohorts Part A

A CRM–based approach will be used to identify the set of AZD9150/MEDI4736 and AZD5069/MEDI4736 dose combinations where the incidence of DLT is no larger than 33%. In each cohort, up to 3 patients will be initially assessed. Dose escalation to the next higher dose level for the next cohort group of 3 patients will occur if all 3 patients in the

initial cohort complete Cycle 1 without DLT. Following the first DLT, the CRM model will be run and the output made available to the SRC to guide further dosing decisions.

The CRM model will use a stopping criterion based on posterior variance (posterior variance <0.03). When this criterion is met, the model will recommend that the trial be stopped. The dose with expected DLT incidence closest and below 0.33 at this point will be "model estimated" MTD. During trial execution, the SRC will determine the MTD. For the purposes of describing the operating characteristics of the model, the stopping criterion based on the posterior variance will be the only criterion considered. Model performance is measured using simulation methods. In each case, the trial is simulated 10,000 times, and trials that select each MTD among the doses explored are counted.

A logistic dose-toxicity model of the following form will be used:

$p = \{1 + \exp(-a - (\exp(beta)*dose)\}^{-1}$,

where p is the probability of occurrence of a DLT; the intercept, a, is assigned a fixed value equal to 3; and the prior distribution of the slope parameter, beta, is assumed to be normal with mean = 0 and variance =1.34.

In the case of AZD9150/MEDI4736, 4 dose levels are included. The start dose is the second highest dose level among the 4 levels. This is also the true MTD. The prior model assumes that the second dose is also the MTD. Using the posterior variance criterion above, the model selects the correct dose combination in 60.1% of simulated trials. The model selects the dose below the true MTD in 18.1% of simulated trials, and the dose above the true MTD in 21.8% of simulated trials. On average, the number of patients treated at each of the 4 dose levels is 6, 5, 3, and 1. The average number of DLTs at each of the 4 doses is 1, 2, 2, and 1.

In the case of AZD5069/MEDI4736, 6 dose levels are included. The start dose is the third highest dose among the 6 dose levels. This true MTD is the fourth highest dose among the 6 dose levels. The prior model assumes that the fourth dose is the true MTD for the simulations. Using the posterior variance criterion above, the model selects the correct dose combination in 50.9% of simulated trials. The model selects the dose below the true MTD in 22.2% of simulated trials, and the dose above MTD in 26.9% of simulated trials. On average, the number of patients treated at each of the 6 dose levels is 0, 1, 6, 5, 1, and 3. The average number of DLTs on each of the 6 doses is 0, 0, 1, 1, 1, and 2.

In Arms A3; 6-12 patients will be enrolled.

Approximately 18 patients will be enrolled in the safety run-in cohorts of AZD9150 or AZD5069 in combination with MEDI4736 and treme (Arms A4).

Approximately 40 patients (approximately 20 in breast cancer and 20 in prostate cancer) will be enrolled in arms A6.

These sample sizes are selected based on the need to gather and confirm safety, MTD/RP2D, PK/pharmacodynamic information in solid relapsed/refractory patient population for further exploration in next trials.

3.6.2. Dose-expansion Part B

The sample size is based on the operating characteristics of a decision procedure using a beta binomial posterior distribution based on observed data assuming a noninformative prior.

For a single arm trial with N planned patients and an interim analysis to occur following N_i patients ($N_i < N$), where n_i of the N_i patients included in the interim response and we need to observe n_s ($n_s > n_i$) patients in order to declare the trial a success then the predictive probability or the chance to observe at least n_s patients out of N patients (at the end of the trial) is:

$$\sum_{k=0}^{N_i} [P(X_1 = k | n_i/N_i) \left(1 - P\left(X_2 \leq \left((n_s - n_i) - 1\right) | \mu_k\right)\right)]$$

$X_1 \sim$ Binomial(N_i, n_i/N_i)

X_1 ranges from 0 to N_i and is the possible number of successes observed at an interim with N_i total observations.

$X_2 \sim$ Binomial($N - N_i$, μ_k)

X_2 is the number of successes that remain following the interim necessary to achieve the target at the end of the trial.

The left-hand factor in the expression being summed above is a vector of probabilities that k responses are observed assuming that the observed response proportion is actually true. The right-hand factor is the probability that at least the balance of the required responses needed is observed in the remaining patients to be observed in the planned sample.

μ_k is typically equal to k/N_i. Exceptions are made for the values $k = 0$ and $k = N_i$. For these values, $0.5/N_i$ and $(N_i – 0.5)/N_i$ are used instead in order to avoid having to use actual 0 and 1 values for μ_k.

For the 2 combination arms in the anti-PD-(L) 1 naïve patients (B3 and B4), approximately 12 to 35 patients will be treated in each of the 2 combination therapy arms. Once 12 efficacy outcomes are observed in the first 12 efficacy evaluable patients in each arm, a predictive probability calculation will be used to assess the chance of observing at least 8 of 35 responses (either partial or complete) in each arm. The method of calculating predictive probability is based on a parameter-free approach to predictive probability as it applies to variables that follow a binomial distribution (Jennison and Turnbull, 2000). Predictive probability (chance to observe at least 8 of 35 responses) will be recalculated following the observation of the efficacy outcome in each efficacy evaluable patient as they were dosed in the trial. If following the observation of any patient's outcome, predictive power falls below 20%; the arm in which this happens will be stopped. If predictive power remains at or above 20% following the 19th efficacy evaluable patient then an interim analysis will be conducted following the 20th efficacy evaluable patient. Each of the combination arms will continue to enroll patients up to a maximum of 35 efficacy evaluable patients following the interim analysis if at least 5 of 20 patients have responded with at least a PR.

Predictive power monitoring will not be performed for the 2 monotherapy groups (B5 and B6) in dose-expansion Part B, where 12 patients will be treated in each of the 2 monotherapy arms. The 2 monotherapy arms will continue recruiting until 12 efficacy evaluable patients have been enrolled in each arm.

In the anti-PD-(L)1 pretreated patients (B1 and B2), approximately 10 to 52 patients will be treated in each of the 2 combination therapy arms. Once efficacy outcomes have been observed in the first 10 efficacy evaluable patients in each arm, a predictive power calculation will be used to assess the chance of observing at least 3 of the 20 responses (either partial or complete) in each arm. Predictive power (chance to observe at least 3 of 20 responses) will be recalculated following the observation of the efficacy outcome in each efficacy evaluable patient as they were dosed in the trial. If, following the observation of any patient's outcome, predictive power falls below 20%, the arm in which this happens will be stopped. However, no formal interim analysis will be conducted for the combination arms in the anti-PD-(L)1 pretreated patients.

In addition, Arms B7 and B8 will enroll patients who have not received prior systemic treatment for RM SCCHN and will receive combination treatment of AZD9150 in combination with MEDI4736. With approximately 48 patients in each arm, the probability of observing ≤ 12 responses (CR or PR) out of 48 patients is 9%, given the true probability

of responses is 35%. . The probability of observing ≥ 15 responses (CR or PR) out of 48 patients is 20%, given the true probability of responses is 25%. In addition, B8 will incorporate predictive power monitoring for futility beginning with the 15th patient. If at any time from the 15th patient through the 48th patient, the chance to observe 13 responses in 48 patients falls below 20%, then the arm will be stopped.

Recruitment will continue while predictive probability is measured. If an arm is stopped, no new patients will be recruited, but patients who are already on study will continue in accordance with study guidelines.

If at least 2 CRs or PRs are observed in the first 20 patients in either of the 2 pretreated expansion arms, an additional 25 to 32 patients may be enrolled to that particular pretreated combination arm.

In addition, Arms B7 and B8 each will enroll up to 48 patients who have not received any PD-L1 therapies and have received no prior systemic treatment for RM SCCHN, and will receive combination treatment of AZD9150 in combination with MEDI4736.

An efficacy evaluable patient is defined as a patient with unidimensional measurable at baseline as per the RECIST version 1.1 criteria who received at least 1 dose of study treatment. Measurable disease is defined as having at least 1 lesion that can be accurately measured in a at least 1 dimension with a minimum size of 10 mm by CT scan, except lymph nodes which must have a minimum short axis size of 15 mm.

3.7. TREATMENT ASSIGNMENT & BLINDING

Both Parts A and B of this study are open-label. Ideal body weight (IBW) will be used to calculate the administered dose in all arms where AZD9150 is to be infused except Arm B8 where fixed dosed AZD9150 is to be administered, i.e., 200 mg as lead-in doses on Days −7, −5, and −3 and 400 mg Q2W thereafter in a 28-day cycle. Ideal body weight will be determined using the Devine formula (Pai and Paloucek 2000; see Section 7.2.1 of final study protocol). If the actual weight is less than the IBW or the patient is less than 5 feet tall, the actual weight will be used to determine the dose.

3.8. STUDY PROCEDURES AND FLOWCHART

Each patient will undergo screening during the 28 days before admission to confirm eligibility. Tumour assessments and other clinical data obtained as standard of care before consent may be used for the study provided the assessments fall within the protocol-specified period before the first dose of study treatment.

Statistical Analysis Plan

For both Part A and Part B, treatments will be administered after a 7-day lead-in period followed by 4-week treatment cycles for as long as the patient is considered to be achieving clinical benefit. Patients will be discontinued from treatment if they have confirmed PD with either clinical deterioration and/or no further benefit from treatment, experience unacceptable toxicity, or discontinue for any other reason.

Study procedures and assessments during study entry, as well as subsequent safety and tumour assessments are the same in Part A and Part B of the study. Pharmacokinetic, pharmacodynamic, and IM assessments, however, differ between Part A and Part B. In the protocol, an overview of the study procedures are shown in Table 5 (Study plan for study entry, treatment, safety and tumour assessments), Table 6 (Study plan for pharmacokinetic, pharmacodynamics, immunogenicity, and pharmacogenetic assessments in Part A), Table 7 (Study plan for pharmacokinetic, pharmacodynamics, immunogenicity, and pharmacogenetic assessments in Part B, Arms B1-B7), and Table 8 (Study plan for pharmacokinetic, pharmacodynamics, immunogenicity, and pharmacogenetic assessments in Part B, Arm B8).

4. ENDPOINTS

4.1. PRIMARY EFFICACY ENDPOINT

4.1.1. Dose-escalation and Safety cohorts Part A

There is no primary efficacy endpoint for Part A.

4.1.2. Dose-expansion Part B

The primary efficacy endpoint for Part B is objective response (OR), which is defined as either a CR or a PR according to RECIST version 1.1.

4.2. SECONDARY EFFICACY ENDPOINTS

4.2.1. Dose-escalation Safety cohorts Part A

The secondary efficacy endpoints for Part A include:

- Best overall response (including CR, PR, Stable Disease (SD) and Progressive Disease (PD), according to RECIST version 1.1, ordered from best to worst)
- Objective response – defined as a CR or PR according to RECIST version 1.1
- Disease control – defined as a CR, PR, or SD, according to RECIST version 1.1 criteria, at 12 weeks.
- Duration of Response (DOR) according to RECIST version 1.1 criteria (measured from the time measurement criteria are first met for CR or PR, whichever is first recorded, until the first date that recurrent or PD is objectively document (taking as reference for PD the smallest measurements recorded on study)
- Progression-free survival (PFS) – defined as the time from treatment allocation to the first documentation of PD as determined by the Investigator or death from any cause, whichever occurs first.
- Overall survival (OS) – defined as the time from treatment allocation to death from any cause.

4.2.2. Dose-expansion Part B

The secondary efficacy endpoints for Part B include:

- Disease control – defined as a CR, PR, or SD, according to RECIST version 1.1 criteria, at 12 weeks.

- DOR according to RECIST version 1.1 criteria (measured from the time measurement criteria are first met for CR or PR, whichever is first recorded, until the first date that recurrent or PD is objectively document (taking as reference for PD the smallest measurements recorded on study).).

- PFS – defined as the time from randomization to the first documentation of PD as determined by the Investigator or death from any cause, whichever occurs first.

- OS – defined as the time from randomization to death from any cause.

- Best overall response (including CR, PR, SD, and PD), according to RECIST version 1.1, ordered from best to worst.

- Survival at 12 months (OS-12) –defined as the percentage of patients who have survived at least 12 months from the date of randomization.

4.3. PHARMACOKINETIC ENDPOINTS

Pharmacokinetic analysis of plasma (for all compounds) and urine (for AZD9150 only) concentration data for AZD9150, AZD5069 and its metabolite AZ13587715, treme and MEDI4736 will be performed by [redacted] on behalf of AstraZeneca. The actual sampling times will be used in the parameter calculations and PK parameters will be derived using non-compartmental methods. As data permit, the following parameters will be determined for each analyte:

Pharmacokinetic parameters for AZD9150:

- Single dose: C_{max}, T_{max}, AUC, $AUC_{(0-t)}$, $AUC_{(0-6)}$, $AUC_{(0-48)}$, CL, V_z, MRT, $t_{1/2}$, as data permits. Urine PK parameters (Ae, fe, and CLr) will be determined as data permits.

- Multiple dose: $C_{ss\ max}$, $C_{ss\ min}$, $T_{ss\ max}$, C_{trough}, $AUC_{(0--246)}$, $AUC_{(0-48)}$, $AUC_{(0-\ )}$, V_{ssz}, extent of accumulation on multiple dosing (R_{ac}), Ae, and %Fe). Urine PK parameters (Ae, fe, and CLr) will be determined as data permits.

Pharmacokinetic parameters for AZD5069 and AZ13587715:

- Single dose: C_{max}, T_{max}, AUC, $AUC_{(0-t)}$, $AUC_{(0-8)}$, $AUC_{(0-10)}$, $AUC_{(0-12)}$, apparent plasma clearance (CL/F) (AZD5069 only), apparent volume of distribution (V_z/F) (AZD5069 only), MRT (AZD5069 only), and $t_{1/2}$

- Multiple dose: $C_{ss\ max}$, $T_{ss\ max}$, C_{trough}, $AUC_{(0-t)}$, $AUC_{(0-8)}$, $AUC_{(0-10)}$, $AUC_{(0-12)}$, V_z/F, apparent plasma clearance at steady state (CL/F), R_{ac}

- Metabolite-to-parent ratio (MR) will be calculated after single and multiple doses

Pharmacokinetic parameters for MEDI4736/treme:

- C_{max}, T_{max}, $C_{trough,}$ and Concentration at the end of infusion (C_{EOI}).

Where possible the terminal elimination rate constant (λz) will be calculated by log-linear regression of the terminal portion of the concentration-time profiles where there are sufficient data and the terminal (elimination) half-life ($t1/2_{\lambda z}$) will be calculated as ln 2/λz. The $AUC_{(0-t)}$ and additional partial AUC values will be calculated using the linear up, log down trapezoidal rule. Where appropriate, the $AUC_{(0-t)}$ will be extrapolated to infinity using λz to obtain AUC. The area under the concentration-time curve across the dosing interval, $AUC_{(0-\tau)}$ will be calculated using the linear up, log down trapezoidal rule. The CL/F following single dose or multiple dosing will be determined from the ratio of dose/AUC or dose/$AUC_{(0-\tau)}$, respectively The volume of distribution (V_z) following single or multiple dosing will be determined as dose/(λz*AUC) or dose/(λz*$AUC_{(0-\tau)}$), respectively. The accumulation ratio (RAC) will be calculated as the ratio of the appropriate partial AUC following single dose to the same partial AUC following multiple dosing. The time dependency (TCP) of the PK on multiple dosing will be assessed by the calculation of the ratio of $AUC_{(0-\tau)}$/AUC(single dose).

4.4. PHARMACODYNAMIC ENDPOINTS

The pharmacodynamic endpoints for dose-escalation Part A include the following:

- For AZD9150: Signal transducer and activator of transcription 3 (STAT3) knockdown in blood

- For MEDI4736: Soluble programmed cell death-ligand 1 (sPD-L1)

- For AZD5069: Circulating myeloid-derived suppressor cells (MDSCs)

In addition to the above pharmacodynamic endpoints, the dose expansion Part B also includes:

- For AZD9150: STAT3 knockdown in tumour issue
- For MEDI4736: Tumour PD-L1 expression

4.5. PRIMARY SAFETY ENDPOINTS

4.5.1. Dose-escalation and Safety cohorts Part A

The primary safety endpoints for Part A include:

- Maximum-tolerated dose (MTD) based on patients who completed the DLT evaluation
- AEs, SAE, laboratory evaluations, vital signs, and physical examinations
- Treatment-emergent AEs (TEAEs), SAEs and deaths, graded in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03.

4.5.2. Dose-expansion Part B

There are no primary safety endpoints for Part B.

4.6. SECONDARY SAFETY ENDPOINTS

The secondary safety endpoints for Part A and Part B include:

- Anti-drug antibodies (ADAs)
- AEs, SAEs, laboratory evaluations, vital signs, and physical examinations
- TEAEs, SAEs and deaths, graded in accordance with NCI CTCAE version 4.03

4.7. OTHER ENDPOINTS

4.7.1. Blood-borne Biomarkers

Blood-borne biomarkers that may correlate with treatment or clinical response may include, but are not limited to, gene expression changes, immunogenomics (genetics associated with immune responses such as homozygosity/heterozygosity of MHC-I genes), T-cell activation or proliferation markers, T-cell repertoire changes, cytokines, CXC chemokine receptor-2 ligands, interleukin 8, and growth-regulated oncogene-alpha.

4.7.2. Tumour-based Biomarkers

Tumour-based biomarkers in archival tumours that may correlate with treatment or prospectively identify patients likely to respond to treatment may include PD-L1 expression, phospho- or total STAT 3 expression, tumour genetics, immunogenomics (genetics associated with immune responses such as homozygosity/heterozygosity of MHC-I genes), characterization of immune infiltrates, gene expression or other stratification markers.

4.7.3. Pharmacogenetics

Saliva samples intended for subsequent DNA analysis will be collected if a patient agrees to participate in this aspect of the study.

5. ANALYSIS SETS

The analysis of data will be based on different subsets according to the purpose of the analysis. Throughout the safety results sections, erroneously treated patients (eg, patients who were assigned to dose X but received dose Y) will be accounted for based on the actual dose received.

Definition of the analysis sets used in this study are presented in Table 2 below.

Table 2. Definition of Analysis Populations

Analysis Set	Definition
All Patients	All patients who provided written informed consent (i.e., including screen failures)
Full Analysis	All patients who were either assigned or randomized to study.
Safety	All patients who received at least 1 dose of AZD9150, AZD5069, or MEDI4736.
Pharmacokinetics (PK)	All dosed patients with reportable AZD9150, AZD5069, treme or MEDI4736 plasma concentrations except for important protocol deviation. The important protocol deviations will be determined by the clinical team during the Blind Data Review Meeting (BRDM) planned to take place just prior to the final Database Lock (DBL).
Pharmacodynamics (PDN)	All patients who provided biological samples for pharmacodynamic research except for important protocol deviation. The important protocol deviations will be determined by the clinical team during the Blind Data Review Meeting (BRDM) planned to take place just prior to the final Database Lock (DBL).

Analysis Set	Definition
Efficacy	All patients with unidimensional measurable disease at baseline as per the RECIST version 1.1 criteria who received at least 1 dose of study treatment (Part A) ~~barring~~ except for important protocol deviation. All patients with unidimensional measurable disease at baseline as per the RECIST version 1.1 criteria who were randomized to study treatment and received at least 1 dose of study treatment (Part B) except for important protocol deviation. Patients who have been manually assigned to treatment in Part B will be excluded from this analysis set. The important protocol deviations will be determined by the clinical team during the Blind Data Review Meeting (BRDM) planned to take place just prior to the final Database Lock (DBL).

While the definitions of several of the various analysis sets apply to both Part A and to Part B of the study, the data for patients from Part A and Part B will be summarized separately.

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The analysis sets which will be used in analyses of the various endpoints are shown in Table 3.

Table 3. Summary of Outcome Populations and Analysis Sets

Outcome variable	***Populations***
Efficacy data	
Disposition	*All Patients, Full analysis*
Demography	*Safety*
OR*, disease control, DOR*, PFS, OS, OS-12	*Efficacy*
Safety data	
Relevant Medical History	*Safety*
Current Medical Condition at Entry	*Safety*
Exposure	*Safety*
Adverse events (including SAEs and DLTs)	*Safety*
Laboratory measurements	*Safety*
Vital signs	*Safety*
Physical examinations	*Safety*
ECGs	*Safety*
Pharmacokinetic data	*Pharmacokinetic*
Pharmacodynamic data	*Pharmacodynamic*

* Patients who are evaluable for the analysis of OR and DOR are those with measurable disease at baseline

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

Statistical analyses of the demographic, safety, and efficacy data will be performed by [redacted] under the direction of the Early Clinical Biometrics Group, AstraZeneca.

[redacted] will perform all PK and PD analyses. [redacted] will provide data listings of the administration information for the collection of PK and PD samples. [redacted] will provide summaries of descriptive statistics for the PK and PD parameters derived by [redacted].

AstraZeneca will be responsible for creating the playbook used to communicate CRM model recommendations to the SRC in dose-escalation Part A. However, [redacted] will independently generate a copy of the playbook that can serve as a back-up, if needed. Astra Zeneca will also be responsible for providing all summaries of predictive probability calculations to be performed in Part B.

The methods outlined below apply to both Part A and Part B unless otherwise specified.

- SAS version 9.3 or higher will be for all statistical analyses, excluding analyses that are Bayesian or involve the CRM.
- R version 3.1.2 or higher software and modules (e.g.: dfcrm package) will be used for CRM analyses in Part A and for the Bayesian analyses in Part B.
- All patients who provided informed consent will be accounted for in this study and have data from patients who were randomized or dosed included in the patient data listings.
- Listings will be sorted by treatment group (see Section 6.1.1 for ordering), patient number and, if applicable, by assessment date and time unless otherwise noted. Patients who are screen failures will be presented in a separate listing.
- The total number of patients in the treatment group and dose level (N) will be used as the denominator for percentage calculations, unless stated otherwise in the table shell.
- Continuous variables, including pharmacodynamic variables, will be summarized using the number of observations (n), mean, standard deviation (StD), median,

minimum, and maximum, unless otherwise specified. The descriptive statistics to be provided for PK data are summarized in Section 6.1.2.

- For log transformed data it is more appropriate to present geometric mean, coefficient of variation (CV), arithmetic mean, SD, median, minimum and maximum.
- Categorical variables will be summarized using number of observations (n), frequency and percentages of patients.
- Multiple assessments at a given time point (planned, repeat, unscheduled) will not be included in summary tables unless otherwise specified, but will be included in the listings and patient profiles if required. For example, if there are multiple laboratory results at a given visit, the latest non-missing value will be included in summary tables.

6.1.1. Presentation of Data by Treatment Group

Data will be summarized separately for each of the 2 treatment combinations (AZD9150/MEDI4736, and AZD5069/MEDI4736) in Part A. Each treatment combination will be presented in separated pages of one table.

IO Naïve 1st Line Combo, consisting of 10 identified B3 patients and all B7 patients, and IO Naïve 2nd Line+ Combo Population, consisting of all B3 subjects not in the previous group will be included in all summaries and analyses and will be presented as any treatment group is presented.

Patients who have a dose modification during the trial will be presented according to the dose group to which they were initially assigned.

6.1.2. Descriptive Statistics for PK Data Summaries

The following summary statistics will be presented for plasma concentrations at each time point and PK parameters, AUC, $AUC_{(0-6)}$, $AUC_{(0-8)}$, $AUC_{(0-10)}$, $AUC_{(0-12)}$, $AUC_{(0-48)}$, $AUC_{(0-t)}$, $AUC_{(0-\ )}$, R_{ac}, C_{max}, $C_{ss\ max}$, C_{trough}, $C_{ss\ min}$:, and C_{EOI}.

- Number of observations
- The geometric mean (gmean) calculated as exp[μ], where μ is the sample mean of the data on a logarithmic scale

- Coefficient of variation, calculated as $100*[\exp(s2) - 1]^{1/2}$, where s is the standard deviation of the data on a log-scale
- Gmean + standard deviation (calculated as $\exp[\mu \pm s]$)
- Gmean - standard deviation (calculated as $\exp[\mu \pm s]$)
- Arithmetic mean calculated using untransformed data
- Standard deviation calculated using untransformed data
- Median
- Minimum
- Maximum

The following summary statistics will be presented for CL, CL/F, CL_{ss}/F, CL_R, MRT, V_{ss}, V_{ss}/F, V_z, V_z/F, $t_{1/2\lambda z}$, , MR, R_{ac}, TCP, Ae, and %Fe:

- Number of observations
- Arithmetic mean
- Standard deviation
- Median
- Minimum
- Maximum

For T_{last}, T_{max} and $T_{max\ ss}$, only the number of observations, median, minimum, and maximum will be presented in summary tables. The PK data for AZD9150, MEDI4736, AZD5069, and treme will also be displayed graphically as appropriate. Displays will include individual patient plasma concentration versus time profiles (on the linear and log-scale) versus time and gmean concentration (± standard deviation) versus time profiles, stratified by cohort and other groupings, as necessary.

6.2. KEY DEFINITIONS

For the purposes of this study, the term "study drug" is restricted to AZD9056, AZD9150, MEDI4736, treme, and the 4 drug combinations, AZD9056/MEDI4736, AZD9150/MEDI4736, AZD9056/MEDI4736/treme and AZD9150/MEDI4736/treme.

Study Day is the day relative to the date of the first dose of study drug in Cycle 1. If a date falls on or after the date of the first dose in Cycle 1, then the corresponding Study Day is calculated as (Study date) – (Date of first dose in Cycle 1) + 1. If a date falls before the date of first dose in Cycle 1, the corresponding Study Day is calculated as (Study date) – (Date of first dose in Cycle 1). Day -1 is the day immediately before the date of the first dose in Cycle 1.

The last dose date is defined as the last non-missing date where a non-zero dose of study drug was recorded. For patients who are ongoing at the time of an interim analysis, the last dose date will be considered the date of the most recent study visit in the database for that patient where a non-zero dose of study drug was recorded.

Unless otherwise specified, baseline is the last non-missing observation before the start of study treatment in Cycle 1.

In treatment arm A1 (AZD9150/MEDI4736), A4 (AZD9150/MEDI4736 or AZD9150/MEDI4736/treme) in dose escalation Part A, an evaluable patient must have received all 3 loading doses of AZD9150 during the 7-day Lead-in period and at least 3 additional doses during Cycle 1 as well as the MEDI4736 and treme infusion during the DLT Evaluation period or have suffered a DLT within the first 35 days of treatment. In treatment arm A2 (AZD5069/MEDI4736) in dose escalation Part A, an evaluable patient must have received all doses during the 7-day Lead-in period (i.e., 14 doses) and at least 42 additional doses as well as the MEDI4736 infusion during the DLT Evaluation period or have suffered a DLT during or before the first 35 days of treatment.

An efficacy evaluable patient is defined as a patient with unidimensional measurable disease at baseline as per the RECIST version1.1 criteria who received at least 1 dose of study treatment.

A cycle length is 28 days. The follow-up visit will occur 28 days after the last dose of study treatment with a window of +7 days. Patients who discontinue treatment for reasons other than PD will undergo follow-up tumour assessments every 2 months until PD is noted. To facilitate the scheduling of tumour assessments, a window of ± 3 days is allowed.

6.3. MISSING DATA

There will be no imputation of missing data unless specified. Imputation methods for missing target lesion data are included in Section 8.3.6 of this SAP.

6.4. SUBGROUPS

No subgroup analyses are planned.

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. PATIENT DISPOSITION AND WITHDRAWALS

All patients who provide informed consent will be accounted for in this study.

The disposition of patients who provided informed consent will be summarized using the All Patients (i.e., to include screen failures) and Full Analysis sets. The total number of patients screened, the number and percentage of patients who were assigned to treatment, and the number and percentage of patients who were screen failures will be included along with the reasons for screen failure. The number and percentage of patients who did not receive treatment and the number and percentage of patients who did receive treatment will be summarized by treatment group.

The disposition of patients who received treatment will be summarized using the Safety Set. The number and percentage of patients in each treatment group, the reason for treatment discontinuation and the reason for study discontinuation will be included.

The number and percentage of patients in each analysis set (i.e., Efficacy, PK, Pharmacodynamics) will be summarized by treatment group using the Safety Set as the denominator. For patients in the Full Analysis Set, the reasons for exclusion from each of the analysis sets mentioned above will be listed.

For all treated patients, the planned treatment arm, the date of all disposition events, the standardized disposition term, and the total number of treatments of each study drug will be listed. For patients not assigned or randomized to study drug, the reasons for screen failure will be listed.

7.2. PROTOCOL DEVIATIONS

Protocol deviations will be captured in eCRF. These protocol deviations are classified into the following categories: prohibited use of concomitant medications, dosing, enrollment, laboratory, non-compliance, visit schedule and other. Important deviations that may affect PK, PDN, Safety, and Efficacy analyses will also be identified and used to exclude patients from their respective Analysis Sets.

All protocol deviations will be summarized by category and treatment group. All protocol deviations will be listed.

7.3. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Age (years) will be calculated as the number of years between the date of birth and the date of informed consent.

Age at screening = (informed consent date – date of birth +1)/365.25 and truncated to complete years.

If height is recorded in inches (in), then height will be summarized in cm using the following conversion:

Height (cm) = Height (in) x 2.54

If weight is recorded in pounds (lb), then weight will be summarized in kilograms (kg) using the following conversion:

Weight (kg) = Weight (lb) x 0.4536

Demographic and baseline characteristic data (sex, race, ethnicity, age (yr), height (cm), weight (kg)) will be summarized by treatment group for subjects in the Safety Set.

All demographic and baseline characteristic data will also be listed, including the protocol version (captured in eCRF) under which the patient screened and the date of informed consent.

7.4. MEDICAL HISTORY

Medical history as recorded at screening will be summarized by treatment group using the number and percentage of patients reporting each system organ class (SOC) and preferred term (PT). Medical history will be sorted by descending overall total by SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary version 17.1 or later in the summary table.

Medical history listings will be sorted by treatment group, patient number, onset date, end date, SOC, and PT. If the condition is ongoing, the CTCAE grade of the medical condition will also be provided.

7.5. OTHER BASELINE CHARACTERISTICS

Cancer diagnosis will be collected as a baseline characteristic. The type of cancer diagnosis (ie, metastatic, locally advanced, or both) will be listed along with the site of the

local/metastatic disease and whether the cancer represented a recurrence of an earlier cancer.

Prior cancer surgeries will also be listed and include the type and date of the surgical procedure. The listing will be ordered by treatment group, patient, and the date of the surgical procedure.

Smoking history will be listed and will include whether the patient has ever smoked, the patient's current smoking status, and the type and number of tobacco products used. Alcohol history will also be listed and will include the patient's drinking status (drinker/non-drinker) and weekly alcohol consumption.

7.6. PRIOR AND CONCOMITANT MEDICATIONS

The summary of medications taken during the course of the study will be presented in tabular form using Anatomical Therapeutic Chemical (ATC) Classification Level 2 and Preferred Term via the World Health Organization Drug classification Dictionary (WHO-DD) version March 2012 or later. All concomitant medications will be summarized by treatment group and sorted by order of decreasing frequency, and by ATC Level 2 Class and PT. Prior medications are medications that started before the start of study treatment in Cycle 1. Concomitant medications are medications that were taken on or after the start of study treatment in Cycle 1, or medication that were started before the start of study treatment dose in Cycle 1 but continued after treatment. That is, medication that started before the start of study treatment dose in Cycle 1 but continued after treatment are considered as both prior and concomitant medication. Concomitant medications will be summarized by treatment group and the ATC Classification Level 2 Term. Prior medications will not be summarized. If a patient has taken a medication more than once, the patient will only be counted once in the total for the summary.

Medications with incomplete end dates will be a concomitant medication if:

- Day and month are missing and the year is equal to or after the year of the first dose date;
- Day is missing and the year is after the year of the first dose;
- Day is missing and the year is equal to the year of the first dose date and the month is equal to or after the month of the first dose date;
- Year is missing; or

- Date is completely missing.

All medication data will be listed and will include the start date, end date, ATC Classification Level 2, Preferred Term, dose form, dose unit, route of administration and frequency of use. Medications will be flagged as being either prior medications, concomitant medications, or both. Within patients, medications will be ordered by start date, end date, ATC Classification Level 2 and preferred name.

7.6.1. Chemotherapy Regimens

Chemotherapy regimens will be summarized and listed separately from other prior and concomitant medications. The classification of the Chemotherapy includes previous, current or post-treatment captured on the *Cancer Therapy* eCRF page.

The number and percentage of patients who had previous, current and post-treatment chemotherapy regimens and disease setting (i.e., metastatic, locally advanced, or other) will be summarized by treatment group. The number of prior chemotherapy regimens administered to patients will be summarized as a categorical variable.

Anticancer therapies will be listed by patient number and treatment group and include the start date, end date, preferred name, disease setting, treatment status, and best response.

7.6.2. Radiotherapy Regimens

The number and percentage of patients who had previous, current or post-treatment radiation therapy will be summarized.

Radiation therapies will be listed by patient number and treatment group and include the start date, end date, the type of radiation received, total dose (Gy) and the number of fraction doses.

8. EFFICACY

The following efficacy endpoints will be summarized and analyzed in dose-escalation Part A and dose-expansion Part B:

- Tumour response according to RECIST criteria version1.1
- Objective response rate (ORR)
- Best overall response rate (BoR)
- Duration of response (DOR)
- Disease control rate (DCR)
- Progression-free survival (PFS)
- Overall survival (OS)

Additionally, survival at 12 months (OS-12) and changes in tumour size will be summarized in Part B.

For dose-escalation Part A, all efficacy data will be summarized by treatment group using descriptive statistics only.

For dose-expansion Part B, all efficacy data will be summarized by treatment group using descriptive statistics and two-sided 80% confidence intervals (CIs) will be provided for the parameter estimates.

No inferential analyses will be conducted to compare the efficacy between treatment groups in either Part A or Part B.

All efficacy data will be analyzed using the Efficacy Set.

8.1. DERIVATION OF RECIST VERSION1.1 TUMOUR RESPONSES

For all patients, the RECIST tumour response data will be used to determine each patient's tumour response at each visit according to the revised RECIST version 1.1 guidelines (Eisenhauer et al 2009) with modifications to account for the unique response kinetics that have been observed in some patients where responses to immunotherapy may occur after progressive disease (PD) is assessed (Wolchok et al 2009). Specifically, RECIST version 1.1 guidelines have been modified so that PD in the absence of clinical deterioration must

be confirmed at least 4 weeks after the initial assessment of PD. The modified RECIST guidelines version 1.1 for measurable, non-measurable, target lesions (TLs), non-target lesions (NTLs) and the objective tumour response criteria are presented in Appendix F of the clinical study protocol. These criteria will also be used to determine if and when a patient has progressed in accordance with RECIST and to determine their best objective response.

Baseline radiological tumour assessments are to be performed no more than 28 days before the start of study treatment and should ideally be performed as close as possible to the start of study treatment. Tumour assessments are then performed on Day 15 of Cycle 2 (i.e., at the start of Week 7), at the beginning of each subsequent even-numbered cycle, and at the End of Treatment (EOT) visit. Patients who discontinue treatment for reasons other than PD will continue to undergo tumour assessments every 2 months until PD is noted. To facilitate tumour assessments, a window of ± 3 days is allowed.

The number and percentage of patients who fell into each of the overall tumour response categories (CR, PR, SD, PD, or NE), into each of the response categories for TLs (CR, PR, SD, PD, or NE), and into the response categories for NLTs (CR, Non-CR/Non PD, PD, NE) will be summarized by treatment group and visit. All tumour response data will be listed.

8.2. PRIMARY EFFICACY ENDPOINT AND ANALYSIS

8.2.1. Dose-escalation and Safety cohorts Part A

There is no primary efficacy endpoint for dose-escalation Part A.

8.2.2. Dose-expansion Part B - Objective Response Rate (ORR)

The primary efficacy endpoint for dose-expansion Part B is the objective response rate (ORR). BoR as derived according to Section 8.1 (above) is the primary efficacy variable. Investigator assessed BoR will also be listed.

ORR will be calculated as the percentage of patients in the Efficacy set who have at least one confirmed overall tumour response of CR or PR before any evidence of progression, as defined by RECIST version1.1. Confirmation of response is made by using 2 consecutive assessments that are at least 4 weeks apart. In the case where a patient has 2 non-consecutive overall visit responses of PR, then, as long as the time between the 2 visits of PR is greater than 4 weeks and there is no PD between the PR visits, the patient will be defined as a responder (PR). Similarly, if a patient has overall visit responses of CR, NE, CR, as long as the time between the 2 visits of CR is greater than 4 weeks, then a best response of CR will be assigned.

Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who discontinue study treatment without progression, receive a subsequent anti-cancer therapy (note that for this analysis radiotherapy is not considered a subsequent anti-cancer therapy) and then respond will not be included as responders in the ORR. ORR and the corresponding exact 2-sided 80% confidence interval (CI), calculated using the Clopper-Pearson method (Clopper and Pearson 1934), will be summarized by treatment group. The listing summarizing tumour responses by visit (see Section 8.1) will also indicate whether the patient was a responder.

8.3. SECONDARY EFFICACY ENDPOINTS AND ANALYSES

With the exception of ORR, survival at 12 months (OS-12), and change in tumour size the secondary efficacy endpoints are identical for Part A and Part B. ORR is the primary efficacy endpoint for Part B but is a secondary efficacy endpoint for Part A. OS-12 and change in tumour size are not included as secondary efficacy endpoints for Part A.

For both Part A and Part B, efficacy data will be summarized using descriptive statistics. For Part B only, two-sided 80% CIs will be provided for the estimates of all efficacy parameters. No adjustments for multiplicity will be made for any of the secondary efficacy endpoints.

8.3.1. Objective Response Rate

The analysis of ORR in Part A will be identical to that described for the primary efficacy endpoint in Part B (see Section 8.2.2), with the exception that no CIs for ORR will be provided for Part A.

If there is a sufficient distribution of objective response observed in Part B, the relationship between biomarkers and ORR may be explored using logistic regression.

8.3.2. Best Overall Response

The patient's best confirmed overall tumour response will be determined using response data from the start of study treatment to the end of study, including any assessments required for confirmation after the EOT. Best overall response will be ordered from best response to worst response as follows: CR, PR, stable disease (SD), or PD, NE (ordered from best to worst). Both CR and PR responses must be confirmed. Patients who achieve CR or PR but for who no confirmation assessment was performed or for who a confirmation assessment was performed but not confirmed will be counted as SD in calculating best overall response. For determination of a best response of SD, the earliest of the dates contributing towards a particular overall visit assessment at least 35 days after study entry will be used. For CR/PR, the initial overall visit assessment that showed a

response will be used, not the confirmatory scan date. If there are more than one RECIST assessment which contributes to a particular visit, e.g. two different body areas, the later of the two would be used to declare CR/PR.

Best overall response (BOR) will be determined programmatically based on RECIST using all site investigator data up until the first progression event. The denominator will be consistent with that 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 ≤ 18 weeks (i.e., 16 weeks + 2 week to allow for a late assessment within the assessment window) after first dose/administration of study medication, then BOR will be assigned to the progression (PD) category. For patients who die with no evaluable RECIST assessments, if the death occurs > 18 weeks after start of treatment then the patient will be counted as a non-responder and BOR will be assigned to the NE category.

A patient will be classified as a responder if the RECIST criteria for a confirmed CR or PR are satisfied at any time following first dose/administration of study medication, prior to RECIST progression and prior to starting any subsequent cancer therapy.

The number and percentage of patients in each of the overall response categories will be reported by treatment group using the Efficacy Set. The best overall response will be listed for each patient.

For Part A, only descriptive summaries of the best overall response will be provided. For Part B, exact 2-sided 80% CIs will be computed for each response level using the method of Clopper-Pearson (Clopper and Pearson 1934).

The Independent Central Review (ICR) adjudicated results of imaging data will be obtained from Paraxel. The data will be used in the standardization of radiological exams from the Investigator Sites for this trial. The objective will be to assess the concordance rate of BOR at both the sample and patient level for the following:

- Best Independent Central Review (BICR) response results compared to programmatically derived BOR
- BICR response results compared to the investigator assessment of BOR, and
- Investigator assessment of BOR compared to programmatically derived BOR.

A contingency table containing the relevant data on the absolute and percentage of agreement and disagreement will be provided, alongside the Cohen's kappa to indicate the level of agreement among pairs of (ICR, investigator and programmatically derived) BOR determinations. In addition, three separate agreement plots among pairs of (ICR, investigator and programmatically derived) BOR determinations and individual patient listings of (ICR, investigator and programmatically derived) BOR determinations will be provided.

8.3.3. Duration of Overall Response (DOR)

The duration of response (DOR) is defined as the time from the date of first documented response (CR or PR) until the date of documented progression or death in the absence of disease progression. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of CR or PR. The end of response should coincide with the date of progression or death from any cause used for the progression-free survival (PFS) endpoint. If progression or death due to any cause does not occur after a response, the patient's DOR will be censored at the date of last tumour assessment (i.e., the PFS censoring time). Only patients who have a CR or PR during the study will be included in the analysis.

The DOR in weeks will be calculated for all patients that experience documented CR or PR during the study in weeks as follows:

> Duration of response (weeks) = ((Date of Progression/Death/Censoring – Date of First recorded CR or PR) + 1)/7.

If there are sufficient data, DOR will be analyzed for all evaluable patients achieving response during the study using a Kaplan-Meier (K-M) survival analysis. Only patients who have a confirmed response will be included in this summary table. A K-M curve will present the distribution of DOR time by treatment group, along with the median DOR, provided it has been reached by the time of analysis. In Part B only, two-sided 80% CIs will be provided for the median DORs (Brookmeyer and Crowley 1982). Swimmer plots that clearly show the profile of each patient who responds will be produced.

In Part B, the Expected Duration of Response (EDOR) will be calculated for each treatment arm by multiplying the proportion of patients responding to treatment and the mean DOR amongst responding patients. Two-sided 80% CIs will also be provided for the EDORs (Ellis et al 2008).

For Part B only, a sensitivity analysis of DOR will be performed where patients who do not progress before dying will be censored at the time of the administrative end of the trial (i.e., the latest of the last know tumour assessment, the last date of collection of clinical laboratory or vital sign data, or the last date of telephone contact with the subject) rather than at the time of death. The K-M plot will show the distribution of this modified DOR by treatment group, along with the median value of the modified DOR and its two-sided 80% CI (Brookmeyer and Crowley 1982).

A single listing will provide values of DOR, PFS, and OS for individual patients and indicate whether the corresponding survival time was censored.

8.3.4. Durable Response Rate

A patient is said to have a durable response if they have a confirmed overall tumour response of either CR or PR that lasts at least 3 months following the initial confirmation of the response. For the purposes of this calculation, 3 months will be defined as 13 weeks or 91 days. The durable response rate, the percentage of patients who have a durable response, will be calculated using the number of patients in the Efficacy Set. The durable response rate will be summarized by treatment group. In Part B only, an exact 2-sided 80% CI for the durable response rate will be computed using the Clopper-Pearson method (Clopper and Pearson 1934).

8.3.5. Disease Control Rate (DCR)

A patient is said to have achieved disease control if they have a tumour response of SD, PR, or CR according to RECIST version 1.1 criteria. Disease control will be assessed at 12 weeks after the start of study drug and is defined as the proportion of all patients in the Efficacy set that have an overall visit response of SD, PR, or CR at Week 12. Therefore, earlier overall visit responses of CR or PR that become PD at Week 12 or NE responses at Week 12 do not constitute disease control at 12 weeks. A time window of 1 week around the Week 12 visit will be applied, and it is recommended that any visits occurring 11 weeks or more after dosing are acceptable; however, if an earlier visit is defined as PD, the overall visit response at Week 12 would also be defined as PD. If the Week 12 overall response is missing or NE but the next evaluable response is SD or better, the patient will be defined as having an overall visit response of SD, PR, or CR at 12 weeks.

For individual patients, disease control at the Week 12 visit will be derived using the algorithm shown in Table 6.

Table 6 – Algorithm for Assessing Disease Control

	Overall Tumour Response at:		
Disease Control At Current Visit	**Previous Visit**	**Current Visit**	**Next subsequent Visit**
No	PD	Any	Any
No	CR, PR, or SD	PD	Any
No	CR, PR, or SD	NE or Missing	NE or Missing
Yes	CR, PR, or SD	NE or Missing	CR, PR, or SD
Yes	CR, PR, or SD	CR, PR, or SD	Any

In Part A and B, the number and percentage of patients who achieved disease control at even-numbered cycles will be summarized starting with Cycle 4 and at EOT. For Part B only, exact 2-sided 80% CIs will also be computed for DCR using the Clopper-Pearson method (Clopper and Pearson 1934).

8.3.6. Change in Tumour Size

The percentage change in tumour size from baseline to week 12 will be summarized for Part B only. However, the change in tumour size over time will be displayed for individual patients in both Part A and Part B. A time window of 1 week around the Week 12 visit will be applied, and it is recommended that any visits occurring 11 weeks or more after dosing are acceptable.

Tumour size is the sum of the longest diameters of a patient's TLs. The percentage change in TL size at Week 12 will be obtained for each patient by taking the difference between the sum of the longest diameters of the TLs at Week 12 and the sum of the longest diameters of the TLs at baseline divided by the baseline value and multiplied by 100. The baseline value for tumour measurements is the last evaluable assessment taken prior to first dose of study drug. The percentage change in tumour size will be summarized by treatment group using the Efficacy set.

If > 1/3 of a patient's TL measurements are missing at Week 12, then the patient's TLs will not be included in the calculation of the percentage change in tumour size.

If =< 1/3 of a patient's TL measurements are missing at Week 12, then the results will be imputed (i.e., scaled up) using the sizes at the nadir visit to provide an estimated sum of diameters. This estimation is equivalent to comparing the week 12 sum of the longest diameters of the non-missing lesions to the nadir sum of diameters excluding the lesions

with missing measurements. An example of scaling up is provided using the lesion lengths shown in Table 7.

Nadir is defined as the previous minimum where all lesions compared to those collected at baseline have a measurement. In the case where the result is being scaled up due to something other than just missing data, the nadir will fit all requirements. For example if tumours that received an intervention were not to be included in addition to missing tumours, then the nadir visit would require no missing data and no tumnore interventions.

Table 7 – Example of Scaling Up in Calculation of Change in Tumour Size

Lesion	Longest Diameter at nadir Visit (cm)	Longest Diameter at Week 12 Visit (cm)
1	7.2	7.1
2	6.7	6.4
3	4.3	4.0
4	8.6	8.5
5	2.5	missing
Sum	29.3	26

In this example, the measurement for lesion 5 is missing at Week 12. The sum of the 4 non-missing lesion lengths at Week 12 is 26 cm. The sum of the lengths of the 4 corresponding lesions at the nadir visit was 26.8 cm. Scale-up gives an estimated Week 12 value of 28.4 cm as follows:

Scaled-up Week 12 length = (26 x 29.3)/26.8 = 28.4

Consequently, assuming a baseline value of 30.4, the imputed percentage change in tumour size from baseline to Week 12 would be reported as:

% Change in tumour size = [100 x (28.4 – 30.4)]/30.4 = -14.5%

If a TL becomes too small to measure at Week 12, a value of 5 mm will be used in calculating the tumour size at Week 12, unless the radiologist has indicated and entered a smaller value that can be reliably measured.

The percentage change in TL size will be presented graphically using waterfall plots for each treatment group, with the percentage change in TL size for each patient shown as a separate bar and with the bars ordered from the largest increase to the largest decrease.

Reference lines will be added to the waterfall plot at the +20% and the -30% change in tumour size levels, which correspond with the definition of disease progression and 'compete or partial' response, respectively. In the waterfall plots, patients whose change in TL size is based on imputation will be clearly identified by different-colored bars on the waterfall plot.

If the patient does not have a Week 12 visit, then a tumour assessment that is taken at 11 to 15 weeks maybe used as the Week 12 measurement.

A similar plot will also be presented for each patient's best percentage change (the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction from baseline based on all post baseline assessments) in TL size up to progression. Individual absolute total TL measurements, changes from baseline, and percent changes from baseline will be listed for each tumour assessment visit.

For both Part A and Part B, a series of spider plots will graphically present the percentage change in total TL size from baseline by study day for each patient, grouped by treatment arm.

8.3.7. Progression-free Survival (PFS)

Progression-free survival (PFS) is defined as the time (days) from the date of treatment allocation (Part A) or randomization to study drug (Part B) to the date of objective disease progression or death due to any cause, whichever occurs first. This definition will apply regardless of whether the patient withdraws from treatment or receives another anti-cancer therapy prior to progression.

The PFS time will be derived based using scan/assessment dates and not visit dates. PFS times will be derived using assessment dates from the "Tumour Assessment" CRF pages or, if needed, the date of death from the "Death" CRF page.

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

- Date of progression will be determined based on the **earliest** of the dates of the component that triggered 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

Patients who have not progressed or died at the time of the analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment.

However, if the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable RECIST version 1.1 assessment. If the patient has no evaluable visits or does not have baseline date, the patient will be censored at Day 0 (i.e., excluded from the K-M analysis), unless the patient dies within 2 visits of baseline in which their date of death will be used to derive PFS. Two visits will be considered to have been missed if more than 126 days have passed since the patient's last visit.

PFS will be analyzed for all evaluable patients using a K-M survival analysis. The distribution of PFS times assessed by RECIST version 1.1 criteria will be displayed graphically by treatment group. The number of events, percentiles for the PFS (25%, 50% (median), and 75% percentiles), and the proportion of patients who are progression-free at 1, 2, 3, and 4 months will be summarized by treatment group. For Part B only, two-sided 80% CIs will be provided for the median PFS times (Brookmeyer and Crowley, 1982), which can be reported using SAS LIFETEST Procedure with CONFTYPE=LINEAR. The 80% CIs for median PFS is the set of all t which meets $|ES(t)-0.5)|/se(ES(t) \leq z_{0.9},$ where ES(t) is the estimated survival function and se(ES(t)) is the standard error of ES(t).

If there is a sufficient number of PFS events observed in Part B, the relationship between biomarkers and PFS may be explored using Cox regression.

8.3.8. Overall Survival (OS)

Overall survival (OS) is defined as the time from the date of the treatment allocation (Part A) or randomization to study drug (Part B) to the date of death from any cause. OS will be estimated using K-M methodology and the Efficacy Set. Any subject not known to have died at the time of analysis will be censored based on the last recorded date that the subject was known to be alive. This date is the latest of the last known tumour assessment, the last date of collection of clinical laboratory or vital sign data, or the last date of telephone contact with the subject.

In dose-expansion Part B, some patients may be allowed to move from a monotherapy arm to a combination arm during the trial. The survival times for these patients will be censored at the date immediately prior to the date of the first dose of the combination drug.

The distribution of OS in the Efficacy Set will be displayed graphically by treatment group. The number of events and estimates for the 25%, 50% (median), and 75% percentiles for OS will be summarized by treatment group. For Part B only, two-sided 80% CIs will be provided of the median OS estimates (Brookmeyer and Crowley, 1982).

8.3.9. Survival at 12 Months (OS-12)

Overall survival at 12 months (OS-12) is defined as the percentage of patients surviving at 12 months after randomization to study drug.

Should a patient's vital status at 12 months be unknown, the patient will be considered to be deceased when estimating OS-12. This approach is a conservative one and assumes that patient loss is related to mortality.

An exact two-sided 80% CI for OS-12 will be computed using the Clopper-Pearson method (Clopper and Pearson 1934). Analysis of this secondary endpoint will use the Safety set.

8.3.10. Time to First Response

Time to first response is defined as the time (days) from the date of treatment allocation (Part A) or randomization to study drug (Part B) to the date of confirmed CR or PR. This definition will apply regardless of whether the patient withdraws from treatment or receives another anti-cancer therapy prior to response.

The time to first response will be derived based using scan/assessment dates and not visit dates. PFS times will be derived using assessment dates from the "Tumour Assessment" CRF pages.

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

- Date of response will be determined based on the **earliest** of the dates of the component that triggered progression

- When censoring a patient for time to first response, the patient will be censored at the study day of last evaluable assessment for subjects without response

Time to first response will be analyzed for all evaluable patients using a K-M survival analysis. The number of events, percentiles for the time to first response (25%, 50% (median), and 75% percentiles), and the proportion of patients who responded at 1, 2, 3, and 4 months will be summarized by treatment group. For Part B only, two-sided 80% CIs will be provided for the median PFS times (Brookmeyer and Crowley, 1982), which can be reported using SAS LIFETEST Procedure with CONFTYPE=LINEAR. The 80% CIs for median PFS is the set of all t which meets $|ES(t)-0.5)|/se(ES(t) \leq z0.9$, where ES(t) is the estimated survival function and se(ES(t)) is the standard error of ES(t).Exploratory Analyses

8.3.11. Association between ORR and ADA Status

Exploratory analyses will assess whether there is a relationship between anti-drug antibody positivity for AZD9150 and MEDI4736 and objective response. Patients will be defined as being ADA positive to a particular drug if the patient has at least 1 post-treatment positive ADA test for that drug. The odds ratio for having an objective response in the ADA-positive groups compared to having an objective response in the ADA-negative groups will be calculated for both Part A and Part B.

Due to the small number of patients in each treatment arm in Part A, patients who received different doses of within a treatment arm might be combined when assessing the relation between ADA status and objective response. The odds ratio for patients having an objective response in the ADA-positive group will be compared to the patients having an objective response in the ADA-negative group. An 80% CI will be provided for the odds ratio using a chi-square assessment, where zero cells are adjusted with a value of 0.5.

In Part B, separate odds ratios will be calculated for each of the relevant treatment arms and anti-PD-(L)1 status combinations. Again, 80% CIs will be provided for each odds ratio estimate, where zero cells are adjusted with a value of 0.5.

For Part B, a logistic regression model may be used to estimate the probability of having an objective response using treatment group and anti-PD-(L)1 status as factors and the maximum post-treatment antibody titer level as a continuous variable.

8.3.12. Association between ORR and Human Papilloma Virus

PD-1/PD-L1 expression has been proposed to play a role in the immune resistance of human papillomavirus-associated squamous cell carcinomas of the head and neck (SCCHN). Consequently, blocking the PD-1/PD-L1 pathway may aid the effectiveness of immunotherapy in the treatment of HPV-associated SCCHN carcinomas. In Part B, the association between HPV-positivity and objective response will be assessed by comparing the odds for patients having an objective response in the HPV-positive group to the odds for patients having an objective response in the HPV-negative group. An 80% CI will be provided for the odds ratio using a chi-square assessment, where zero cells are adjusted with a value of 0.5.

9. ANALYSIS OF PHARMACOKINETICS

The PK population will be used in all PK analyses. The PK parameters identified in Section 4.4 will, where possible, be determined from the plasma concentrations of AZD9150, AZD5069, treme, and MEDI4736, using non-compartmental procedures performed by Covance on behalf of AstraZeneca.

Actual blood sampling times post-dosing will be used in calculation of PK parameters. Concentrations are used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with the amount or concentration in the unit, will be presented as they are received from the analytical laboratory.

Presentation of Pharmacokinetic Concentration and Parameter Data

Plasma concentrations of AZD9150, AZD5069, treme, MEDI4736 and any significant metabolites will be summarized by nominal time point and visit for each treatment group.

The PK data for AZD9150, MEDI4736, treme and AZD5069 will also be displayed graphically. Displays will include individual patient plasma concentration versus time profiles, on both the linear and log-scales. Additionally, the gmean ± StD concentration versus time profiles will be summarized by treatment group. These plots will include the extensive concentration data collected at the specified study times for AZD9150, AZD5069, treme, and MEDI4736 according to the schedule of study assessments.

If data permits, for both Part A and Part B, the gmean ± StD concentration versus time profiles for the AZD9150 groups will be displayed graphically by anti-AZD9150 antibody status (i.e., positive/negative).

All plasma concentration data for AZD9150, AZD5069, MEDI4736, treme and any active metabolites will be listed. All PK parameters will be listed.

10. ANALYSIS OF PHARMACODYNAMICS

The Pharmacodynamics population will be used in all pharmacodynamic analyses. No inferential analyses will be performed on the pharmacodynamic endpoints, which will be summarized using descriptive statistics.

10.1.1. STAT3 Knockdown by AZD9150

These results will be reported separately and will not be part of the CSR.

10.1.2. Soluble Programmed Cell Death-Ligand 1 (sPD-L1)

The soluble programmed cell death-ligand 1 (sPD-L1) assay uses a quantitative competitive electrochemoluminescence (ECL) immunoassay format to measure the concentration of MEDI4736-free sPD-L1 protein (soluble target not bound to drug) in human serum with a lower limit of quantitation (LLoQ) of 15.6 pg/mL.

In both the dose-escalation (except safety cohorts A3, A4, and A6) Part A and dose-expansion Part B (B1-B6) of the study, blood samples (3.5 mL) for evaluation of circulating sPD L1 protein (MEDI4736) will be collected from patients on Day 1 of Cycle 1; on Day 15 of Cycle 2; and on Day 1 of all subsequent even-numbered cycles. On Day 1 of Cycle 1 and on Day 1 of Cycle 8, in addition to the predose sample, a sample will also be obtained at the end of the MEDI4736 infusion. For patients who discontinue MEDI4736, a sample will be drawn 90 days after their last dose of MEDI4736 coinciding with an IM (ADA) sample. For patients in Arm B1, B2, and B4 sPDL1 samples will not be collected after the first 20 patients. The sPDL1 samples will also not be collected for Arms B7and B8. Summary tables will report descriptive statistics for sPD-L1 levels and the change from baseline by visit for each MEDI4736 treatment group. A line plot with error bars presenting the median sPD-L1 level by visit and treatment group will be provided. All sPD-L1 data will be listed.

10.1.3. Circulating Myeloid-Derived Suppressor Cells (MDSCs)

For all patients, blood samples for MDSC (5 mL), will be collected pre-dose at the specified time points to assess the treatment effect on circulating MDSCs: At screening, Day -7 of the lead-in period, Day 1 of Cycles 1, 2, 3, 5, and at the EOT visit.

For patients in Arm B1, B2, and B4 MDSC samples will not be collected after the first 20 patients. MDSC samples will also not be collected for Arms B7and B8. Summary tables will report descriptive statistics including median results for circulating MDSC levels and the change from baseline by visit for each AZD5069 treatment group. A line plot with

error bars for the median circulating MDSC level by study day and treatment group will be provided. All circulating MDSC data will be listed.

For each sample per patient, there are 9 reportable parameters at most. For some samples, the parameters with "CD33" have this or similar lab error comments, "Abnormal expression identified, raw data available upon request". AstraZeneca analyzed the raw data, identified the basis of the lab error, and found the following three parameters of these samples were affected by this lab error:

1. Lin-HLA-DR-/loCD33+CD11b+ %(Lin-) %

2. Lin-CD15+HLA-DR-/loCD33+CD11b+ %(CD15+) %

3. Lin-CD15+HLA-DR-/loCD33+CD11b+ %(total) %

Thus, the above reportable parameters for subjects with lab error at the relevant visits will be excluded from summary plots or figures. All other verifiable visits for such subjects will be included.

10.1.4. Tumour PD-L1

Summary tables will report descriptive statistics for tumour PD-L1 levels at baseline. All post-baseline tumour PD-L1 data will be reported separately and will not be part of the CSR.

11. SAFETY

No inferential testing will be performed on safety data, which will be summarized using descriptive statistics.

Part A focuses primarily on determination of the MTD for the AZD9150/MEDI4736 and the AZD5069/MEDI4736 drug combinations in patients who have completed the DLT evaluation. Section 11.1 discusses the safety assessments unique to identifying the MTD in dose-escalation Part A.

The remaining safety endpoints—treatment exposure, AEs, SAEs, laboratory evaluations, vital signs, and physical examinations, ADAs—are common to both Part A and Part B. These common safety endpoints will be analyzed using the same methods, which are discussed starting in Section 11.2 of this SAP.

For patients who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the associated initial dose combination/dose level.

Safety data will be presented graphically as deemed appropriate. This may include, but is not restricted to, presentation of parameters against time or shift plots. Appropriate scatter plots will also be considered to investigate trends in parameters compared to baseline.

11.1. DOSE-ESCALATION AND SAFETY COHORTS – PART A

11.1.1. Starting Dose and Dose-escalation Scheme

AZD9150 will be administered at a starting dose of 2 mg/kg IBW. Additional dose levels up to 3 mg/kg IBW may be evaluated.

AZD5069 will be administered at a starting dose of 40 mg PO BID (ie, daily dose of 80 mg). Additional dose levels up to 120 mg BID (for a maximum total daily dose of 240 mg) may be evaluated.

MEDI4736 will be administered at a dose of 20 mg/kg Q4W. A dose of 10 mg/kg Q4W might be investigated as an additional dose level.

Combination treatment in treatment arm A1 (AZD9150/MEDI4736) will start with doses of AZD9150 2 mg/kg IBW and MEDI4736 20 mg/kg; combination treatment in treatment arm A2 (AZD5069/MEDI4736) will start with doses of AZD5069 40 mg BID and MEDI4736 20 mg/kg.

A CRM–based approach will be used to identify the set of AZD9150/MEDI4736 and AZD5069/MEDI4736 dose combinations where the incidence of DLT is no larger than 33%. In each cohort, up to 3 patients will be initially assessed. Dose escalation to the next higher dose level for the next cohort group of 3 patients will occur if all 3 patients in the initial cohort complete Cycle 1 without DLT. Following the first DLT, the CRM model will be run and the output made available to the SRC to guide further dosing decisions (see Section 11.1.2 for details).

Tolerated combination doses will be defined as combinations for which the DLT incidence is no larger than 33%. Prior to the occurrence of the first DLT, a cohort will consist of 3 patients; following the first DLT, cohorts will require a minimum of 6 patients before dose escalation may occur. In all cohorts, the sample size refers to patients who are evaluable for dose escalation; patients who are nonevaluable for dose escalation will be replaced (See Section 5.4.3 of the study protocol for the criteria to be deemed evaluable for dose-escalation purposes).

Dose escalation will be defined as an increase in the dose of at least 1 of the drugs without decreasing the dose of the other.

Dose escalation for the 2 combination treatments (ie, AZD9150/MEDI4736 and AZD5069/MEDI4736) will advance independent of each other. In addition to determining DLT in the DLT evaluation period, the SRC will critically review all available data pertaining to safety, tolerability, and IM as well as PK, pharmacodynamic, and antitumour activity before deciding on the next dose levels to be explored. Dose escalation in each arm will be considered completed once 1 of the following criteria is met:

- The MTD (for definition of MTD see Section 5.3.3 of the study protocol) for the 2 agents in combination have been identified
- The SRC has recommended doses for the 2 agents in combination to be further explored in the dose-expansion Part B
- The maximum doses of the 2 agents in combination have been reached (ie, AZD9150 3 mg/kg IBW, AZD5069 120 mg BID [for a maximum total daily dose of 240 mg], and MEDI4736 20 mg/kg)

11.1.2. Use of the CRM to Select Recommended Doses to the SRC

The CRM computations that are needed to generate the dose-escalation recommendations will be made using the R package, dfcrm (Dose Finding for the Continual Reassessment Method). Documentation regarding the dfcrm package can be found in Cheung (2011) and online at http://www.r-project.org/

Because there are only a few possible outcomes for the number of DLTs that can be observed in a cohort, it is possible to provide the model estimated MTD for all possible outcomes of DLTs within a cohort in advance of an SRC meeting. Similarly, the posterior variances can be calculated for each possible outcome, allowing us to define whether the CRM will recommend stopping or proceeding to dosing of the next cohort. These recommendations can be summarized in a "playbook", which can be provided to the SRC in advance of each meeting. The playbook will be generated using only data from evaluable patients as defined in the protocol (Section 6.2).

Appendix 1 shows the playbook contents for the first cohort of 3 patients treated at the starting doses for the 2 combination drugs. For each of the possible DLT outcomes for the first cohort (i.e., 0 DLTs/3 patients,1 DLT/3 patients, 2 DLTs/3 patients, or 3 DLTs/3 patients), the playbook provides the model estimated MTD for the next cohort, the posterior variance, and a stop/continue dosing recommendation.

While the SRC will consider the model estimated MTD in Part A, the SRC alone will be responsible for making the recommendations for the dose-escalation, including the assignment of a dose-level not recommended by the playbook.

The playbook for each subsequent cohort will be provided by AstraZeneca or INC once the SRC has agreed upon the number of DLTs that occurred in the previous cohort INC will generate back-up copy of the playbook in case it may be needed for the SRC.

11.1.3. Confirmation of the Presumed Recommended Dose

Once the MTDs for each of the 2 agents in combination with MEDI4736 have been identified or the maximum doses of each of the 2 agents in combination with MEDI4736 have been reached, the SRC may decide to enrol an additional cohort of at least 6 evaluable patients per treatment arm to confirm the presumed recommended dose for each of the 2 agents in combination with MEDI4736 to be further explored in the dose-expansion Part B.

Once all patients have completed Part A, the final estimates of the proportion of DLTs for each tested dose-level of the 2 combination will be summarized.

The subsequent sections of Section 11 describe the analyses that will be conducted on the safety variables common to Part A and Part B.

11.2. TREATMENT EXPOSURE AND DURATION

Exposure is defined as the total amount (in mg) of a study drug component (AZD9150, AZD5069, and MEDI4736) that is received by a patient.

Total treatment duration will be calculated separately for each of the components of study medication. Because the pharmacokinetic profiles of AZ9150, AZD5069, and MEDI4736 differ, the total treatment duration is defined differently for each component of study medication:

For AZD9150:
Total treatment duration (days) = (Date of last dose - date of first dose in Cycle 1) + 7).

For AZD5069:
Total treatment duration (days) = (Date of last dose - date of first dose in Cycle 1) + 1).

For MEDI4736:
Total treatment duration (days) = (Date of last dose - date of first dose in Cycle 1) + 28).

For treme in arm A4:
Total treatment duration (days) = (Date of last dose - date of first dose in Cycle 1) + 28).

Actual treatment duration (days) will be calculated as the total duration of exposure, excluding periods of dose interruption (AZD5069) and planned “no dose” periods for intermittent dosing (AZD9150 and MEDI4736). For AZD5069, periods of dose interruption will be defined as days within the treatment period on which the patient took no tablets of AZD5069. For AZD9150, each planned “no dose” period will be counted as 7 days. For MEDI4736 or treme, each planned “no dose” period will be counted as 28 days.

Duration of therapy (months) is the actual treatment duration for the dose to which the patient was originally assigned or randomized. Duration of therapy will be calculated only for Part B.

The relative dose intensity is the percentage of the actual dose intensity delivered (mg/kg based on ideal body weight) divided by the intended dose intensity (mg/kg based on ideal body weight) through to treatment discontinuation multiplied by 100. The duration of the intended cumulative intended dose is defined as the time up to the earlier of progression (or a censoring event) or the actual last day of dosing.

The percent intended dose (PID) is the actual cumulative dose delivered up to progression (or a censoring event) divided by the intended cumulative dose up to progression (or a censoring event). The intended cumulative dose is the total dose that would be delivered, if there were no modifications to dose or schedule.

Time on study will be calculated as follows:

Time on study (days) = (Date of study discontinuation – date of first dose in Cycle 1) + 1

The patient's date of study discontinuation will be taken from the "End of Study" eCRF page. For the combination drugs, only the first dose date of the AZD9150 or AZD5069 component will be used in the calculation of time on study.

The total number of doses received and exposure to each drug component, the total and actual treatment durations, the time on study, the relative dose intensity and PID will be summarized by treatment group using descriptive statistics for continuous variables. Additionally, the summary of relative dose intensity will present 25th and 75th percentiles.

The number and percentage of patients who experience at least 1 dose interruption or dose delay and the number percentage of patients who experience at least 1 dose reduction will be summarized for Cycle 1 and for all subsequent cycles combined.

All AZD9150, AZD5069, and MEDI4736 dosing data recorded on the eCRF will be listed including any treatment modification. Additionally, the derived parameters will be included on the listing.

11.3. ADVERSE EVENTS

Adverse events will be collected throughout the study, from informed consent until the end of the follow-up period. All adverse events that occur after administration of the first dose of study drug or that are present at baseline but worsen in intensity after the first dose of study drug will be summarized. All adverse events will be listed.

Adverse events will be summarized by the SOC and PT based on the MedDRA dictionary version 17.1 or later.

The grading scales found in the current CTCAE version 4.03 (14 June 2010) will be utilized for all AEs with an assigned CTCAE grading. For those AEs without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades will be used.

For summaries of AEs by SOC and PT, a patient will be counted once at the SOC level and once at each PT within the SOC level. For summaries by SOC, PT, and maximum intensity, a patient will be counted once at the highest intensity level for which the event occurred at the SOC level and the highest intensity level for each unique PT within that SOC level. Therefore, patients may only contribute once to each PT and once to each SOC level.

The summaries presenting frequency of AEs by SOC and PT will be ordered by overall descending frequency of SOC and then, within an SOC, by overall descending frequency of PT.

During the evaluation of the AE data, an INC medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation of investigational product. Based on the expert's judgment, AEs of particular clinical importance may, after consultation with the Global Safety Physician, be considered other significant AEs (OAEs) and reported as such in the CSR.

The following AE tables will be provided:

- An overall summary of the number and percentage of patients reporting AEs, treatment-related AEs, serious AEs, < Grade 3 or ≥ Grade 3 AEs, AEs considered to be DLTs (see Protocol Section 5.3.2. for definition of DLTs), AEs leading to dose withdrawn, and fatal AEs.
- AEs by SOC and PT
- Most common AEs (i.e., frequency >= 5%) by PT
- Serious AEs, by SOC and PT
- DLTs
- Study-treatment-related AEs, by SOC and PPT
- Causality Related AEs by CTCAE Grade
- AEs by CTCAE Grade, by SOC and PT
- AEs leading to death, by SOC and PT
- AEs < grade 3 or ≥ grade 3, by SOC and PT

- AEs leading to study withdrawal, by SOC and PT
- AEs leading to withdrawal of study medication, by SOC and PT
- AEs leading to dose reduction
- Other significant AEs (OAEs), by SOC and PT
- AEs from the start of monotherapy up to the beginning of combination therapy, overall and by SOC and PT
- Bleeding or hemorrhage AEs by SOC and PT.

For analysis purposes, only the following TEAEs or treatment-emergent SAEs will be summarized in the summary tables.

1. For monotherapy arms (AZD9150 or AZD5069 with no MEDI4736), TEAEs from the first dose date of the study drug up to 30 days after the last dose date. Similarly, treatment-emergent SAEs from the first dose date of the study drug up to 35 days after the last dose date. [Note: replace AZD9150 and MEDI4736 with actual names if applying that globally]

2. For combination therapy arms (AZD9150 or AZD5069 with MEDI4736), use both TEAEs and treatment-emergent SAEs from the first dose date of the study drug up to 90 days after the last dose date of MEDI4736.

For patients who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial dose group.

Additional listings will be provided for AEs marked as DLTs. TEAEs will be flagged in the listings. Adverse events that occurred during the monotherapy cycle will also be flagged.

11.4. LABORATORY EVALUATIONS

All samples will be analysed at the central laboratory for the study on behalf of AstraZeneca.

The study plan shown in Table 9 lists the variables that will be measured for routine haematology, serum chemistry, coagulation, and urinalysis. All summaries of haematology, coagulation, and chemistry will be based on the results of Standard International (SI) system of units. Unit conversion will be performed according to the Data

Management Plan (DMP) prior to the transfer to [redacted] Biostatistics. The indication of clinically significant laboratory results will be recorded on the CRF page. The high and low classifications will be derived relative to the result and normal ranges in SI units.

Summary tables for haematology, coagulation, chemistry and urinalysis (pH, specific gravity) laboratory variables will include the following: descriptive statistics for SI values and change from baseline for all continuous variables by visit and treatment group. Shifts from baseline to maximum post-baseline for CTCAE grades and laboratory reference ranges will be reported for each laboratory parameter.

For urinalysis parameters, any qualitative assessments will be summarized for all patients using the number of patients with results of negative, trace, or positive.

All laboratory results in original and SI units will be presented in data listings and presented graphically as box plots and shift plots. Tests will be listed in alphabetical order within their respective panels (haematology, clinical chemistry, urinalysis). Abnormal values will be flagged.

Hy's law

The following summaries by treatment group will include number (%) of patients who have elevated ALT, AST, and total bilirubin during the study:

ALT > 3x –<= 5x, > 5x – <=10x and > 10x Upper Limit of Normal (ULN) during the study

AST > 3x – <=5x, > 5x – <=10x and > 10x ULN during the study

Total bilirubin >2x ULN during the study

Individual patient data where ALT or AST plus total bilirubin are elevated (ALT ≥ 3xULN and total bilirubin ≥ 2xULN or AST ≥ 3xULN and total bilirubin ≥ 2xULN) at any time will be listed. Individual patient profile plots will display values of ALP, ALT, AST, total bilirubin, and GGT relative to ULN by study day for patients where any individual where ALT or AST plus total bilirubin are elevated (ALT ≥ 3xULN and total bilirubin ≥ 2xULN or AST ≥ 3xULN and total bilirubin ≥ 2xULN) at any time.

Plots of ALT and AST vs. total bilirubin by treatment group will also be produced with reference lines at 3xULN for ALT, AST, and 2xULN for total bilirubin. In each plot, total bilirubin will be on the vertical axis.

Neutrophil-to-Lymphocyte Ratio

A series of line plots will present the mean neutrophil-to-lymphocyte ratio over time (Day -7, Day 0 and every 2 weeks subsequently) and by treatment arm for both Part A and Part B. For Part A, a single line plot will show the mean neutrophil-to-lymphocyte ratio for all AZD9150 + MEDI4736 doses combined and for all AZD5069 + MEDI4736 doses combined. For Part B, 2 separate line plots will be provided that display the mean neutrophil-to-lymphocyte ratio over time by treatment group—one for anti-PD-(L)1 naive patients and one for anti-PD-(L)1 pre-treated patients. If necessary, a slight lateral offset will be used to prevent data points from different treatment groups with similar mean neutrophil-to-lymphocyte ratios from being obscured.

A corresponding series of tables will summarize the descriptive statistics (mean, StD, median, mix, max) for the neutrophil-to-lymphocyte ratio by study visit and treatment arm for both Part A and Part B.

Table 9 Routine laboratory safety assessments

Haematology/Haemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
B-Haematocrit (HCT)	S/P-Albumin
B-Haemoglobin (Hb)	S/P-Alkaline phosphatase
B-Platelet count	S/P-ALT
B-Red blood cell count	S/P-AST
B-White blood cells	S/P-Bilirubin, total
B-WBC differential (%)	S/P-Bilirubin, direct
B-Absolute neutrophil count	S/P-Bilirubin, indirect
B-Absolute lymphocyte count	S/P-GGT
B-Mean corpuscular volume	S/P-Calcium, total
B-Mean corpuscular haemoglobin concentration	S/P-Creatinine
	S/P-Glucose
	S/P-LDH
Urinalysis (dipstick)	S/P-Magnesium
U-Specific gravity	S/P-Phosphate
U-pH	S/P-Potassium
U-Bilirubin	S/P-Sodium
U-Blood	S/P-Total protein
U-Glucose	S/P-Urea nitrogen
U-Ketones	S/P-Chloride
U-Protein	S/P-Bicarbonate
U-Color	S/P-Uric acid
U-WBC/HPF and RBC/HPF (macroscopic)	S/P-Creatine phosphokinase
U-Appearance	S/P-Cholesterol
	S/P-Triglycerides
Coagulation	S/P-C-reactive protein
PT (sec)	
aPTT (sec)	
INR	
Fibrinogen	
Haptoglobin	

Abbreviations: ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; B=blood; GGT=gamma-glutamyl transpeptidase; INR=international normalised ratio; HPF=high power field; LDH=lactate dehydrogenase; P=plasma; PT=prothrombin time; RBC=red blood cell count; RBC/HPF= red blood cells per high power field; S=serum; WBC/HPF= white blood cells per high power field.

11.5. VITAL SIGNS

Body temperature will be summarized in °C. If body temperature is recorded as °F, then temperature will be converted to °C using:

Temperature (in °C) = 5/9 (Temperature [in °F]-32).

Summary tables by visit and time point and change from baseline to visit and time point for each vital sign parameter will be provided.

11.6. ECG

Summary tables by visit and time point and change from baseline to visit and time point for each ECG parameter(pulse rate (bpm), R-R (msec), QRS interval (msec), QT interval (msec), QTcB interval (msec) and QTcF interval (msec) will be provided.

The number and percentage of patients will be reported who have QTcB or QTcF values: >450 ms; > 480 ms; and > 500 ms. The number and percentage of patients will be reported who have changes from baseline in QTcB or QTcF: > 30 ms; and > 60 ms.

Additionally, the number and percentage of patients will be reported for patients who have the following QTcB or QTcF values and changes in QTcB or QTcF from baseline: QTcF > 450 ms and change in QTcF > 30 ms; QTcF > 450 ms and change in QTcF > 60 ms; QTcF > 480 ms and change in QTcF > 30 ms; QTcF > 480 ms and change in QTcF > 60 ms; QTcF > 500 ms and change in QTcF > 30 ms; QTcF > 500 ms and change in QTcF > 60 ms.

The maximum on-treatment change in QTcF from baseline versus the C_{max} will be displayed graphically for both AZD9150 and AZD5069, using unique symbols for each of the following 4 QTcF categories: < 450 ms; >= 450 ms to <480 ms; >=480 ms to < 500 ms; and > 500 ms.

All ECG results including overall results of the ECGs recorded as ‘normal’, ‘abnormal, not clinically significant (NCS)’ or ‘abnormal, clinically significant (CS)’ will be listed by treatment group at each time point.

11.7. PHYSICAL EXAMINATION

Physical examination data will be listed.

11.8. ECOG PERFORMANCE STATUS

For Part A and Part B, the ECOG performance status at baseline will be summarized using the number and percentage of patients within each ECOG performance category by treatment group. All ECOG data will be listed.

11.9. IMMUNOGENICITY

In all patients treated with MEDI4736, venous blood samples for IM assessments will be obtained. Using results from the tiered analysis, the number and percentage of patients who are positive for ADA will be summarized by visit and treatment group using the Safety Set. For patients who test positive for ADA, titer values will be listed. Samples will be stored for assessing the neutralization capacity in the future.

In all patients treated with AZD9150, the number and percentage of patients who are positive for anti-AZD9150 antibody will be summarized by visit and treatment group using the Safety set. For patients who test positive for anti-AZD9150 antibody, titer values will be listed.

For AZD9150 treated patients, the geometric mean AZD9150 concentration versus time profiles will be presented by anti-AZD9150 antibody status (i.e., positive or negative). PK parameters (C_{max} and AUC) of AZD9150 will be presented separately for anti-AZD9150 antibody positive and negative patients. A patient will be considered to be antibody positive if at least one post-treatment antibody assessment was positive.

Similarly, for MEDI4736 treated patients, the geometric mean trough concentration versus time profile will be presented by ADA status. C_{max} values of MEDI4736 treated patients will be presented separately for ADA-positive and ADA-negative patients.

The association between immune-related AEs and ADA positivity will be assessed by comparing the odds of a patient having an immune-related AE in the ADA positive group to the odds of a patient having an immune-related AE in the ADA negative group. Separate odds ratios (adjusted by replacing zero cells with 0.5) will be calculated for AZD9150 and MEDI4736 ADAs.

For Part B, a logistic regression model may be used to estimate the probability of having an objective response using treatment group and anti-PD-(L)1 status as factors and the maximum post-treatment antibody titer level as a continuous variable.

11.10. EXPLORATORY ANALYSES

11.10.1. Blood-borne Biomarkers

These results will be reported separately and will not be part of the CSR.

11.10.2. Tumour-based Biomarkers

These results will be reported separately and will not be part of the CSR.

11.10.3. Sensitivity Analysis for Overall Survival

In dose-expansion Part B, some patients may switch from a monotherapy arm to the corresponding combination drug. In such cases, the patient's time for OS will be censored at the time of the switch to the combination drug. Consequently, the follow-up time for the monotherapy and combination drugs may differ.

A sensitivity analysis may be performed to compare the follow-up times of the monotherapy and combination drug arms B5 and B6 in Part B. An overall measure of follow-up will be calculated for OS by calculating the median time from randomization to death or censoring for all patients, regardless of treatment arm using the Kaplan-Meier methodology. Then, this same calculation will be repeated for each arm but including all observed deaths and censoring patients at last contact agnostic to the time of switch.

12. INTERIM ANALYSES

There will be no interim analysis for dose-escalation Part A.

The dose-expansion Part B will use an adaptive approach to sample size based on Bayesian statistical methodology, so the number of actively enrolling treatment arms may decrease as the study continues. For the 2 combination arms in the anti-PD-(L)1 naïve patients (B3 and B4), once 12 efficacy outcomes are observed in the first 12 efficacy evaluable patients in each arm, a predictive probability calculation will be used to assess the chance of observing at least 8 of 35 responses (either PR or CR) in each arm. The method of calculating predictive probability will be based on a parameter free approach to predictive probability as it applies to variables that follow a binomial distribution (Jennison and Turnbull 2000). Predictive probability (chance to observe at least 8 of 35 responses) will be recalculated following the observation of the efficacy outcome in each efficacy evaluable patient as they were dosed in the trial. Following the observation of any patient's outcome, if predictive probability falls below 20%, the corresponding arm will be stopped. If predictive probability remains at or above 20% following the 19th efficacy evaluable patient, then an interim analysis will be conducted following the 20th efficacy evaluable patient. Each of the combination arms will continue to enrol patients up to a maximum of 35 efficacy evaluable patients following the interim analysis if at least 5 of 20 patients have responded with at least a PR.

For the 2 combination arms in the anti-PD-(L)1 treated patients (B1 and B2), the predictive probability to assess the chance of observing at least 3 of 20 of responses (either PR or CR) will be calculated when observing the efficacy outcomes for the first 10 efficacy evaluable patients, then recalculated following the observation of efficacy outcome in each efficacy patients. However, no formal interim analysis will be conducted for the 2 combination arms in the anti-PD-(L)1 treated patients.

Recruitment will continue while predictive power is measured. If an arm is to be stopped, no new patients will be recruited but patients who are already on study will continue in accordance with study guidelines outlined in Section 4 of the protocol.

If at least 2 CRs or PRs are observed in the first 20 patients in either of the 2 pretreated expansion arms, an additional 25 to 32 patients may be enrolled to that particular pretreated combination arm.

12.1.1. Efficacy Endpoints for Interim Analysis

Interim analysis of efficacy will be limited to the following variables:

- ORR
- Predictive probability for observing at least 8 of 35 overall responses (CR or PR)
- DOR

No confidence limits will be produced for the ORR. The calculation of predictive probability will be performed by AstraZeneca.

DOR will be summarized as described in Section 8.3.3 of this SAP.

12.1.2. Safety Endpoints for Interim Analysis

Interim analyses of the safety endpoints will use the same methods, summaries and listings identified in Sections 11.2 through 11.7 of this SAP.

13. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

For PK, PD, and Efficacy Analysis Sets defined to analyze data for this study, we modified the definitions slightly by adding the phrase “except for important protocol deviation”. The important protocol deviations will be determined by the clinical team during the BRDM planned to take place just prior to the final DBL.

14. REFERENCE LIST

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15. MOCK-UPS

15.1. TABLE MOCK-UPS

Figure mock-ups will be provided in a separate document.

15.2. FIGURE MOCK-UPS

Figure mock-ups will be provided in a separate document.

15.3. LISTING MOCK-UPS

Listing mock-up will be provided in a separate document.

16. APPENDICES

Appendix 1 – Playbook Summarizing Dose-escalation Recommendations from the CRM