Clinical Study Protocol	
Drug Substance	AZD9150, AZD5069, MEDI4736, tremelimumab
Study Code	D5660C00004
Version	**Amendment 11 v 12.0**
Date	20 Nov 2019

A Phase 1b/2, Open-Label, Multicentre Study Assessing the Safety, Tolerability, Pharmacokinetics, and Preliminary Anti-tumor 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

Sponsor: AstraZeneca AB, 151 85, Södertälje, Sweden

AstraZeneca Research and Development site representative

Date

AstraZeneca
One MedImmune Way
Gaithersburg, MD 20878 USA

The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1	18 August 2015		
2	14 December 2015		
3	22 March 2016		
4	31 July 2016	5.1 (Version 6.0)	17 February 2017 (UK)
		5.2 (Version 6.0)	10 May 2017 (UK)
5	10 May 2017		
6	12 February 2018		
7	31 July 2018		
8	12 August 2018		
9	**24 August 2018**	9.1 (Version 10.1)	26 May 2019 (Germany)
10	**18 June 2019**		
11 (Version 12)	**20 November 2019**	11.1 (Version 12.1)	13 November 2019 (Germany)

VERSION HISTORY

Amendment 11 Version 12, 20 Nov 2019
This protocol amendment has been prepared globally for all patients currently enrolled in this study, with the exception of patients enrolled in Germany (Germany must use the Germany-specific protocol amendment 11.1, version 12.1, 13 Nov 2019). The key protocol amendment changes are as follows: • Amendment number and version number updated on the cover page and header. • Addition of pemphigoid as a potential risk for durvalumab in Section 1.3.2. • Revisions to Section 6.12 to provide additional guidance on continuation of patient's treatment after last subject last visit for the primary endpoint. In addition, the actual study start date and the data cut-off date for primary endpoint were updated. • Revisions to Appendix I to align with the updated Toxicity Management Guidelines for durvalumab (MEDI4736) and tremelimumab issued based on CTCAE version 4.03 dated 17 October 2019. Please note: Appendix I has been replaced with an Annex to the protocol. • Minor formatting changes were made, and the table of contents were updated accordingly.

Amendment 10 Version 11.0, 18 June 2019
This protocol amendment has been prepared globally for all patients currently enrolled in this study, except for patients enrolled in Germany (Germany must continue to use the Germany-specific protocol amendment 9.1, version 10.1, 26 May 2019 until a future protocol amendment is generated for Germany). The key protocol amendment changes are as follows: • Revision of sponsor signatory on cover page. • Amendment number and version number updated on the cover page and header. • Administrative amendment to correct inconsistencies/formatting in the text. • Revisions throughout to reflect the current status (closed) of enrolment across all cohorts. • Revision to delete the secondary objective with the outcome measure of tumor PD-L1 expression as this was added in error in a previous amendment. PD-L1 expression in prostate cancer is not yet validated. • Revision to clarify the exploratory objective with the outcome measure of tumor-derived DNA mutations at baseline, and changes upon treatment that may correlate with treatment or response. • Revision to Sections 1.1.1, 1.3.1, 1.3.2, 6.7.1, 6.7.2, and 6.9.1, to align with the AZD9150

Investigator's Brochure (IB) edition 9.0, dated 14 June 2019.

- Addition of Section 6.4.8 (Serious bleeding events with combination drug MEDI4736 (durvalumab) in squamous cell carcinoma of the head and neck patients) to align with the AZD9150 IB edition 9.0, dated 14 June 2019.
- For Arm B8, global revisions to clarify that the urine PK sampling is mandatory for up to 12 patients and then optional consent thereafter. Additionally, noted that this collection applies to the US enrolled patients only and that instructions will be provided to patients to collect samples, as applicable, at home. Further, the testing requirement for "Cycle 1, Day 1: 6 to 24 hours after start time of AZD9150 infusion" has been removed as a requirement for Arm B8.
- Global revisions to clarify that weight obtained on Day 1 of each cycle will be used to calculate the weigh-related doses for each cycle.
- Global revisions to clarify for Arm B8 the relationship between 1 and 2 hours post AZD9150 infusion ECG measurements.
- Global revisions to clarify that for Arm B8 vital signs will not be required for Day 8 and Day 22 (all cycles) as there are no dosing visits scheduled for these patients on these days.
- Global revisions to clarify a few inconsistencies in text around the PBMC sample collection days. It was clarified that the collection of PBMC samples will be collected on Day −7 of the lead-in period; Days 1, 8, and 15 of Cycle 1; on Day 1 of Cycles 3, 6, and 9; and at the EOT visit.
- Global revisions (see **bold text**) to clarify the screening biopsy sample timing as follows: "if patient has a biopsy report and sample from **fewer than** 45 days prior to start of treatment **(Day -7),** it would be considered acceptable.
- Revision to Section 5.8.1.3 (see **bold text**) to clarify the number of archival tumor samples as follows: "Freshly prepared unstained slides (minimum of **3**, but preferably **10** to **20**) from the archival tumor block will be accepted if tumor blocks cannot be submitted."Revisions to Table 10 (Volume of blood to be drawn from each patient during screening, lead-in period, and Cycle 1 of Part 1 and Part B) to reflect the blood volumes listed in the Laboratory Manual for this study.
- Revision to the study team contacts for emergencies in Section 6.10.
- Revisions to Appendix G (Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law) to align with Hy's Law version 2.0 (dated 10 January 2019) as described in the SOP Detection and Handling of Potential Hy's Law Cases in Clinical Studies.

Amendment 9 Version 10.0, 24 Aug 2018

Key Protocol Amendment Changes:

- Administrative amendment to correct inconsistencies in the text
- Version history updated to include the initial version and wording changed from Version to Amendment
- For B8, corrected the anti-AZD9150 antibody immunogenicity sample collection in the study plan for pharmacokinetic, pharmacodynamic, immunogenicity, and pharmacogenetic assessments in Part B (B8) (Table 8 in Section 5.2) from Cycle 2

Day 15 to Cycle 2 Day 1 to match text in Section 5.7
- For B8, corrected time points for circulating-free deoxyribonucleic acid (cfDNA) samples in Table 8 in Section 5.2 and Section 5.8.1.1 to be aligned, and to ensure that these samples are taken on Day −7 of the lead-in period, Day 1 of all even-numbered cycles, Day 1 of Cycle 3, and at the End-of-Treatment (EOT) visit
- For B8, corrected time points for serum, plasma and peripheral blood mononuclear cell (PBMC) sample collection in Section 5.8.1.1 to match the updated the footnotes in Table 8 in Section 5.2.

Amendment 8 Version 9.0, 12 Aug 2018 –Not submitted

Key Protocol Amendment Changes:

- Updated AZD9150 PK collection & ECG time point for B8 from Day -1 to Day -7 (Table 8 in Section 5.2, Section 5.4.3 & Section 5.5.1)
- Added Day -7 anti-AZD9150 antibody immunogenicity sampling for B8 (Table 8 in Section 5.2 & 5.7)
- Corrected typographical error in Figure 6 from ≤30mg to ≤30kg (Section 7.7.1)
- Removed reference to personnel remaining blinded as this is not a blinded study (Section 8.1)

Amendment 7 Version 8.0, 31 Jul 2018 – Not submitted

Throughout Document
Transferred to a new template with updates of protocol structure and protocol language
Updated Version Number and Date throughout
Updated paging and internal references
Added treatment arm B8
Further minor clarifications

Key Protocol Amendment Changes

- Update of protocol structure/organization according to the new template with a Doc ID of LDMS_001_00026737 and the authoring instructions presented in the new template.
- A removal of treatment arms of A5 and A7 from Part A as decided by AstraZeneca to not open the cohort for enrolment based on data analysed for combination of AZD5069 and MEDI4736
- An additional treatment arm of B8 to enroll 48 patients who are efficacy evaluable first-line squamous cell carcinoma of the head and neck (SCCHN) (no prior systemic treatment for recurrent or metastatic SCCHN [RM SCCHN]) to test the flat dosing of AZD9150 in combination with MEDI4736 as dosed every 2 weeks (Q2W)

Resulting updates to the following sections:

Section 1 Introduction
- Minimized the information according to the new template instruction and the IB is referenced in order to avoid amending the protocol following to the annual update of the IB.

Section 2 Study objectives
- Established the additional primary objective based on the details provided in the respective IBs, for dose-expansion Part B to evaluate response rate (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 RM SCCHN (1L RM SCCHN).

Section 3 Subject selection, enrolment, randomisation, restrictions, discontinuation and withdrawal
- Added the criteria applicable to B8.
- Provided minor clarifications.

Section 4.1 Dose-escalation and safety cohorts Part A
- Removed a section for the food effect study for AZD5069.
- Removed text for Arm A5 and Arm A7.

Section 4.2 Dose-expansion Part B
- Added treatment arm B8 to Table 4 for assessment schedule.
- Added text for B8.
- Removed text for B7.

Section 5 Study assessments
- Added treatment arm B8 to Table 5 and modified the footnote accordingly.
- Removed treatment arms A5 and A7 from Table 6.
- Added B2, B4, and B8 to the footnote of Table 6.
- Clarified that Table 7 indicated the assessment scheduled for treatment arms B1 through B7.
- Provided a new Table 8 for treatment arm B8 (pharmacokinetic, pharmacodynamic, immunogenicity, and pharmacogenetic assessments in Part B).

Section 5.4.1 Laboratory safety assessments
- Added text to clarify that the central laboratory will analyse all the blood samples.

Section 5.4.4 Vital signs
- Added text regarding treatment arm B8.

Section 5.5 Pharmacokinetics
- Added text regarding treatment arm B8.
- Removed text regarding the food effect evaluation
- Removed treatment arm A5
- Added text for treatment arm B8 regarding a requirement of consent for urine samples for PK assessments.
- Added the time points in detail for the PK samples.

Section 5.8.1 Exploratory biomarker research
- Added text for biological samples.

Section 6.4.12 Disease under study (DUS)
- Added new text regarding DUS.

Section 6.6 Overdose
- Changed the definition of overdose of AZD9150: >10% above the recommended

dose and added advice to Investigators who are required to closely monitor any patient who receives a higher dose than that intended.

Section 6.9.1 Dose modifications

- Clarified the dose for AZD9150 and MEDI4736.

Section 6.10 Study team contacts for emergencies

- Replaced Minal Mehta to Gail Doughton.

Section 6.11 Duration of treatment

- Added text for details of the MEDI4736 monotherapy treatment.

Section 6.12 Expected start and end of study

- Added new text for post-analysis and reporting access to study treatment.

Section 7.2 Dose and treatment regimens

- Section 7.2.1: Added text for administration of AZD9150 in treatment arms, A1, A4, A6, B1, B3, B5, B7, and B8.
- Section 7.2.2: Added text for administration of AZD5069 in treatment arms A5, A7, B2, B4, and B6 and removed text for A3 in regard to recommended Phase 2 dose (RP2D).
- Section 7.2.3: Added text for administration of MEDI4736 in treatment arms A1, A7, B1, B4, B7, and B8.

Section 7.7.1 Starting dose and dose-escalation scheme

- Clarified the dose-reduction levels for treatment arm B8

Section 7.7.7 Confirmation of the presumed recommended dose

- Removed text for A3 in regard to RP2D.

Section 7.8 Concomitant and other treatments

- Changed the time point to correct information on any treatment to 30 days before starting study treatment from 28 days.

Section 8.2.1 Dose-escalation Part A

- Removed text for Arms A5 and A7.

Section 8.2.2 Dose-expansion Part B

- Updated the number of the patients to be enrolled.
- Added text regarding treatment arm B8.

Section 8.10 Methods of statistical analysis

- Added treatment arm B8.

Section 9.2.1 Source data

- Added new text regarding source data.
- Added new information for the case report form that serves as the source.

Section 9.4 Data management by AstraZeneca

- Added new text for data management of genotype data**.**
- Added new text for data associated with human biological samples.

Amendment 6 Version 7.0, 12 February 2018
As documented in Clinical Study Protocol Amendment 6

Amendment 5 Version 6.0, 10 May 2017
As documented in Clinical Study Protocol Amendment 5

Amendment 4 Version 5.0, 31 July 2016
As documented in Clinical Study Protocol Amendment 4
Amendment 3 Version 4.0, 22 March 2016
As documented in Clinical Study Protocol Amendment 3

Amendment 2 Version 3.0, 14 December 2015
As documented in Clinical Study Protocol Amendment 2

Amendment 1 Version 2.0, 18 August 2015
As documented in Clinical Study Protocol Amendment 1

Version 1.0
Initial creation

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

CLINICAL STUDY PROTOCOL SYNOPSIS

A Phase 1b/2, Open-Label, Multicentre Study Assessing the Safety, Tolerability, Pharmacokinetics, and Preliminary Anti-tumor 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

Principal Investigator: [redacted]

Study design

This multicentre, open-label, Phase 1b/2 study is designed as a 2-part study consisting of 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).

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 tumor 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 (durvalumab)/tremelimumab. Up to 30 evaluable patients per treatment arm are planned to be enrolled in dose-escalation cohorts; approximately 18 patients are planned to be enrolled in each of the safety run-in cohorts (in combination with MEDI4736/tremelimumab), and approximately 20 patients per tumor 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 are allocated sequentially to treatment arm A1 (AZD9150/MEDI4736) or treatment arm A2 (AZD5069/MEDI4736). A continual

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 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 Arm A1 and Arm 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 DLTs of neutropenia occurring in patients treated with AZD5069 were due to 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 Safety Review Committee (SRC) decided to enroll an additional cohort of at least 6 to 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 and Arm A5) that include tremelimumab, patients with solid tumor were planned to be allocated to AZD9150/MEDI4736/tremelimumab or AZD5069/MEDI4736/tremelimumab 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 tumor 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 tumor and 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 is to not open the cohort for enrolment based on data analysed for combination of AZD5069 and MEDI4736.

In summary, the status of all Part A arms conducted at study sites in the United States at the time of protocol amendment 7 were as follows:

- Treatment arm A1: enrolled 2 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 2 cohorts of AZD5069 (40 mg BID capsules/tablet and 80 mg tablet BID) respectively in combination with MEDI4736 (20 mg/kg Q4W). Cohort is closed to enrolment.
- Treatment arm A3: AZD5069 (80 mg BID tablet) in combination with MEDI4736 (20 mg/kg Q4W) Cohort is closed to enrolment.
- Treatment arm A4: enrolled into 3 cohorts AZD9150 3 mg/kg QW +tremelimumab 1 mg/kg Q4W +MEDI4736 20 mg/kg Q4W, AZD9150 2 mg/kg QW +tremelimumab 1 mg/kg Q4W+MEDI4736 20 mg/kg Q4W and AZD9150 3 mg/kg every 2 weeks (Q2W)+tremelimumab 1mg/kg Q4W +MEDI4736 20 mg/kg Q4W. The latter 2 cohorts were opened based on observed DLT in the cohort that dosed with AZD9150 at 3 mg/kg QW. These Cohorts are closed to enrolment
- Treatment arm A5: AZD5069+MEDI4736+tremelimumab was originally planned. Sponsor portfolio decision was to not open the cohort for enrolment based on data analysed for combination of AZD5069 and MEDI4736.
- Treatment arm A6: AZD9150 3 mg/kg QW + MEDI4736 20 mg/kg Q4W was originally planned to enroll prostate and breast cancer patients. Enrolment occurred in patients with prostate cancer. Cohort is closed to enrolment.
- Treatment arm A7: AZD5069+MEDI4736 was originally planned for patients with breast and prostate cancer. Sponsor portfolio decision to not open the cohort for enrolment was based on data analysed for combination of AZD5069 and MEDI4736.

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 recurrent and/or metastatic (RM) SCCHN. 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 across Part B (B1-B6), 10 to 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 have been planned, for a total of approximately 48 efficacy evaluable first-line SCCHN patients (no prior systemic treatment for RM SCCHN).

In summary, for Arms B1-B6, 2 patient types were planned to be studied, those pretreated with prior programmed cell death-ligand 1 (PD-L1) treatment and those naïve to PD-L1 treatment. Patients were randomized in a 1:1 ratio on the pretreated arms and 2:2:1:1 ratio on

the naïve combination arms (combination: combination: monotherapy: monotherapy). The enrolment in Part B of the study is closed.

- Treatment arm B1: 10-52 2L+ RM SCCHN patients were planned to be enrolled in this Arm where patients were dosed with AZD9150 3 mg/kg QW in combination with MEDI4736 20 mg/kg Q4W in patients with prior exposure to anti-PD-(L)1 antibodies. Cohort is closed to enrolment.
- Treatment arm B2: 10-52 2L+ RM SCCHN patients were planned to be enrolled in this Arm where patients were dosed with AZD5069 80 mg BID in combination with MEDI4736 20 mg/kg Q4W in patients with prior exposure to anti-PD-(L)1 antibodies. Cohort is closed to enrolment.
- Treatment arm B3: 12-35 2L+ RM SCCHN patients were planned to be enrolled in this Arm where patients were dosed with AZD9150 3 mg/kg QW in combination with MEDI4736 20 mg/kg Q4W in patients with no prior exposure to anti-PD-(L)1 antibodies. Interim analysis for this cohort was planned at 20 patients. There were patients who were 1L RM SCCHN enrolled in this Arm which were replaced. Cohort is closed to enrolment.
- Treatment arm B4: 12-35 2L+ RM SCCHN patients were planned to be enrolled in this Arm where patients were dosed with AZD5069 40 mg BID in combination with MEDI4736 20 mg/kg in patients with no prior exposure to anti-PD-(L)1 antibodies. Interim analysis for this cohort was planned at 20 patients Provision was made to extend enrolment in this Arm to 55 patients if at Interim analysis the dose of AZD5069 was changed from 40 mg BID to 80 mg BID. Cohort is closed to enrolment.
- Treatment arm B5: 12 2L+ RM SCCHN patients were planned to be enrolled in this Arm where patients were dosed with AZD9150 3 mg /kg QW alone in patients with no prior exposure to anti-PD-(L)1 antibodies. Cohort is closed to enrolment.
- Treatment arm B6: 12 2L+ RM SCCHN patients were planned to be enrolled in this Arm where patients were dosed with AZD5069 40 mg BID alone in patients with no prior exposure to anti-PD-(L)1 antibodies. Cohort is closed to enrolment.

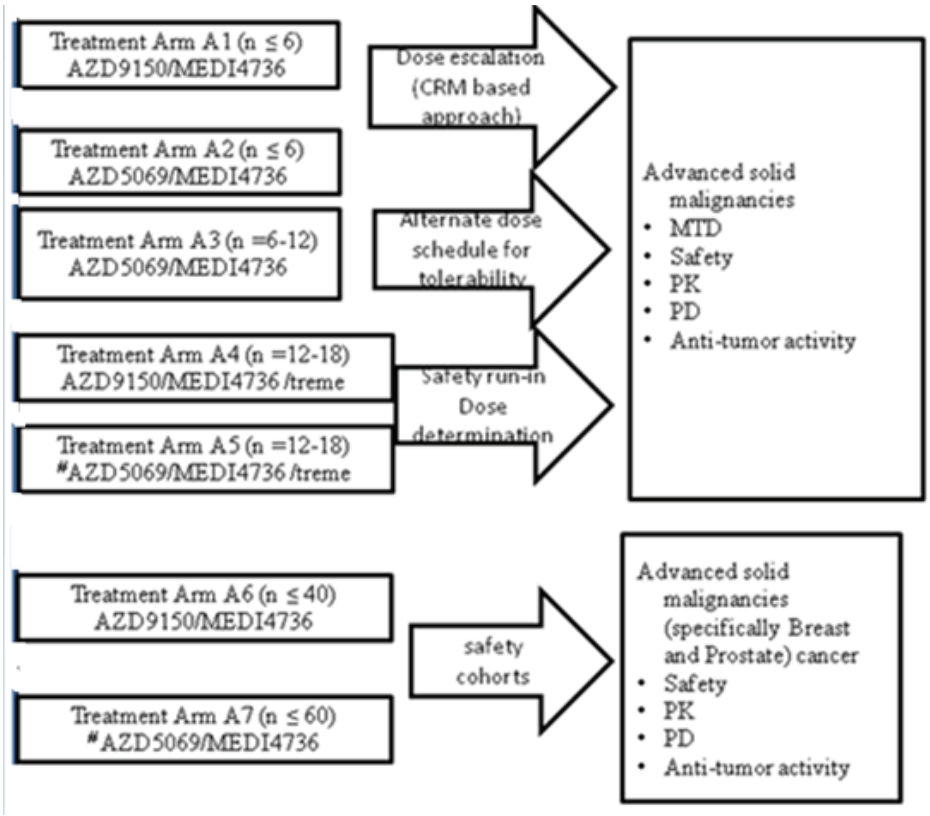
In addition, the following non-randomized Arms were planned to enroll patients with no prior exposure to anti-PD-(L)1 therapies and patients who have not received prior systemic treatment for RM disease.

- Treatment arm B7: 48 1L RM SCCHN patients were planned to be enrolled in this Arm where patients were planned to be dosed with AZD9150 3 mg/kg QW in combination with MEDI4736 20 mg/kg Q4W. Cohort is closed to enrolment.
- Treatment arm B8: 48 1L RM SCCHN patients were planned to be enrolled in this Arm where patients were planned to dosed with an alternate-week dosing schedule and with flat dose of both combination drugs. AZD9150 400 mg Q2W (200 mg in lead-in period) in combination with MEDI4736 1.5 g Q4W. Cohort is closed to enrolment.

Study flow chart

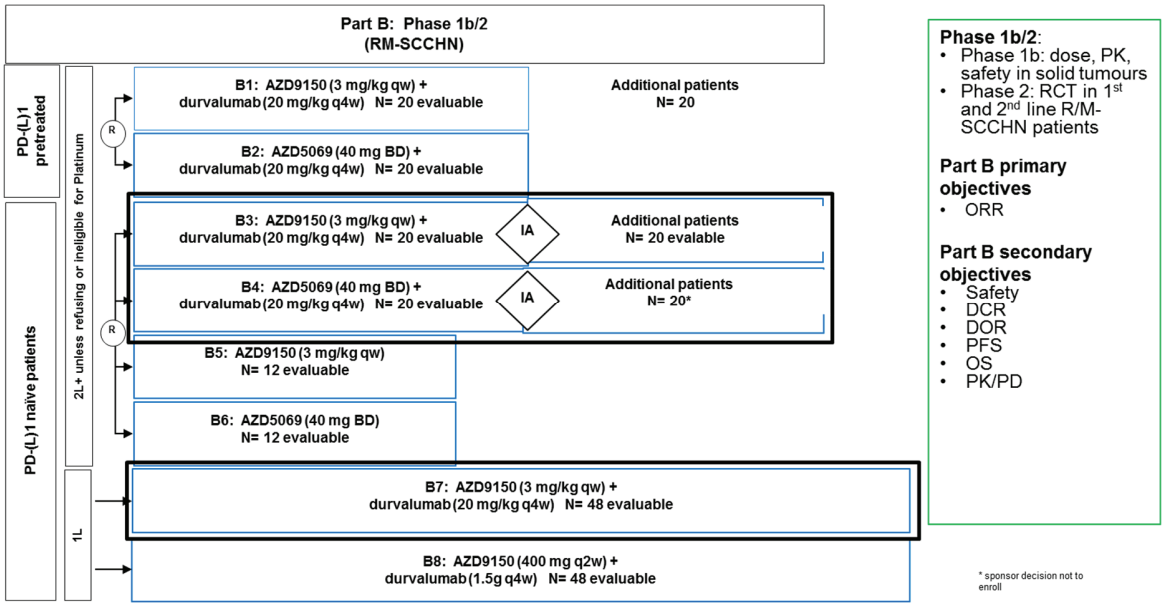
Part A: Dose-escalation & Safety Cohorts

Patients with advanced solid malignancies refractory to standard therapy or for which no standard of care regimen currently exists.



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



Abbreviations: CRM=continual reassessment method; DCR=disease control rate; DOR=duration of response; IA=interim analysis; MTD=maximum tolerated dose; OS=overall survival; PD-(L)1=programmed cell death 1 (CD279) and/or programmed cell death-ligand 1 (also known as B7 homolog 1, CD274); PFS=progression-free survival; PK/PD=pharmacokinetics/pharmacodynamics; SRC=Safety Review Committee; SCCHN=squamous cell carcinoma of the head and neck; treme=tremelimumab.

Note: Treatment arms B1, B2, B3, B4, B5, B6, B7, and B8 are closed to enrolment.

Objectives

Primary Objective:	**Outcome Measure:**
Dose-escalation and safety cohorts Part A	
To determine the 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 in patients with advanced solid malignancies refractory to standard therapy or for which no standard of care regimen currently exists.	MTD based on patients who completed the DLT Evaluation AEs, SAEs, laboratory evaluations, vital signs, and physical examinations Treatment-emergent AEs (TEAEs), SAEs and death(s), graded in accordance with NCI CTCAE v4.03
Dose-expansion Part B	
To evaluate the 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 recurrent or metastatic SCCHN (1L RM SCCHN). To 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).	Objective response − defined as a complete response (CR) or partial response (PR) according to RECIST version 1.1

Secondary Objective:	**Outcome Measure:**
Dose-escalation and safety cohorts Part A	
To assess the PK of AZD9150, AZD5069, and MEDI4736 and/or MEDI4736/tremelimumab in the selected dose combinations.	PK parameters as outlined in Section 8.5
To determine the IM of MEDI4736 and/or MEDI4736/tremelimumab in combination with AZD9150 or AZD5069 and the IM of AZD9150 in combination with MEDI4736 and/or MEDI4736/tremelimumab	ADAs
To assess pharmacodynamic response in blood for AZD9150.	STAT3 knockdown (signal transducer and activator of transcription 3 [STAT3] knockdown)

Dose-expansion Part B	
To assess secondary measures of efficacy (DCR at 12 weeks; duration of overall response [DOR], PFS, OS; and proportion of patients alive at 12 months).	Disease control defined as a CR, PR, or stable disease (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 progressive disease (PD) is objectively documented (taking as reference for PD the smallest measurements recorded on study) PFS - defined as the time from randomisation 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 randomisation to death from any cause Best overall response (including CR, PR, SD, and PD, according to RECIST version 1.1 criteria), ordered from best to worst Survival at 12 months
To assess the PK of AZD9150 and AZD5069 both as monotherapy and in combination with MEDI4736.	PK parameters as outlined in Section 8.5
To assess the urinary PK of AZD9150 and MEDI4736 in combination with AZD9150 or AZD5069.	PK parameters as outlined in Section 8.5
To determine the IM of AZD9150 alone or in combination with MEDI4736 and the IM of MEDI4736 in combination with AZD9150 or AZD5069.	ADAs
To assess pharmacodynamic response in blood for AZD9150 and MEDI4736 (sPD-L1 will not be evaluated for Arm B1, B2, and B4 post the first 20 patients and for Arm B7 and B8).	(STAT3 knockdown) and sPD-L1 in blood Pharmacodynamics of MEDI4736 (sPD-L1) and tremelimumab (will not be evaluated for Arm B1, B2, and B4 post the first 20 patients and for Arm B7 and B8)
To assess tumor cell pharmacodynamics (STAT3 knockdown).	Pharmacodynamics of AZD9150 (STAT3 knockdown) in tumor tissue
To assess baseline circulating MDSCs and effect of treatment on circulating MDSCs (will not be evaluated for Arm B1, B2, and B4 post the first 20 patients and for Arm B7 and B8).	Circulating MDSCs
To evaluate baseline tumor PD-L1 expression for potential correlation with drug activity or the ability to prospectively identify patients likely to respond to treatment.	Tumor PD-L1 expression

Safety Objective:	**Outcome Measure:**
Dose-expansion Part B	
To evaluate the safety and tolerability of AZD9150 and AZD5069 both as monotherapy and in combination with MEDI4736.	AEs, SAEs, laboratory evaluations, vital signs, and physical examinations TEAEs, SAEs, and death, graded in accordance with National Cancer Institute (NCI) CTCAE version 4.03

Exploratory Objectives	**Outcome Measures**
Dose-escalation (Part A) and Dose-expansion (Part B)	
To evaluate baseline levels of and changes in blood-borne biomarkers that may correlate with treatment or clinical response.	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 and other soluble factors
To assess serum samples for pharmacodynamic response to AZD5069.	Transient increase in CXCR2 ligands interleukin-8 and GRO-α
To evaluate tumor-based biomarkers in archival/baseline tumor 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/tremelimumab.	These may include but are not limited to PD-L1 expression, phospho- or total STAT3 expression, tumor genetics, immunogenomics (genetics associated with immune responses such as homozygosity/heterozygosity of MHC-I genes), characterisation of immune infiltrates, gene expression or other stratification markers
To evaluate circulating-free deoxyribonucleic acid (cfDNA; including circulating tumor deoxyribonucleic acid [DNA] as well as non-tumor 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]).	For tumor-derived DNA mutations at baseline, and changes upon treatment that may correlate with treatment or response.
To collect and store tumor, blood, plasma, and serum samples or analyse surplus blood or tissue including patient-specific archival tumor tissue, if available.	For potential future exploratory research into factors that may influence development of the tumor or response to treatment (where response is defined broadly to include efficacy, tolerability, or safety). In the event that additional tumor molecular profiling is required to understand further any response to

	treatment, AstraZeneca may request a sample of the most recent tumor biopsy for additional research. Any sample collection can be discontinued or suspended at the discretion of the Sponsor, without the need for a protocol amendment
To explore the relationship between PK and selected endpoints	Which may include pharmacodynamics, efficacy, and/or safety, where deemed appropriate
To collect and store DNA	Carry out 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/tremelimumab) and/or development of cancer
Part B Only	
To evaluate changes in tumor-based biomarkers that may correlate to treatment or response	Changes including but not limited to immune cell infiltrate, gene expression changes, cell activation or proliferation markers, and cytokines

Target subject population

The dose-escalation Part A targets 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.

The dose-expansion Part B (B1 to B8) is targeting patients with histologically and/or cytologically confirmed SCCHN that is 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 RM SCCHN (B7 and B8) as described in more detail in Section 3. Patients must have at least 1 tumor 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 EOT are optional but encouraged.)

Section 3 provides the full and detailed eligibility criteria; key inclusion requirements for patients in both parts of the study are:

- Able and willing to give written informed consent including consent for collection of formalin fixed paraffin-embedded blocks or slides from archival diagnostic histology samples, where available. For inclusion in the optional genetic research, patients must provide a separate informed consent.

- Male and female patients, at least 18 years of age
- Eastern Cooperative Oncology Group performance status score of 0 or 1
- Measurable disease
- Number of prior lines of treatment by Arm:
  - Arms A1 to A4 and A6: Has undergone ≤3 previous regimens of cytoreductive chemo-therapies including, but not limited to, platinum-based compounds, taxanes, or 5-fluorouracil
  - Arms B1 to B6: Has undergone 1-3 previous regimens of cytoreductive chemo-therapies including, but not limited to, platinum-based compounds, taxanes, or 5-fluorouracil
  - Arm B3: Has undergone at least 1 previous regimen of systemic chemotherapy and received up to 3 previous regimens of cytoreductive treatments in the recurrent metastatic disease setting. If a patient has received systemic chemotherapy for local disease only, they would not be considered eligible for Arm B3.
  - Arms B7 and B8: Has not received any previous systemic therapies for recurrent metastatic disease, nor had any prior exposure to anti-PD-(L)1 therapies. Patients who have received chemotherapy for local disease may be considered for eligibility to Arms B7 and B8.
- Adequate organ and marrow function
- Women of childbearing potential and men who are sexually active with a female partner of childbearing potential must prevent pregnancy and women may not be breast feeding

Section 3 provides the full and detailed eligibility criteria; key exclusion requirements for patients in both parts of the study are:

- Symptomatic spinal cord compression
- Second malignancy
- Concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer
- Ongoing toxicity related to prior treatment and assessed as grade >1

- Immune-related AEs while receiving prior immunotherapy (including anticytotoxic T-lymphocyte-associated protein 4 treatment) and assessed as grade ≥3
- Has active or prior documented autoimmune disease within the past 2 years with the exception of vitiligo, Grave's disease, and/or psoriasis not requiring systemic treatment
- Active or prior documented inflammatory bowel disease
- History of primary immunodeficiency
- Prior organ transplant that requires use of immunosuppressive treatment
- Cardiac conditions that render the patient unsuitable for participation in the study
- Inability to take oral medications and/or has a clinical or radiological diagnosis of bowel obstruction
- History of allergic reactions attributed to the study treatments (AZD9150, AZD5069, tremelimumab [for Part A, Arm A4 only] or MEDI4736), their compounds, or agents of similar chemical or biologic composition
- Suffers from a comorbidity that in the opinion of the Investigator renders the patient unsuitable for participation in the study
- As judged by the Investigator, any evidence of severe or uncontrolled diseases such as active bleeding diatheses, or has an active viral infection of human immunodeficiency virus (HIV), hepatitis B virus (HBV), and/or hepatitis C virus (HCV)
- History of tuberculosis
- Condition that, in the opinion of the Investigator, would interfere with the evaluation of the study drugs or the interpretation of patient safety or study results
- Live attenuated vaccine within 30 days before the first dose of study drug
- Judgement by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements
- Patients with brain metastases considered stable may be enrolled into Part A of the study; they are excluded from Part B of the study
- Patients must not be included in the optional genetic research if they have previously received an allogeneic bone marrow transplant or have received

Duration of treatment

Patients participating in either part of the study will be administered study drug(s) for the 7-day lead-in period in 4-week treatment cycles. This may continue for as long as they are continuing to show clinical benefit, as judged by the Investigator, unless a patient has confirmed progression of disease (PD) with either clinical deterioration and/or no further benefit from treatment, experiences unacceptable toxicity, or discontinues for any other reason. If a patient on either monotherapy arm (treatment arms B5 or B6) has confirmed PD, they may, at Investigator's discretion and with notification to the Medical Monitor, add MEDI4736 to their treatment regimen. These patients, post addition of MEDI4736 to the monotherapy treatment will continue to be part of the safety analysis but will be censored from the efficacy analysis. After discontinuation of treatment, all patients will continue to be followed for safety, subsequent anticancer therapy, and survival. During this time, all patients will be followed for safety (including concomitant medication) for 28 days (+7 days) after the last dose of study drug or until the initiation of a subsequent anticancer therapy. In addition, patients who received MEDI4736 as part of their combination treatment will be followed for immunogenicity for 90 days (±7 days) after the last dose of MEDI4736 or until the initiation of alternative anticancer therapy. Patients who discontinued treatment for reasons other than PD will continue to undergo tumor assessments every 2 months (±7 days) until PD is noted. All patients will be followed for subsequent anticancer therapy every 2 months (±7 days) and will also be followed for overall survival every 2 months (±7 days) from the date of randomisation to the date of death due to any cause, assessed for approximately 40 months. The patients will be censored on the date of last follow-up visit.

Investigational product, dosage and mode of administration

AZD9150: Arms A1, A4, A6, B1, B3, B5, B7, and B8: Patients will receive a loading dose of AZD9150 (Days −7, −5, and −3) at the defined dose in each treatment arm as described in the study design. Following loading dose, patients will receive QW dosing of AZD9150 (except in Cohort 2 of Arm A4 and Arm B8 where the schedule of AZD9150 is Q2W). AZD9150 will be administered as a 1-hour (± 10 minutes) infusion. In all cases, infusion of AZD9150 is planned to be completed at least 1 hour (Cycle 1) or at least 30 minutes (in subsequent cycles if no infusion reaction in first cycle) before the start of the MEDI4736 infusion on days that both drugs are administered. For Arm A4 specifically the sequence of dosing for the first 4 cycles would be AZD9150 infused over 1 hour (± 10 minutes) followed by tremelimumab infused over 1 hour (± 10 minutes) followed by MEDI4736 infused over 1 hour (± 10 minutes). 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). 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. During the 7-day lead-in period, AZD9150 will be administered as a loading dose on Days -7, -5, and -3. Starting with Cycle 1, AZD9150 will be administered QW on Days 1, 8, 15, and 22 of each treatment cycle.

AZD5069: Arms A2, A3, A5, A7, B2, B4, and B6: Patients will receive AZD5069 as 40 mg BID starting with Day −7 of a 7-day lead-in period at the defined dose in each treatment arm as described in the study design. Following the lead-in period, patients will receive BID dosing of AZD5069 daily for a 28-day cycle. On days when both AZD5069 and MEDI4736 are given, the morning dose of AZD5069 is administered at least 30 minutes before starting infusion of MEDI4736. For Arm A5 specifically, the sequence of dosing for the first 4 cycles was planned to be AZD5069 followed 30 minutes later by tremelimumab infused over 1 hour (± 10 minutes) followed by MEDI4736 infused over 1 hour (±10 minutes). As discussed in the study design Arm A5, Arm A7, and the food effect substudy will not open for enrolment. In all cases, AZD5069 should be administered either 2 hours before or 2 hours after (with ± 2 hours) food consumption at approximately the same time each day.

MEDI4736: Arms A1-A7, B1-B4, B7, and B8: Patients will receive MEDI4736 starting on Day 1 of Cycle 1 and will be administered as 20 mg/kg infusion administered over 1 hour Q4W in a 28-day cycle. In addition to the above arms, patients in monotherapy Arms (B5 and B6) who develop confirmed disease progression may have MEDI4736 added, at the discretion of the Investigator and after notifying the Medical Monitor. MEDI4736 will be added to the dosing schedule beginning on Day 1 of the following treatment cycle. Thereafter, all study treatment will follow the same schedule as for a patient on a combination therapy arm. For Arm B8, a flat dose of 1.5 g will be administered. In Arms B5 and B6, MEDI4736 could be added to treatment after progression on AZD9150 or AZD5069 monotherapy agents, respectively.

Tremelimumab: Arms A4 and A5: Patients will receive tremelimumab starting Day 1 of Cycle 1 and will be administered as 1 mg/kg infusion administered over 1 hour Q4W in a 28-day cycle. Tremelimumab will be infused for a maximum of 4 cycles.

Statistical methods

The dose-escalation Part A used a continual reassessment method-based approach to identify the set of AZD9150/MEDI4736 and AZD5069/MEDI4736 dose combinations where the incidence of DLT is no larger than 33%. Once the MTDs for each of the 2 agents in combination with MEDI4736 were identified or the maximum doses of each of the 2 agents in combination with MEDI4736 were reached, the SRC decided (based on emerging and maturing data) to enroll an additional 6-12 patients to Arm A3 to test alternative dosing schedule of AZD5069. Also, Arms A4, A5, A6 and A7 are designed with a small number of

patients (6 to 18) to gather and confirm safety information and will start/continue to enroll for A5 and A7, based on emerging safety and efficacy data from Part B. The dose-expansion Part B for Arms B1-B6 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 maximum number of evaluable patients to be included in naïve combination arms is N=35. The maximum number of patients to be included in pretreated combination arms is N=52.

For the 2 combination arms in the anti-PD-(L)1 naïve patients (Arms B3 and B4), once 12 efficacy outcomes have been observed in the first 12 efficacy evaluable patients in each arm, a predictive power 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 power is based on a parameter free approach to predictive power as it applies to variables that follow a binomial distribution (Jennison and Turnbull 2000). Predictive power (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 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 and the 1L RM SCCHN patients in Arm B7. The 2 monotherapy arms will continue recruiting until 12 efficacy evaluable patients have been enrolled in each arm.

For the 2 combination arms in the anti-PD-(L)1 pretreated patients (B1 and B2), 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 20 responses (either PR or CR) 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 chance that

fewer than 12 patients with CR or PR (responding) will be observed, given the true fraction of patients responding is 35%, is 9%. The chance that at least 15 patients responding is observed, given the true fraction of patients responding is 25%, is 20%. 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 power is measured. If an arm is to be stopped, no new patients will be recruited to that arm, but patients who are already on study in that arm will continue in accordance with study guidelines outlined in Section 4.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Clinical Study Protocol (CSP).

Abbreviation or special term	**Explanation**
2′-MOE	2′-methoxyethyl
Ab(s)	Antibody(ies)
ADA(s)	Antidrug antibody(ies)
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE(s)	Adverse event(s) (see definition in Section 6.1)
AESI(s)	Adverse event(s) of special interest (see definition in Section 6.3)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
$Apc^{Min/+}$	Adenomatous polyposis coli/multiple intestinal neoplasia
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
$AUC_{(0\text{-}12)}$	Area under the plasma concentration-time curve from zero to 12 hours
$AUC_{(0\text{-}48)}$	Area under the plasma concentration-time curve from zero to 48 hours
$AUC_{(0\text{-}t)}$	Area under the plasma concentration-time curve from zero to the time of the last measurable concentration
$AUC_{(0\text{-}\infty)}$	Area under the plasma concentration-time curve from zero to infinity
β-hCG	Beta human chorionic gonadotropin
BCRP	Breast cancer resistance protein
BID	Bis in die (i.e., twice daily)
BP	Blood pressure
CD	Cluster of differentiation
cEt	Constrained ethyl
cfDNA	Circulating-free deoxyribonucleic acid
CI	Confidence interval
CL	Clearance
CL/F	Apparent plasma clearance

Abbreviation or special term	**Explanation**
CLp	Plasma clearance
CL_{ss}/F	Apparent plasma clearance at steady state
C_{max}	Maximum plasma concentration
CR	Complete response
CRF	Case report form (electronic/paper)
CRM	Continual reassessment method
CSP	Clinical Study Protocol
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
CTLA4	Cytoxic T-lymphocyte-associated protein 4
C_{trough}	Concentration at the end of a dosing interval
CXCR2	CXC chemokine receptor-2
CYP	Cytochrome P450
D	Day
DCR	Disease control rate
DILI	Drug-induced liver injury
DLBCL	Diffuse large B-cell lymphoma
DLT(s)	Dose-limiting toxicity(ies)
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
ECL	Electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End-of-Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase

Abbreviation or special term	**Explanation**
gmean	Geometric mean
GRO-α	Growth regulated oncogene-alpha
h	Hour(s)
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCC	Hepatocellular carcinoma
HIV	Human immunodeficiency virus
HPF	High-power field
HL	Hy's Law
IATA	International Air Transport Association
IB	Investigator's Brochure
IBW	Ideal body weight
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC(s)	Independent Ethics Committee(s)
Ig	Immunoglobulin
IgG1κ	Immunoglobulin G1 kappa
ILD	interstitial lung disease
IM	Immunogenicity
imAE	Immune-mediated adverse events
IP	Investigational product
irAE	Immune-related adverse events
IRB(s)	Institutional Review Board(s)
IV	Intravenous(ly)
IWRS	Interactive web-based randomisation system
kg	Kilogram(s)
KM	Kaplan-Meier
L	Litre(s)
LDH	Lactate dehydrogenase
mAb(s)	Monoclonal antibody(ies)
MDSC(s)	Myeloid-derived suppressor cell(s)

Abbreviation or special term	**Explanation**
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute(s)
mL	Millilitre
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MRT_{last}	Mean residence time
MTD(s)	Maximum tolerated dose(s)
NC	Not calculated
NCI	National Cancer Institute
NE	Not evaluable
NTL	Nontarget lesion
OAE(s)	Other significant adverse event(s)
ORR	Objective response rate
OS	Overall survival
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)
PDRNA	Pharmacodynamic RNA
PFS	Progression-free survival
PHL	Potential Hy's Law
PK	Pharmacokinetic(s)
PO	Per os (i.e., by mouth)
PR	Partial response
PS	Performance status
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q4W	Every 4 weeks

Abbreviation or special term	**Explanation**
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 Tumors
RM	Recurrent and/or metastatic
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
SAE(s)	Serious adverse event(s) (see definition in Section 6.2)
SC	Subcutaneous
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
sPD-L1	Soluble programmed cell death-ligand 1
SRC	Safety Review Committee
STAT3	Signal Transducer and Activator of Transcription 3
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Concentration half-life
$t_{1/2}\lambda z$	Terminal (elimination) half-life
T3	Triiodothyronine
T4	Thyroxine
TBD	To be determined
TBL	Total bilirubin
TEAE(s)	Treatment-emergent adverse event(s)
TGI	Tumor growth inhibition
TL	Tumor lesion
T_{max}	Time to reach C_{max}
TMG	Toxicity Management Guidelines

Abbreviation or special term	**Explanation**
TSH	Thyroid-stimulating hormone
$T_{ss\ max}$	Time to reach C_{max} at steady state
Tx	Treatment
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/F	Apparent volume of distribution
WBC	White blood cell(s)
WBDC	Web-based data capture

1 INTRODUCTION

1.1 Background and rationale for conducting this study

Below are brief summaries introducing the properties of the investigational agents used in this CSP and their mechanism of action. Further details are provided in the respective Investigator's Brochures (IBs). This CSP was written based on the following IBs: 1) For AZD9150, the AZD9150 IB by AstraZeneca Pharmaceuticals, 2) for AZD5069, the AZD5069 IB by AstraZeneca "CXCR2 inhibition in oncology indications," and 3) for MEDI4736 and tremelimumab, the MEDI4736 and the tremelimumab IBs by MedImmune, LLC, a wholly owned subsidiary of AstraZeneca. When relevant, updates with data cut off dates more recent than those presented in the 4 IBs are provided and referenced.

1.1.1 AZD9150

AZD9150 (ISIS 481464) is a 16-nucleotide antisense oligonucleotide (16-mer ASO) designed to target down-regulate expression of human Signal Transducer and Activator of Transcription 3 (STAT3) messenger ribonucleic acid (mRNA).AZD9150 is a phosphorothioate-modified chimeric ASO, with a 10-base oligonucleotide centre that is flanked by 3 constrained ethyl (cEt)-modified nucleosides on both the 5′ and 3′ ends [Generation 2.5 ASO] (Seth et al 2009).

STAT3 belongs to the STAT family of transcription factors. STAT3 is considered to be a promising cancer drug target because of its pleiotropic involvement in tumorigenesis. STAT3 not only regulates the expression of many genes directly important to the survival of tumor cells (Alvarez et al 2005), but it is also an important factor in non-tumor cells of the tumor microenvironment involved in immune evasion of tumor cells, angiogenesis, and metastasis (Kortylewski et al 2009).

1.1.2 AZD5069

AZD5069 is a highly selective and potent small-molecule CXC chemokine receptor-2 (CXCR2) antagonist. CXCR2 is a G-protein coupled receptor expressed on a number of inflammatory cells (monocytes, macrophages, neutrophils) as well as epithelium that are believed to be critical in the pathogenesis of inflammation related disorders. CXCR2 can also be expressed on endothelium.

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

1.1.3 MEDI4736

MEDI4736 (durvalumab) is a human monoclonal antibody (mAb) of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of programmed cell death-ligand 1 (PD-L1) to PD-1 and cluster of differentiation (CD) 80 (B7-1). PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T cell activation through delivery of inhibitory signals (Fife and Bluestone 2008) and is one of the immunosuppressive mechanisms keeping the immune system from identifying and eliminating cancerous cells. In vivo studies show that MEDI4736 inhibits tumor growth in a xenograft model via a T cell dependent mechanism. Moreover, an anti-mouse (m)PD-L1 antibody demonstrated improved survival in a syngeneic tumor model when given as monotherapy and resulted in complete tumor regression in >50% of treated mice when given in combination with chemotherapy. Combination therapy (dual targeting of PD-L1 and cytotoxic T lymphocyte associated protein 4 [CTLA4]) resulted in tumor regression in a mouse model of colorectal cancer.

1.1.4 Tremelimumab

Tremelimumab (formerly CP-675,206) is a human IgG2 mAb being investigated as a cancer immunotherapeutic agent. Tremelimumab is expressed in NS0 (murine myeloma) cells and has an overall molecular weight of approximately 149 kDa. Tremelimumab is specific for human CTLA-4, with no cross-reactivity to related human proteins. Tremelimumab blocks the inhibitory effect of CTLA-4 and therefore enhances T cell activation. Tremelimumab shows minimal specific binding to Fc receptors, does not induce natural killer (NK) antibody-dependent cell-mediated cytotoxicity (ADCC), and does not deliver inhibitory signals following platelet-bound aggregation.

1.1.5 Disease background

Squamous cell carcinoma is the most frequent malignant tumor of the head and neck region and develops from the mucosal linings of the upper aerodigestive tract, comprising 1) the nasal cavity and paranasal sinuses; 2) the nasopharynx; 3) the hypopharynx, larynx, and trachea; and 4) the oral cavity and oropharynx. The American Cancer Society estimated 55,000 new cases of head and neck cancer would be diagnosed in the United States in 2014, with 12,000 patients dying from the disease (American Cancer Society 2014). Although the majority of patients present with loco regional disease, more than 50% will succumb to recurrent and/or metastatic (RM) disease despite aggressive therapy with surgery, radiation, and/or chemotherapy; 14% of patients present with distant disease at the time of diagnosis (Jemal et al 2010).

Despite progress in the therapeutic management of patients with squamous cell carcinoma of the head and neck (SCCHN), the mortality rate of patients presenting with advanced disease remains high. Recurrent or metastatic SCCHN is an incurable disease with a poor prognosis. Platinum-based combination chemotherapy has been the standard first-line treatment for RM-

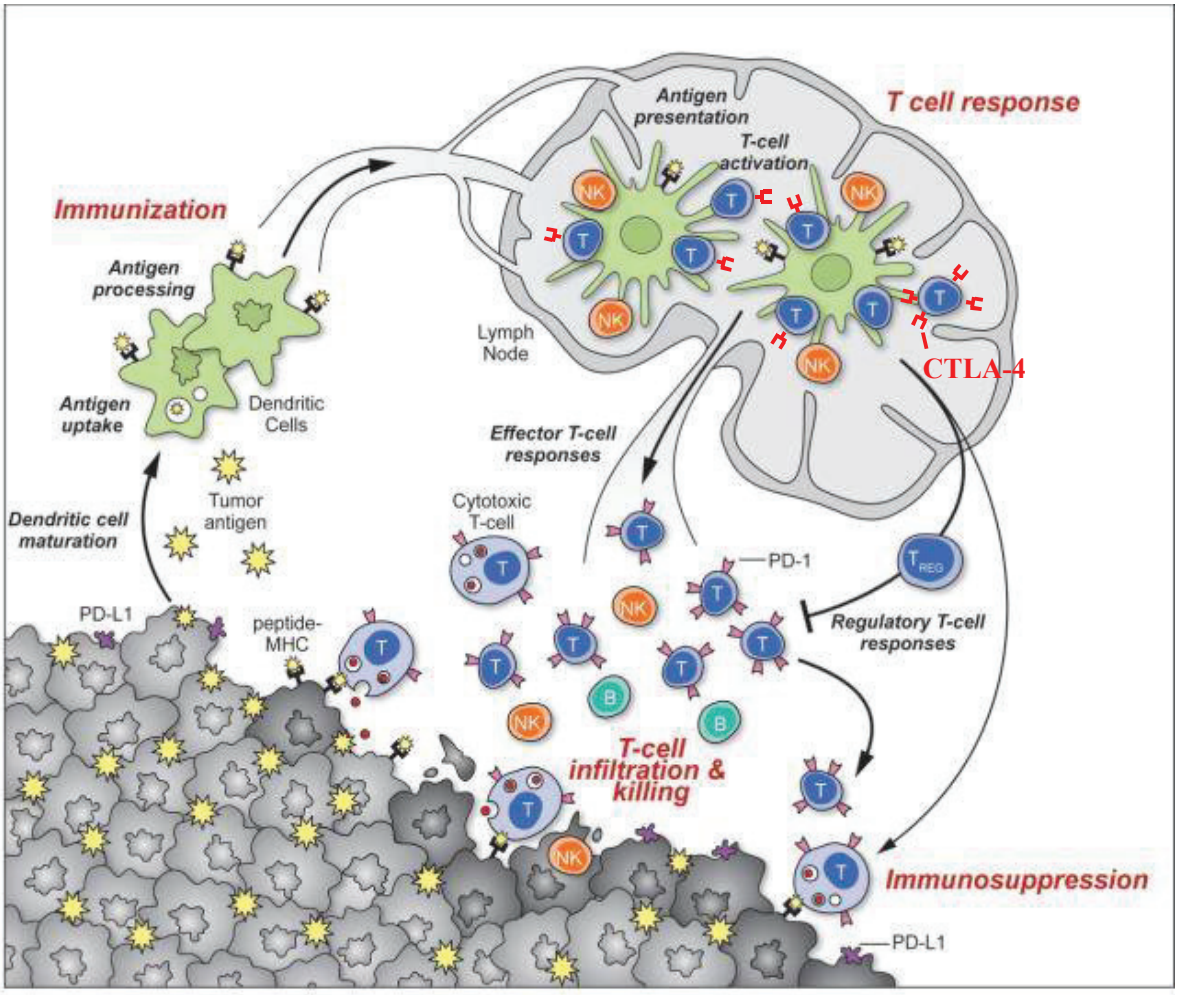
SCCHN, providing a median overall survival (OS) of 6 to 9 months (Forastiere et al 1992, Gibson et al 2005, Hussain et al 1999, Molin and Fayette 2011, Vermorken et al 2008). Since the EXTREME Phase 3 trial has shown the addition of the epidermal growth factor receptor inhibitor cetuximab (Erbitux) to a platinum doublet to be superior to chemotherapy alone (Vermorken et al 2008), cetuximab has become a key drug for first-line treatment of RM patients. The addition of cetuximab to cisplatin and 5-fluorouracil was associated with statistically significant improvements in all cancer control outcomes: response rate (36% versus 20%), progression-free survival (PFS) (5.6 months versus 3.3 months), and OS (10.1 months versus 7.4 months). However, the benefit is modest and comes at the expense of increased toxicity and cost. Further, virtually all patients who have a meaningful tumor regression on a cetuximab treatment regimen ultimately develop acquired tumor resistance after a few months of treatment.

In patients who have progressive disease (PD) while they are receiving platinum-based regimens, the projected median survival falls to approximately 3.5 months (León et al 2005). Active treatment options for patients with platinum-refractory RM-SCCHN include taxanes alone (Fayette et al 2010, Guardiola et al 2004), taxane- and vinorelbine-based regimens (Iop et al 1998, Moroni et al 2003, Numico and Merlano 2002), taxanes in combination with cetuximab (Hitt et al 2012, Péron et al 2012a), capecitabine (Martinez-Trufero et al 2010, Péron et al 2012b), or methotrexate (Forastiere et al 1992). Second-line treatments are often reserved for patients who have a good performance status (PS); many patients will receive only best supportive care. Because current treatment options are so limited, there is a clear need for new therapies for patients with RM-SCCHN.

1.2 Rationale for study design, doses and control groups

Activating the immune system for therapeutic benefit in cancer has long been a goal in immunology and oncology. Based on our current understanding of the immune response, one can identify 3 distinct steps that must be achieved, either spontaneously or therapeutically, in order to mount effective anti-tumor immunity (see Figure **1**, Mellman et al 2011) to initiate immunity, dendritic cells must sample antigens derived from the tumor, mature and differentiate, and ultimately process and present tumor antigens; 2) next, in lymphoid organs, tumor antigen-loaded dendritic cells must generate protective T cell responses; and 3) finally, cancer specific T cells must enter the tumor bed to perform their function. To do so, they have to overcome the challenge of stromal immune suppression. Targeting immunosuppression in the tumor bed provides novel opportunities for cancer therapy, in general and for tumors of the head and neck in particular. Myeloid-derived suppressor cells play a key immunosuppressive role in various types of cancer (Filipazzi et al 2007, Gabrilovich and Nagaraj 2009, Hoechst et al 2009) and are abundant in SCCHN (Chikamatsu et al 2012, Pak et al 1995, Vasquez-Dunddel et al 2013).

Figure 1 Generation and regulation of anti-tumor immunity



After Mellman et al 2011 and Luke et al 2015

It follows that combining a PD-L1 antagonist, MEDI4736, with an agent targeting immunosuppression in the tumor bed (either AZD9150 or AZD5069) is a complementary anti-tumor strategy, as the 2 immunotherapeutics attempt to restore effective anti-tumor immunity at 2 distinct stages: promoting the effector function of T cell responses (MEDI4736) while hindering immune escape in the tumor bed (AZD9150, AZD5069).

In addition to the PD-1 pathway described above, the CTLA-4 receptor for CD 80 and CD86 also plays a key role in the early activation of naïve and memory T cells. Because the PD-1 and CTLA-4 pathways are nonredundant modulators of immunocyte selection and survival that have individually shown to be important therapeutic targets, combination therapy with antibodies directed toward both is now being explored in a variety of tumor types.

The rationale for simultaneously combining anti-PD-L1 and anti-CTLA-4 treatment with either an inhibitor of STAT3 or of CXCR2 ("triplet" therapy) is identical to that described above for therapy with durvalumab alone in combination with either AZD9150 or AZD5069. Specific data considering the potential risks and benefits of triplet therapy are discussed below as well.

In the second part of this study, the recommended Phase 2 dose (RP2D) from the first phase will 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, a patient population with a currently unmet medical need. Both parts of this study will also evaluate PK, immunogenicity (IM), and pharmacodynamic parameters as well as biomarkers that may correlate with activity or prospectively identify patients likely to respond to the various treatments. The results from this study will form the basis for decisions for future studies.

The combination of MEDI4736 (or any other prior anti PD-(L)1 therapy) with either AZD9150 or AZD5069 has not been tested in humans; therefore, this study has been designed to evaluate the safety and tolerability of the combination in patients with advanced solid malignancies (other than hepatocellular carcinoma [HCC]) refractory to standard therapy or for which no standard of care regimen currently exists.

Approximately 25% of RM-SCCHN patients treated with an anti-PD-1 antibody (pembrolizumab) alone exhibit complete response (CR) or partial response (PR) (Seiwert et al 2015). This rate is at least comparable to the results of treatment with platinum- or taxane-based regimens, with significantly less toxicity than that observed with cytoreductive therapies. Furthermore, because 75% of patients treated with an anti-PD-1 antibody alone still exhibit disease progression, these patients will likely constitute a group with significant unmet medical need.

Since host anti-tumor immune responses depend upon a number of steps in addition to those directly controlled by T cell checkpoint molecules such as PD-1, agents that enhance antigen presenting cell function (AZD9150, by inhibiting STAT3) or prevent MDSCs from entering tumor tissue (AZD5069, by inhibiting CXCR2) may reasonably be expected to relieve a block to the generation and function of anti-tumor T cells.

Because release of this block may sensitise previously resistant tumors to CTL-mediated killing, 2 cohorts of patients whose disease previously progressed in the face of prior PD-1 pathway directed therapeutics alone will be included in this study. These patients will be treated with combinations of either MEDI4736 and AZD9150 or MEDI4736 and AZD5069.

Additionally, preliminary data from the KEYNOTE-012 trial (Seiwert et al 2015) showed that patients with RM-SCCHN sequentially failing different lines of therapy could respond to

PD-1 pathway blockade. Because 37.9% of the responding patients in that trial had previously been treated with 3 or more different lines of therapy, this trial will allow enrolment of patients who have failed 0 to 3 previous lines of therapy based on platinum compounds or other agents.

Further, because initial overall response rates to PD-1 pathway directed therapy are substantial, patients initially receiving either AZD5069 or AZD9150 (anti-CXCR2 or anti-STAT3 treatments, respectively) alone and who progress will be deemed eligible for the addition of MEDI4736 to their original therapeutic agent.

Rationale for adding first-line recurrent/metastatic SCCHN patients

Emerging response data from the AZD9150 and MEDI4736 combination of the D5660C00004 trial conducted to date suggests that treatment of first-line RM-SCCHN patients may benefit this population at a rate exceeding that observed to date for PD-1 pathway blockade alone.

- Response rates for patients treated to date in the D5660C00004 trial exceed those currently published for second line treatment of RM-SCCHN with anti-PD-1 pathway monotherapies with antibodies these include durvalumab (11%; Segal et al 2016), nivolumab (13.3%; NEJM 2016), and pembrolizumab (16%; Bauml et al 2017). By comparison, our currently observed confirmed response rate to date in the SCORES trial is 20% (4/20 subjects), plus one unconfirmed PR in a population of patients most directly comparable to those reported by Segal et al 2016.
- At the time of protocol amendment 5, activity in a limited number of first-line RM-SCCHN patients has been observed in the study. Because the CSP currently allows enrollment of first-line patients who refuse or are ineligible for platinum-based therapies. To date 6 such patients have been treated with MEDI4736+AZD9150: of note, 2 exhibited PR. This initial data, although limited, suggests this combination may impact disease in this population and clearly warrants further investigation.
- At the time of protocol amendment 5, the clinical course of a fifth RM-SCCHN patient on Study D5660C00004, Arm B3, receiving durvalumab+AZD9150 strongly suggests this patient responded to the combination as well. Sequential Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 target lesion reductions of 24% and 48% 6 weeks after beginning AZD9150 (six doses in total) and durvalumab (1 dose in total) were observed and persisted up to six months after initiation of treatment. Unfortunately, pneumonitis initially identified after 6 weeks of treatment required discontinuation of dosing and the patient subsequently developed additional non-target disease lesions, preventing formal confirmation by RECIST. These lesions were observed 16 weeks after last combination treatment with AZD9150 and MEDI4736.
- Further updated efficacy data for the combination of AZD9150 and MEDI4736 are presented in the latest IB.

In summary, appreciating the preliminary nature of findings from a group of 20 patients (14 in 2L and 6 in 1L RM setting) treated with MEDI4736+AZD9150 it is considered that the

observed data warrant vigorous further exploration in the first-line population, and this study amendment enables further study of the combination in these 2 populations.

Rationale for study design

A 2-part study design was initially chosen to allow for rapid transition from an initial dose-escalation in patients with advanced solid malignancies (Part A) determining the dose for further clinical exploration to a dose-expansion (Part B) investigating the anti-tumor activity of AZD9150 and AZD5069 alone or in combination with MEDI4736 as second-line treatment for patients with RM SCCHN. To minimise patient exposure during the dose-escalation phase, a continual reassessment method-based approach was used to devise the set of AZD9150/MEDI4736 and AZD5069/MEDI4736 dose combinations where the incidence of dose-limiting toxicity (DLT) is no larger than 33%. This approach tends to incur fewer toxic events and more accurately estimates the maximum tolerated dose (MTD) as compared to standard Phase 1 dose-escalation designs (Cheung 2011).

The starting doses and additional dose levels chosen for each agent in this study were based on the clinical experience with each agent as monotherapy in previous trials. Considering practical aspects for the combination of AZD9150 and MEDI4736, the infusion time for AZD9150 was shortened from 3 hours in previous studies to a 1-hour infusion. The change seemed appropriate as this study specifically evaluates safety and tolerability of AZD9150 in combination. The Safety Review Committee (SRC) will continue to monitor patients dosed with AZD9150 for any toxicities possibly associated with the shortened infusion time and may recommend to modify the length of infusion if any toxicities associated with maximum plasma concentration (C_{max}) are observed. The rationale for the starting dose of MEDI4736 in this study is described in detail in Section 1.1.3.

Additional combinations of MEDI4736 plus tremelimumab with either AZD9150 or with AZD5069 will similarly be investigated during Part A of the study. Because previous clinical trials have established recommended doses of tremelimumab and durvalumab in combination, a safety run-in initiated at that dose level with addition of either AZD9150 or AZD5069 will be carried out. The starting doses of AZD9150 or AZD5069 will be the RP2Ds established from dose escalations of each in combination with MEDI4736 alone in oncology patients. AZD5069, AZD9150, and durvalumab may be reduced by 1 or 2 levels during Part A of the trial, as shown in Figure 4, Figure 7, and Figure 8.

Because of the possibly greater complexity of interpreting safety data from Part A for triplet therapy, these triplets (AZD9150/durvalumab/tremelimumab or AZD5069/durvalumab/tremelimumab) will be explored only in Part A of the trial.

A Bayesian adaptive design approach for the dose-expansion Part B of the study has been employed to limit the exposure of patients to treatment arms that provide little clinical benefit.

As part of the clinical drug development program for AZD9150/AZD5069, AstraZeneca plans to include investigations into differences in pharmacodynamic and exploratory biomarker profiles and their relationship to drug effect. These biomarkers may be derived from deoxyribonucleic acid (DNA), ribonucleic acid (RNA), proteins, and/or metabolites. There are many potential benefits of this exploratory research, including the possibility to identify patients most likely to benefit from treatment, explain outliers or nonresponders, or explain adverse reactions related to drug exposure. This research may result in an understanding of the impact of variation between individuals and how it can be utilised to bring better drugs to the clinic. The ability to acquire appropriate consent to collect biological samples is important to establish an archive and allow future meta-analysis of data derived across studies with these agents.

Rationale for an AZD9150 flat dose (Arm B8)

A population pharmacokinetic (PK) model was developed for AZD9150 using PK data from 3 completed or ongoing Phase I/II studies (481464-CS1, D5660C00001 [NCT01839604], D5660C00004 [NCT02499328]) in patients with diffuse large B-cell lymphoma (DLBCL), HCC, and SCCHN, respectively. A total of 123 patients received AZD9150 doses ranging from 1 to 4 mg/kg from both monotherapy or in combination with durvalumab data, with most of them on 3 mg/kg (n=70). A 2-compartment model with linear absorption and linear elimination well described the data. Population PK analysis revealed ideal body weight (IBW) is not a significant covariate on the PK of AZD9150. The impact of an IBW-based dose at the R2PD AZD9150 dose of 3 mg/kg versus a flat dose of 200 mg was evaluated by comparing simulated steady state area under the curve (AUC) and C_{max} using the population PK model. A total of 1000 patients for each dosing regimen were simulated using body weight distribution of 30 to 100 kg. Simulation results demonstrate that IBW-based and flat dosing regimens (3 mg/kg versus 200 mg) yield similar median steady state AUC and C_{max} with slightly less overall between-subject variability with the flat dosing regimen. Since a flat dosing approach is preferred by the prescribing community and there is lack of influence of body weight on PK, a flat dose of 200 mg will be used instead of 3 mg/kg.

Rationale for an AZD9150 alternate-week dosing schedule (Arm B8)

An alternate-week (every 2 weeks [Q2W]) dosing schedule for an intravenously delivered drug is expected to yield better patient adherence when compared to a weekly-dosing schedule.

In order to investigate the impact of AZD9150 dosing schedule on platelet response, a population PK-pharmacodynamic model was developed for AZD9150 using PK and platelet data from 2 completed or ongoing Phase I/II studies (481464-CS1, D5660C00004 [NCT02499328]) in patients with DLBCL and SCCHN, respectively. Study D5660C00001 [NCT01839604] in HCC was not included in the analysis due to very different platelet profile (e.g., lower baseline platelet count) in this patient population compared to DLBCL and

SCCHN. A total of 87 patients received AZD9150 doses ranging from 1 to 4 mg/kg with 981 platelet data points were used in the modeling.

A 2-compartment model with linear absorption and linear elimination and an indirect response model well described the PK and platelet data. AZD9150 concentration from the effective compartment linked the PK and platelet response.

The PK-pharmacodynamic model revealed that none of the covariates (study, sex, baseline platelet count, age, IBW, and creatinine clearance) significantly impacted platelet response. The impact of dosing frequency was evaluated by comparing simulated incidence rate of grade 3 or higher of thrombocytopenia for 200 mg every week (QW) versus 400 mg every other week for 6 months after the same loading dose (200 mg on Days 1, 3, and 5 in Week 1). A total of 100 trials, each with 87 patients (reflecting characteristics of patients in Study D5660C00004) were simulated for each dosing schedule. Simulation results demonstrate that 200 mg QW resulted in a similar percentage of grade 3 or above thrombocytopenia at 400 mg every other week dosing.

Since a less frequent dosing schedule (every other week) is preferred by the prescribing community and the thrombocytopenia (Grade 3 or above) incidence rate is similar, an AZD9150 dose of 400 mg every other week was tested for safety/tolerability and PK in Part A Arm A 1 of study D5660C00016. Preliminary safety data from study D5660C0016 examining alternate weekly dosing of AZD9150 has revealed no DLTs and only mild thrombocytopenia occurring at approximately Week 5 of therapy. Based on this clinical safety and preliminary PK data, Arm B8 will evaluate 400 mg at an every other week schedule in first-line RM-SCCHN patients.

1.3 Benefit/risk and ethical assessment

1.3.1 Potential benefits

Patients with advanced solid tumors refractory to standard treatment or for which no standard therapy exists represent a patient population with unmet medical needs. In the case of patients with RM-SCCHN, an incurable disease with a poor prognosis, second-line treatments are often reserved for patients who have a good PS, and many patients will receive only best supportive care. Because current treatment options are so limited, there is a clear need for new therapies for patients with RM-SCCHN.

MEDI4736, a human mAb directed against human PD-L1, may offer benefit to this patient population. MEDI4736 has a high affinity for human PD-L1 and is able to completely block the interaction of recombinant human PD-L1 with both recombinant human PD-1 and recombinant human CD80 in a biochemical assay. In vitro, MEDI4736 enhances the proliferation and activation of primary human T cells cultured in the presence of recombinant PD-L1. Non-clinical studies demonstrate that MEDI4736 inhibits tumor growth in mouse

xenograft models. This activity is shown to be dependent upon the presence of human T cells, supporting the hypothesis that PD-L1 blockade can enhance anti-tumor immune response. An early clinical efficacy signal observed in the SCCHN dose-expansion cohort in Study CD ON MEDI4736-1108 strongly suggests that further exploration of the clinical activity of MEDI4736 in SCCHN is warranted.

AZD9150 has also shown signs of clinical activity in early clinical studies. The clinical activity of AZD9150 in patients with third-line DLBCL as evidenced by an overall response rate of 9% was remarkable although deemed insufficient for further clinical development as a monotherapy in this disease.

AZD5069 has not been tested in an oncology indication. However, MDSCs have been hypothesised to play an important role in the tumor microenvironment, potentially down regulating host immune responses to malignancies as well as affecting tumor cell senescence. Because CXCR2 signalling has been shown to affect myeloid cell traffic from the marrow and transit from the circulation into tissues, strong antagonism to this chemokine receptor may favourably affect host cell immune responses to tumors of different histological types. Modest reductions in the numbers of peripheral blood neutrophils are to be expected and may actually prove to reflect dosing of AZD5069 at levels adequate to reduce intratumoral MDSCs and tumor-associated neutrophils.

During the review of data with data cut-off date of 10 January 2019, a total of 428 patients have been exposed to AZD9150 in AstraZeneca-sponsored studies. The safety profile and benefit risk was acceptable and warrants the continuation of studies. No new risks have been identified during the review of data with data cut-off date of 10 January 2019. The safety profile of AZD9150 is maintained even when administered in combination with MEDI4736 (durvalumab) in the clinical trials of patients with advanced solid malignancies, recurrent and/or metastatic SCCHN, relapsed or refractory DLBCL.

Combining a PD-L1 antagonist, MEDI4736, with an agent targeting immunosuppression in the tumor bed (either AZD9150 or AZD5069) is a complementary anti-tumor strategy, as the 2 immunotherapeutics attempt to restore effective anti-tumor immunity at 2 distinct stages: promoting the effector function of T cell responses (MEDI4736) while hindering immune combination therapy with antibodies directed toward both the PD-1 and CTLA-4 pathways is now being explored in a variety of tumor types. For example, in melanoma, (Larkin et al 2015) have recently demonstrated overall response rates to a combination of nivolumab (anti-PD-1) plus ipilimumab (anti-CTLA-4) that significantly exceed (57.6%) the response rates observed in comparable patients treated with nivolumab (43.7%) or ipilimumab (19.0%) as monotherapies. Similar trials with other agents have been proposed or are underway in SCCHN (Swanson et al 2015).

The combination of MEDI4736 (or any other prior anti-PD-(L)1 therapy) with either AZD5069 has not been tested in humans, nor have the combinations of AZD5069/durvalumab/tremelimumab or AZD9150/durvalumab/tremelimumab. Therefore, this study has been designed to evaluate the safety and tolerability of each combination. The starting doses and additional dose levels chosen for each agent in this study are based on the clinical experience with each agent as monotherapy or in combination during previous trials; the selected starting doses for this study are within the range that is predicted to provide biological activity based upon prior clinical experience.

1.3.2 Potential risks

Risks with durvalumab include, but are not limited to, diarrhoea, colitis and intestinal perforation/large intestine perforation, pneumonitis/interstitial lung disease (ILD), endocrinopathies (hypo- and hyper-thyroidism, blood thyroid stimulating hormone (TSH) increased, blood TSH decreased, type I diabetes mellitus, diabetes insipidus, hypophysitis/hypopituitarism, and adrenal insufficiency), hepatitis/hepatotoxicity/increases in transaminases, amylase and lipase increases, neurotoxicities, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/pruritus/dermatitis, myocarditis, myositis/polymyositis, other rare or less frequent inflammatory events including neurotoxicities, infusion-related reactions, anaphylaxis, hypersensitivity or allergic reactions, pemphigoid, and infections/immune complex disease and serious infections.

For information on all the identified and potential risks with durvalumab always refer to the current edition of the durvalumab IB.

In monotherapy clinical studies, AEs (all grades) very commonly (≥ 10% of patients) reported are fatigue, nausea, decreased appetite, dyspnoea, cough, constipation, diarrhoea, vomiting, back pain, pyrexia, abdominal pain, asthenia, anaemia, arthralgia, peripheral oedema, headache, rash, and pruritus. Approximately 98% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 6% of patients experienced a serious AE (SAE) that was considered to be related to durvalumab by the study Investigator.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity with the Dosing Modification and Toxicity Management Guidelines in Annex 1.

A detailed summary of durvalumab monotherapy AE data can be found in the current edition of the durvalumab IB.

For AZD9150, liver enzyme elevation (aspartate aminotransferase [AST]/alanine aminotransferase [ALT]) is an important identified risk, especially in the liver compromised HCC patient population, which has been excluded from this study. Thrombocytopenia is also

an important identified risk. Reduced haemoglobin/anaemia and reduced absolute neutrophil count/neutropenia are important potential risks. When AZD9150 is given in combination with durvalumab, there is a potential for increased frequency and/or magnitude of liver enzymes (since AST/ALT increase is an identified overlapping adverse drug reaction for both drugs; referred to as increased frequency of immune reactions in combination with durvalumab). Risks associated with other combination drugs in recently initiated studies, or studies in course of being initiated (including for example acalabrutinib, or different chemotherapy agents) are yet unknown. For a complete characterisation of each risk, see Section 6 of the IB for AZD9150, Summary of data and guidance for the Investigators.

Effects on blood neutrophils, including reduction in their number (neutropenia) is an identified risk with AZD5069. These effects have been observed at mild levels in healthy volunteers' studies. Across all respiratory studies, now completed, events suggestive of this risk occurred at both mild, moderate, but also 1 severe occurrence (event that was considered serious by the Investigator). In the ongoing D5660C00004 oncology trial so far, although reductions in peripheral blood neutrophil counts have been observed, these have been reversible, not associated with significant clinical symptoms, and not considered serious by the Investigators. Therefore, for regulatory reporting purposes that consider seriousness, events suggestive of this risk are considered expected in patients treated in respiratory indications only, and not yet in the oncology population. Host defence (infections) is a potential risk for AZD5069. However, while reduction of neutrophils in peripheral blood or sputum could have an impact on host defense with regard to infections, previous studies with AZD5069 in healthy subjects and in patients with chronic obstructive pulmonary disease, bronchiectasis, and asthma did not show an increased rate of overall infections compared with placebo. For a complete list of potential risks and their characterisation, see Section 6 of the IB for AZD5069, Summary of data and guidance for the Investigators.

Risks with tremelimumab monotherapy include, but are not limited to, GI effects (colitis, diarrhoea, enterocolitis and intestinal perforation), endocrine disorders (hypo- and hyperthyroidism, hypophysitis and adrenal insufficiency), skin effects (rash and pruritus), elevations in lipase and amylase and clinical manifestations of pancreatitis, other gastrointestinal events (e.g., ulcerative colitis, dehydration, nausea, and vomiting); hepatic events including hepatitis, and liver enzyme elevations; pneumonitis and ILD; clinical manifestations of pancreatitis; nervous system events including encephalitis, peripheral motor and sensory neuropathies, Guillain-Barre and proximal muscle weakness; cytopenias including thrombocytopenia, anaemia and neutropenia; infusion-related reactions, anaphylaxis, and allergic reactions; renal events including renal failure, acute kidney injury, nephritis, nephrotic syndrome, autoimmune nephritis and electrolyte abnormalities such as hypokalaemia; autoimmune diseases including autoimmune arthritis, Sjögren's syndrome and giant cell temporal arteritis; hyperglycaemia and diabetes mellitus; and pyrexia.

For information on all the identified and potential risks with tremelimumab always refer to the current edition of the tremelimumab IB.

Using pooled data from monotherapy clinical studies AEs (all grades) reported very commonly (≥10% of patients) were diarrhoea, nausea, fatigue, pruritus, decreased appetite, rash, vomiting, dyspnoea, constipation, cough, pyrexia, abdominal pain, decreased weight, headache, asthenia, and anaemia. Approximately 16% of patients experienced an AE that resulted in permanent discontinuation of tremelimumab and approximately 45% of patients experienced an SAE.

A detailed summary of tremelimumab monotherapy AE data can also be found in the current edition of the tremelimumab IB. The safety of durvalumab+tremelimumab combination therapy was initially evaluated in the ongoing dose-escalation and dose-expansion Study 006, in patients with non-small cell lung cancer. It is being studied in a number of other ongoing clinical trials as well as, in a number of different indications, and has to date shown a manageable safety and tolerability profile.

The types of potential risks with the combination of durvalumab+tremelimumab (based on an equivalent durvalumab dose of 20mg/kg and a tremelimumab dose of 1mg/kg) are similar to those for durvalumab and tremelimumab monotherapy. Emerging data from study 006, other studies evaluating the combination, and from combinations of other agents in the same class indicate an increased frequency and/or severity of some of these potential immune-mediated toxicities.

For information on all identified and potential risks with the durvalumab+tremelimumab combination always refer to the current edition of the durvalumab IB.

In durvalumab+tremelimumab combination studies at the dose of durvalumab 20mg/kg and tremelimumab 1mg/kg AEs (all grades) reported very commonly (≥10% of patients) are fatigue, diarrhoea, nausea, dyspnea, decreased appetite, pruritus, vomiting, anaemia, constipation, cough, abdominal pain, pyrexia, back pain, arthralgia, hypothyroidism, asthenia, oedema peripheral, weight, decreased hyponatraemia, and rash.

Approximately 15% of patients experienced an AE that resulted in permanent discontinuation of study drug and approximately 15% of patients experienced an SAE that was considered to be related to durvalumab and tremelimumab by the study Investigator.

A detailed summary of durvalumab + tremelimumab combination AE data can be found in the current edition of the durvalumab IB. There is a potential for increase in severity and frequency of AST and ALT increase when MEDI4736/tremelimumab is given in combination with AZD9150. There is no additional risk of increase in myelosuppressive adverse events (AEs) observed with either AZD9150 or AZD5069 when given in combination with

MEDI4736 in dose escalation. Hence, patients will be closely monitored for all irAEs, liver toxicities, and myelosuppression in the current study.

In summary, the risks of combined CTLA-4 and PD-(L)1 inhibition have been partly characterized and deemed tolerable in patients with several tumor types (Larkin et al 2015, Antonia et al 2014). While the rates of AEs leading to discontinuation of study drugs in combination are significant (e.g., 7.7% for nivolumab alone, 14.8% for ipilimumab alone, or 36.4% for the combination for patients with previously untreated advanced melanoma; Larkin et al 2015), the nature of the adverse effects are consistent with the profiles for individual agents and are reversible at rates of 85-100% for most organ systems excepting the endocrine.

Bleeding has been reported in up to 10% or greater in patients with head and neck cancer. Reports of bleeding, including fatal reports, have been received from head and neck cancer patients enrolled in AstraZeneca clinical trials with durvalumab as monotherapy or in combination. While it is not yet conclusively known whether the risk of bleeding would be higher or lower with the experimental treatment than with standard chemotherapy, an interim internal safety analysis conducted by the Sponsor concluded that a reasonable possibility of a causal relationship between bleeding complications in SCCHN patients and treatment with durvalumab, either alone or in combination with tremelimumab, could not be established. Given the minimal toxicity profiles of PD-1/CTLA-4 inhibition and either STAT3 blockade or CXCR2 blockade, the potential benefit of combining 2 T cell checkpoint inhibitors (durvalumab, anti-PD-L1 and tremelimumab, anti CTLA-4) with either AZD5069 or AZD9150 can reasonably be regarded as offering the possibility of enhanced anti-tumor effects with a manageable rate of AEs in very difficult- to-treat patients who have failed previous lines of therapy in a variety of tumors.

1.3.3 Overall benefit-risk and ethical assessment

The combination of MEDI4736 and/or MEDI4736/ tremelimumab (or any other prior anti-PD-(L)1 therapy) with either AZD9150 or AZD5069 has not been tested in humans; therefore, this study has been designed to evaluate the safety and tolerability in patients treated with this combination. The study design aims to minimise potential risks and, although the potential benefits in patients are unknown at this time, prior early clinical signs, and non-clinical data provide a sound basis supporting the hypothesis that combining a PD-L1 antagonist, MEDI4736 (and/or CTL4 inhibitor, tremelimumab), with an agent targeting immunosuppression in the tumor bed (either AZD9150 or AZD5069) is a complementary anti-tumor strategy. Thus, the benefit/risk assessment for this Phase 1b/2 study is anticipated to be favourable based on the lack of effective alternative treatments, the limited life expectancy due to malignant disease, and the strength of the scientific hypothesis under evaluation.

1.4 Study Design

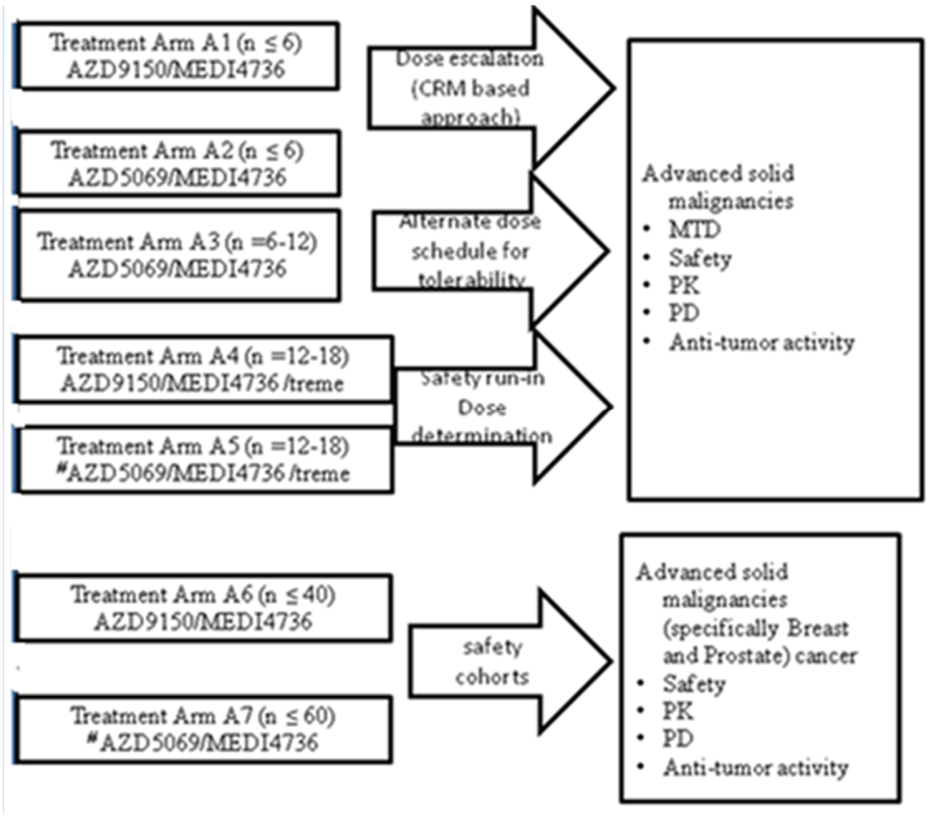
This multicentre, open-label, Phase 1b/2 study is designed as a 2 part study consisting of dose-escalation and safety cohorts in Part A and a dose-expansion in Part B. A study flow chart for both phases is presented in Figure 2, and a study scheme for both phases is shown in Figure 3.

Patients will be allocated to treatment in both parts of the study after first considering their history, and any anticipated need to use herbal supplements and/or foods prohibited with concurrent administration of AZD5069. During Part B only, the patient's history of exposure to anti-PD-(L)1 antibodies and prior treatment received for recurrent metastatic disease will also determine their eligibility to be enrolled in specific treatment arms.

Figure 2 Study flow chart

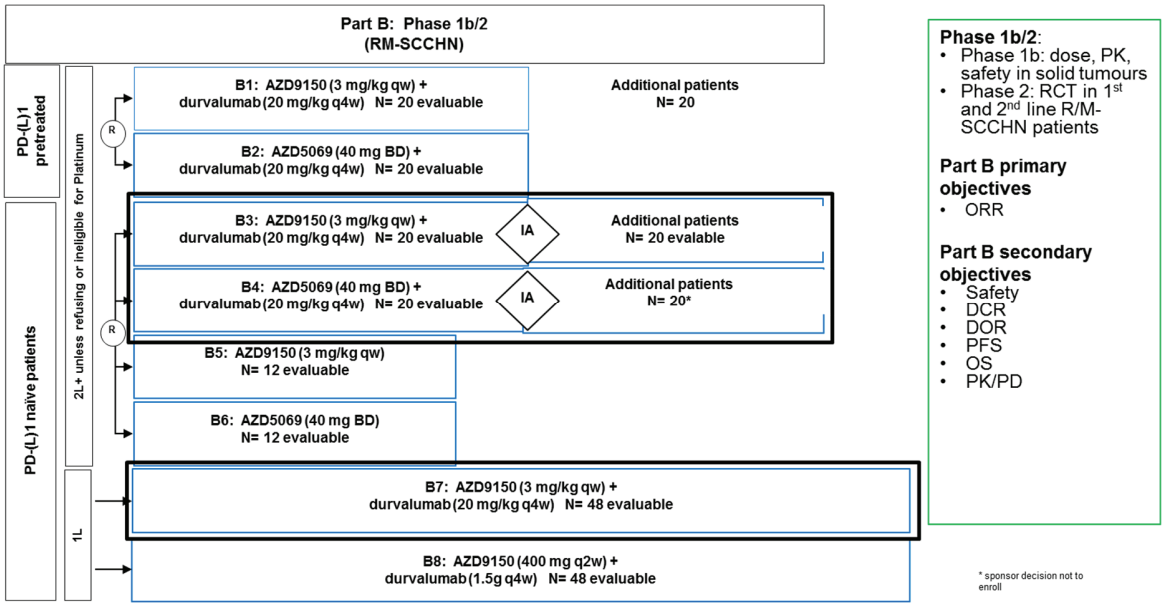
Part A: Dose-escalation & Safety Cohorts

Patients with advanced solid malignancies refractory to standard therapy or for which no standard of care regimen currently exists.



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

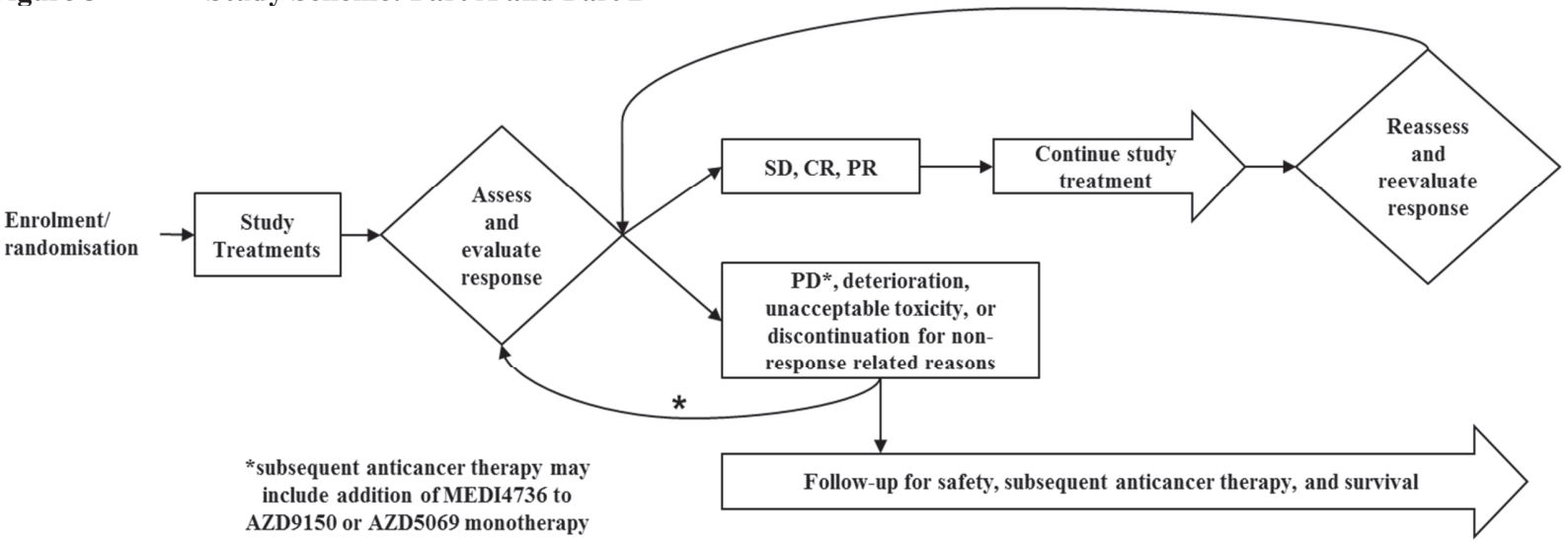
Part B: Dose-Expansion



Abbreviations: CRM=continual reassessment method; DCR=disease control rate; DOR=duration of response; IA=interim analysis; MTD=maximum tolerated dose; OS=overall survival; PD-(L)1=Programmed cell death 1 (CD279) and/or programmed cell death-ligand 1 (also known as B7 homolog 1, CD274); PFS=progression-free survival; PK/PD=pharmacokinetics/pharmacodynamics; SRC=Safety Review Committee; SCCHN=squamous cell carcinoma of the head and neck.

Note: Treatment arms B1, B2, B3, B4, B5, B6, B7, and B8 are closed to enrolment.

Figure 3 Study Scheme: Part A and Part B



[a] Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.

2 STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	**Outcome Measure:**
Dose-escalation and safety cohorts Part A To determine the 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 in patients with advanced solid malignancies refractory to standard therapy or for which no standard of care regimen currently exists.	MTD based on patients who completed the DLT Evaluation AEs, SAEs, laboratory evaluations, vital signs, and physical examinations Treatment-emergent AEs (TEAEs), SAEs and death(s), graded in accordance with National Cancer Institute (NCI) CTCAE version 4.03
Dose-expansion Part B To evaluate the 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 recurrent or metastatic SCCHN (1L RM SCCHN). To evaluate ORR of AZD9150 as 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).	Objective response - defined as a CR or PR according to RECIST version 1.1

2.2 Secondary objectives

Secondary Objective:	**Outcome Measure:**
Dose-escalation and safety cohorts Part A	
To assess the PK of AZD9150, AZD5069, and MEDI4736 and/or MEDI4736/tremelimumab in the selected dose combinations.	PK parameters as outlined in Section 8.5
To determine the IM of MEDI4736 and/or MEDI4736/tremelimumab in combination with AZD9150 or AZD5069 and the IM of AZD9150 in combination with MEDI4736 and/or MEDI4736/tremelimumab.	ADAs
To assess pharmacodynamic response in blood for AZD9150.	STAT3 knockdown (signal transducer and activator of transcription 3 [STAT3] knockdown)

Dose-expansion Part B	
To assess secondary measures of efficacy (DCR at 12 weeks; duration of overall response [DOR], PFS, OS; and proportion of patients alive at 12 months)	Disease control defined as a CR, PR, or stable disease (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 documented (taking as reference for PD the smallest measurements recorded on study) PFS - defined as the time from randomisation 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 randomisation to death from any cause Best overall response (including CR, PR, SD, and PD, according to RECIST version 1.1 criteria), ordered from best to worst Survival at 12 months
To assess the PK of AZD9150 and AZD5069 both as monotherapy and in combination with MEDI4736	PK parameters as outlined in Section 8.5
To assess the urinary PK of AZD9150 and MEDI4736 in combination with AZD9150 or AZD5069	PK parameters as outlined in Section 8.5
To determine the IM of AZD9150 alone or in combination with MEDI4736 and the IM of MEDI4736 in combination with AZD9150 or AZD5069	ADAs
To assess pharmacodynamic response in blood for AZD9150 and MEDI4736 (sPD-L1 will not be evaluated for Arms B1, B2, and B4 post the first 20 patients and for Arms B7 and B8)	(STAT3 knockdown) and sPD-L1 in blood Pharmacodynamics of MEDI4736 (sPD-L1) and tremelimumab (will not be evaluated for Arm B1, B2, and B4 post the first 20 patients and for Arm B7 and B8)
To assess tumor cell pharmacodynamics (STAT3 knockdown)	Pharmacodynamics of AZD9150 (STAT3 knockdown) in tumor tissue
To assess baseline circulating MDSCs 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)	Circulating MDSCs
To evaluate baseline tumor PD-L1 expression for potential correlation with drug activity or the ability to prospectively identify patients likely to respond to treatment	Tumor PD-L1 expression

2.3 Safety objectives

Safety Objective:	**Outcome Measure:**
Dose-expansion Part B To evaluate the safety and tolerability of AZD9150 and AZD5069 both as monotherapy and in combination with MEDI4736.	AEs, SAEs, laboratory evaluations, vital signs, and physical examinations TEAEs, SAEs, and death, graded in accordance with NCI CTCAE version 4.03

2.4 Exploratory objectives

Exploratory Objective:	**Outcome Measure :**
Dose-escalation (Part A) and Dose-expansion (Part B)	
To evaluate baseline levels of and changes in blood-borne biomarkers that may correlate with treatment or clinical response.	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 and other soluble factors
To assess serum samples for pharmacodynamic response to AZD5069.	Transient increase in CXCR2 ligands interleukin-8 and GRO-α
To evaluate tumor-based biomarkers in archival/baseline tumor 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/tremelimumab.	These may include but are not limited to PD-L1 expression, phospho- or total STAT3 expression, tumor genetics, immunogenomics (genetics associated with immune responses such as homozygosity/heterozygosity of MHC-I genes), characterisation of immune infiltrates, gene expression, or other stratification markers
To evaluate circulating-free DNA (cfDNA; including circulating tumor DNA as well as non-tumor 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]).	For tumor-derived DNA mutations at baseline, and changes upon treatment that may correlate with treatment or response
To collect and store tumor, blood, plasma, and serum samples or analyse surplus blood or tissue including patient-specific archival tumor tissue, if available.	For potential future exploratory research into factors that may influence development of the tumor or response to treatment (where response is defined broadly to include efficacy, tolerability, or safety). In the event that additional tumor molecular profiling is required to understand further any response to treatment, AstraZeneca may request a sample of the most recent tumor biopsy for additional research. Any sample collection can be discontinued or suspended at the discretion of the Sponsor, without the need for a protocol amendment.

To explore the relationship between PK and selected endpoints.	Which may include pharmacodynamics, efficacy, and/or safety), where deemed appropriate
To collect and store DNA.	Carry out 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/tremelimumab) and/or development of cancer
Part B Only	
To evaluate changes in tumor based biomarkers that may correlate to treatment or response	Changes including but not limited to immune cell infiltrate, gene expression changes, cell activation or proliferation markers, and cytokines

3 SUBJECT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

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

3.1 Inclusion criteria

3.1.1 All patients

For inclusion in the study subjects should fulfil the following criteria:

1. The patient or legal representative (legal representative not permitted to consent in Germany) must be able to read and understand the Informed Consent Form (ICF) and must have been willing to give written informed consent and any locally required authorisation (e.g., Health Insurance Portability and Accountability Act in the United States; European Union Data Privacy Directive in the European Union) before any study-specific procedures, including screening evaluations, sampling, and analyses.
2. For inclusion in the optional genetic research, patients must provide a separate ICF for genetic research.
3. Male and female patients must be at least 18 years of age
4. Has an Eastern Cooperative Oncology Group (ECOG) PS score of 0 or 1.
5. Has measurable disease, defined as at least 1 lesion that can be accurately measured in at least 1 dimension (longest diameter to be recorded) with a minimum size of 10 mm by computerised tomography (CT) scan, except lymph nodes, which must have minimum short axis size of 15 mm (CT scan slice thickness no greater than 5 mm in both cases). Indicator lesions must not have been previously treated with surgery, radiation therapy, or radiofrequency ablation unless there is documented progression after therapy.
6. Number of prior lines of treatment by Arm:

Arms A1 to A4 and A6: Has undergone ≤3 previous regimens of cytoreductive chemo-therapies including, but not limited to, platinum-based compounds, taxanes, or 5-fluorouracil.

Arms B1 to B6: Has undergone 1-3 previous regimens of cytoreductive chemo-therapies including, but not limited to, platinum-based compounds, taxanes, or 5-fluorouracil

Arm B3: Has undergone at least 1 previous regimen of systemic chemotherapy and received up to 3 previous regimens of cytoreductive treatments in the recurrent metastatic disease setting. If a patient has received systemic chemotherapy for local disease only, they would not be considered eligible for Arm B3.

Arms B7 and B8: Has not received any previous systemic therapies for recurrent metastatic disease, nor had prior exposure to anti-PD-(L)1 therapies. Patients who have received chemotherapy for local disease may be considered for eligibility to Arms B7 and B8.

7. Has adequate organ and marrow function as defined below. Transfusions intended to elevate any parameters below solely for the intent of meeting study eligibility are not permitted.
    - Leukocytes ≥3000 mcL
    - Absolute neutrophil count ≥1500 mcL
    - Platelets ≥100 000 mcL
    - Haemoglobin ≥9 g/dL
    - Total bilirubin (TBL) ≤1.5 x upper limit of normal (ULN); TBL ≤3 × ULN in patients with documented Gilbert's Syndrome (unconjugated hyperbilirubinaemia) or in the presence of liver metastases
    - ALT and AST ≤2.5 × ULN if no demonstrable liver metastases or ≤5 × ULN in the presence of liver metastases
    - Creatinine within normal limits
      OR, for patients with levels above institutional normal:
        - Creatinine clearance measured by 24-hour urine collection ≥60 mL/min,
          OR
        - Calculated corrected creatinine clearance ≥60 mL/min/1.73 m^2 using the Cockcroft-Gault formula (Cockcroft and Gault 1976) (see Section 8.4).
8. Women of childbearing potential and men who are sexually active with a female partner of childbearing potential must be surgically sterilised, practicing abstinence, or agree to

use 2 birth control methods before study entry, for the duration of study participation, and for 20 weeks after the final dose of study drug (180 days after final dose if patients enrolled in Arm A4); cessation of birth control after this point should be discussed with a responsible physician.

Women of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause). Section 3.8.1 and Table 1 lists the methods of contraception considered adequate; note that 2 methods must be combined. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

9. Women of childbearing potential also may not be breast feeding and must have a negative serum or urine pregnancy test within 72 hours before the start of study treatment.
10. The patient or legal representative (legal representative not permitted to consent in Germany) must be willing to provide written consent for collection of formalin fixed paraffin-embedded blocks or slides from archival diagnostic histology samples, where available.

3.1.2 Additional inclusion criteria Dose-escalation and safety cohorts Part A

1. Has a histological confirmation of a solid malignancy (other than HCC) that is refractory to standard therapy or for which no standard of care regimen currently exists.

3.1.3 Additional inclusion criteria Arm A6 of Part A

1. Has a histological confirmation of castrate-resistant prostate cancer.

3.1.4 Additional inclusion criteria-Dose-expansion Part B

For inclusion into the dose-expansion Part B of the study, each patient must fulfil all of the criteria listed in Section 3.1.1 as well as the following conditions:

1. Has histologically and/or cytologically confirmed SCCHN that is RM and not amenable to curative therapy by surgery or radiation. Squamous cell carcinoma of the head and neck originating from the following sites is eligible: oral cavity, oropharynx, larynx, or hypopharynx.
   Not eligible are:
   - Patients with squamous cell carcinoma of any other primary anatomic location in the head and neck (e.g., paranasal cavity)
   - Patients with squamous cell carcinoma of unknown primary
   - Patients with nonsquamous histologies of head and neck tumors

2. Has at least 1 SCCHN tumor lesion (TL) 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 PD, biopsies at the End-of-Treatment [EOT] are optional but encouraged.) Tumor lesions used for biopsy should not be lesions used as RECIST TLs, unless there are no other lesions suitable for biopsy. If a RECIST TL is used for biopsy, the lesion must be ≥2 cm in longest diameter.
3. For patients in Arm B1-B6, patients must have failed 1 prior platinum-based chemotherapy for RM-SCCHN.
4. Patients in Arms B7 and B8 should have received no prior anti-PD-(L)1 therapies nor systemic treatment for RM SCCHN.

3.1.5 Additional inclusion criteria - Dose-expansion Part B: treatment arms B1 and B2

1. Has had prior exposure to any anti-PD-(L)1 antibody.

3.2 Exclusion criteria

3.2.1 All patients

A patient must not enter either part of the study if any of the following exclusion criteria are fulfilled:

1. Has a spinal cord compression unless asymptomatic and not requiring steroids for at least 4 weeks before the start of study treatment.
2. Presently has a second malignancy other than SCCHN, or history of treatment for invasive cancer other than SCCHN in the past 3 years. Exceptions are:
   - Previously treated in-situ carcinoma (i.e., noninvasive)
   - Cervical carcinoma stage 1B or less
   - Noninvasive basal cell and squamous cell skin carcinoma
   - Radically treated prostate cancer (prostatectomy or radiotherapy) with normal prostate-specific antigen, and not requiring ongoing antiandrogen hormonal therapy
3. Patients must have completed any previous cancer-related treatments before enrolment. Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer excludes the patient (concurrent use of hormones for noncancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable). The following intervals between the end of the prior treatment and first dose of study drug must be observed:
   - Port-a-cath placement: No waiting is required.

- Minor surgical procedures (as defined by the Investigator): ≥7 postoperative days
- Major surgery (as defined by the Investigator): ≥4 weeks
- Ongoing therapy at a stable dose greater than 2 months duration prior to enrolment and directed to maintaining a stable hormonal milieu (e.g., Lupron in prostate cancer patients) is allowed.
- Radiotherapy: ≥4 weeks (patients who receive palliative radiation for non-target tumor lesions need not be subjected to this washout period and can be enrolled immediately)
- Chemotherapy: within 21 days or 5 half-lives (whichever is shorter) from enrolment
- Immunotherapy and/or investigational anticancer therapy with agents including mAbs: ≥4 weeks (with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent)

4. Is still experiencing toxicity related to prior treatment and assessed as CTCAE grade >1. Exceptions are alopecia and/or anorexia. The eligibility of patients who are still experiencing irreversible toxicity that is not reasonably expected to be exacerbated by the study drugs in this study (e.g., hearing loss) must be reviewed and approved by both the Principal Investigator and Medical Monitor.
5. Has experienced immune-related AEs (irAEs) while receiving prior immunotherapy (including anti-CTLA4 treatment) and assessed as CTCAE grade ≥3
6. Has active or prior documented autoimmune disease within the past 2 years with the exceptions of vitiligo, Grave's disease, and/or psoriasis not requiring systemic treatment
7. Has active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)
8. Has a history of primary immunodeficiency
9. Has undergone an organ transplant that requires use of immunosuppressive treatment
10. Has any of the following cardiac criteria:
    - Any abnormalities in rhythm, conduction or morphology of resting 12-lead ECG that in the opinion of the Investigator render the patient unsuitable for participation in the study
    - Mean resting corrected QT interval (QTc) calculated using Fridericia's formula (QTcF) >450 msec for males and >470 msec for females according to local assessment and obtained from 3 ECGs within 5 minutes (exception: patients stable on pacemaker with higher QTc).

- Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, any concomitant medication known to prolong the QT interval, or family history of long QT syndrome, or unexplained sudden death under 40 years of age

11. Is unable to take oral medications and/or has a clinical or radiological diagnosis of bowel obstruction. Patient may not have a percutaneous endoscopic gastrostomy tube and may not be receiving total parenteral nutrition. (only applicable for patients enrolled on the oral pill arms)
12. Has a history of allergic reactions attributed to the study treatments (AZD9150, AZD5069, tremelimumab [for Part A, Arm A4 only] or MEDI4736), their compounds, or agents of similar chemical or biologic composition (e.g., antibody therapeutics)
13. Suffers from a comorbidity that in the opinion of the Investigator renders the patient unsuitable for participation in the study. Such comorbidity may include, but is not limited to, uncontrolled intercurrent illness such as active infection, severe active peptic ulcer disease or gastritis, myocardial infarction within 6 months before entry, congestive heart failure, symptomatic congestive heart failure, active cardiomyopathy, unstable angina pectoris, cardiac arrhythmia, uncontrolled hypertension, or psychiatric illness/social situations that would limit compliance with study requirements.
14. As judged by the Investigator, has any evidence of severe or uncontrolled diseases such as active bleeding diatheses, or has an active viral infection for human immunodeficiency virus (HIV), hepatitis B virus (HBV), and/or hepatitis C virus (HCV)
15. Has a known history of tuberculosis
16. Has a condition that, in the opinion of the Investigator, would interfere with the evaluation of the study drugs or the interpretation of patient safety or study results
17. Has received a live attenuated vaccine within 30 days before the first dose of study drug
18. Judgement by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements

3.2.2 Additional exclusion criteria: Dose-escalation and safety cohorts Part A

1. Patients with clinically active brain metastases (known or suspected) are excluded unless the brain metastases have been previously treated and are considered stable. Stable brain metastases are defined as no change on CT scan or magnetic resonance imaging (MRI) scan for a minimum of 2 months AND no change in steroid dose for a minimum of 4 weeks, unless change due to intercurrent infection or other acute event.
2. Has had prior exposure to AZD9150, AZD5069, tremelimumab (only Arm A4), MEDI4736, or any other anti PD (L)1 antibody.

3.2.3 Additional exclusion criteria: Dose-expansion Part B

1. Patients with brain metastases (known or suspected) are excluded.

3.2.4 Additional exclusion criteria: Dose-expansion Part B: treatment arms B3, B4, B5, B6, B7, and B8

1. Has had prior exposure to AZD9150, AZD5069, MEDI4736, or any other anti PD (L)1 antibody.

3.2.5 Additional exclusion criteria: Optional genetic research

A patient must not be included in the optional genetic research if any of the following exclusion criteria are fulfilled.

1. Patients who have previously received an allogeneic bone marrow transplant are excluded from the optional genetic research.
2. Patients who have received nonleukocyte depleted whole blood transfusion(s) within 120 days before the date of the genetic sample collection are excluded from the optional genetic research.

3.3 Subject enrolment and screening

Each potential patient must provide informed consent before starting any study-specific procedures (see Appendix D of this CSP "Ethical and Regulatory Requirements"). All patients must sign the main ICF for this study. In addition, there are 2 separate optional ICFs:

- One optional ICF for:
    - Additional optional PK blood samples for first 10 patients in Part B of the study randomised to AZD5069 in combination with MEDI4736 (i.e., treatment arms B2 and B4) (on the first day of the Lead-in, Day -7 at 10 hours after the first morning dose of AZD5069 and on Day 1 of Cycle 2 at 10 hours after the first morning dose of AZD5069) (see Section 5.5.1)
    - Additional optional PK urine samples the first 12 patients in Arm B7, the first 12 patients in Arm B7, and mandatory consent for up to 12 patients (USA only) in Arm B8 (optional consent thereafter) (see Section 5.5.1)
    - Additonal optional consent for blood samples for cfDNA for patients enrolled prior to 10 May 2017
    - Additional optional consent for patients in Part B for an additional tumor biopsy for additional tumor molecular profiling research for patients who discontinue study treatment
- One optional ICF for:
    - Optional pharmacogenetic testing for all patients in Part A and Part B (see Section 5.8.2)

Investigator(s) should keep a record on the subject screening log of subjects who entered prestudy screening. Each patient must meet all of the inclusion criteria and none of the

exclusion criteria for this study at the time of allocation in Part A and randomisation in Part B of the study. Under no circumstances can there be exceptions to this rule.

The Investigator(s) will:

1. Obtain signed informed consent from the potential subject or legal representative before any study-specific procedures are performed.
2. Assign potential subject a unique enrolment number, beginning with 'E#'.
3. Determine subject eligibility. See Section 3.1 and 3.2.

If a subject withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused.

3.4 Procedures for handling incorrectly enrolled or randomized subjects

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

Where a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the Investigator regarding whether to continue or discontinue the subject from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

For Part A, eligible patients are to be allocated to treatment arms in parallel. The details of the enrolment in the arms are provided in Sections 4.1.1 and 4.1.2.

For Part B, eligible/evaluable patients are to be randomized to treatment arms via an interactive web-based randomisation system (IWRS) in a ratio specified to each arm, while the treatment Arms B7 and B8 are non-randomized arms. The details are provided in Sections 4.2.1 and 4.2.2.

3.6 Methods for ensuring blinding

Not applicable as this is an open-label study.

3.7 Methods for unblinding

Not applicable as this is an open-label study.

3.8 Restrictions

3.8.1 Birth control

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

- Female patients who are of childbearing potential (as defined in Section 4.1 above) must use highly effective methods of contraception from the time of screening until 20 weeks after the final dose of study drug (180 days after final dose if patients enrolled in Arm A4); cessation of birth control after this point should be discussed with a responsible physician.
- Acceptable highly effective methods of contraception include total sexual abstinence in line with the preferred and usual lifestyle choice of the patient, tubal ligation, vasectomised partner, and methods listed in Table 1.
- All highly effective methods of contraception (with the exception of total abstinence) must be used in combination with the use of a condom by their male sexual partner for intercourse. Periodic abstinence, the rhythm method, triphasic combined oral contraceptives, all progesterone only pills except, Cerazette™, all barrier methods, if intended to be used alone, non-copper containing intrauterine devices s, fertility awareness methods, and the withdrawal method (coitus interruptus) are not acceptable highly effective methods of birth control.
- Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

Table 1 Highly effective methods of contraception

Intrauterine Device Methods	Hormonal Methods
• Copper T • Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	Any registered and marketed contraceptive agent that contains an oestrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents) such as • Medroxyprogesterone injections (Depo-Provera®) • Etonogestrel implants (e.g., Implanon, Norplant) • Hormone shot or injection • Normal and low dose combined oral pills • Norelgestromin ethinyl estradiol transdermal system

[a] This is also considered a hormonal method.

- Male patients must be asked to avoid unprotected sex with all sexual partners but use condoms during the study, and for 20 weeks after the last dose of study drug (180 days after last study drug for patients in Arm A4).
- Where a sexual partner of a male participant is a woman of childbearing potential, patients must avoid procreation for 20 weeks after completion of study drug treatment.
- Patients must refrain from donating sperm from the start of dosing until 20 weeks after discontinuing study treatment. If male patients wish to father children, they must be advised to arrange for freezing of sperm samples before the start of study treatment.

3.8.2 Eligibility of patients for treatment with AZD5069

As described in Section 1.1.2 and detailed in the IB for AZD5069, in patients treated with AZD5069, coadministration of drugs that are known potent or moderate CYP3A4 inhibitors, potent or moderate CYP3A4 inducers, P-glycoprotein 1 (P-gp) substrates with narrow therapeutic index, sensitive CYP2B6 substrates, warfarin or any other coumarin derivatives, breast cancer resistance protein (BCRP)-substrates that reduce blood neutrophils, Seville orange or grapefruit products, and any herbal medications should be avoided.

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

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

A list of the main potent or moderate CYP3A4 inhibitors, potent or moderate CYP3A4 inducers, P-gp substrates with narrow therapeutic index, sensitive CYP2B6 substrates, warfarin or any other coumarin derivatives, and BCRP-substrates that reduce blood neutrophils is shown in Table 2. This is not an exhaustive list and further details can be found in Bloomer et al 2013. In addition, Investigators should look at a frequently updated drug reference such as Lexicomp to see if any medicine they want to prescribe is on a list of drugs to avoid.

Any further questions regarding concomitant treatments in patients treated with AZD5069 should be referred to study personnel listed in Section 6.10.

Table 2 Prohibited medications and foods for patients administered AZD5069

Class	Examples (including and not limited to)	
Potent/moderate CYP 3A4 inhibitors	amprenavir	imatinib
	aprepitant	indinavir
	atazanavir	indinavir/ritonavir
	atazanavir/ritonavir	itraconazole
	boceprevir	ketoconazole
	casopitant	ledipasvir
	cimetidine	lomitapide
	ciprofloxacin	lopinavir/ritonavir
	clarithromycin	mibefradil
	cobicistat (GS-9350)	nefazodone
	conivaptan	nelfinavir
	crizotinib	netupitant
	cyclosporine	posaconazole
	danoprevir/ritonavir	ritonavir
	darunavir	saquinavir
	darunavir/ritonavir	saquinavir/ritonavir
	diltiazem	schisandra sphenanthera
	dronedarone	telaprevir
	elvitegravir/ritonavir	telithromycin
	erythromycin	tipranavir/ritonavir
	fluconazole	tofisopam
	fosamprenavir	troleandomycin
	grapefruit juice	verapamil
	idelalisib	voriconazole
Potent/moderate CYP 3A4 inducers	avasimibe	modafinil
	bosentan	nafcillin
	carbamazepine	phenytoin
	efavirenz	rifampin
	etravirine	St. John’s wort
Sensitive CYP 2B6 substrates	bupropion	efavirenz
P-gp substrates with narrow therapeutic index	digoxin	dabigatran
Coumarin derivatives	acenocoumarol	warfarin
	phenprocoumon	
Breast cancer resistance protein (BCRP) substrates that reduce blood neutrophils	topotecan	
Any herbal medications		

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

Abbreviations: CYP=cytochrome P450; P-gp=P-glycoprotein 1.

3.9 Discontinuation of investigational product

Subjects may be discontinued from investigational product (IP) in the following situations:

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment
- AE
- Severe noncompliance with the CSP as judged by the Investigator and/or AstraZeneca.
- Confirmed PD with either clinical deterioration and/or no further benefit from treatment
- Patients incorrectly initiated on IP (see Section 5.10)
- If a female patient becomes pregnant during the course of the study
- Investigator discretion
- Sponsor decision (Section 6.13)

EOT evaluations, including safety assessments, shall be performed as soon as possible following the decision to discontinue treatment in all patients. Any patient who is discontinued from IP will be followed up for safety. In addition, patients who discontinued treatment for reasons other than PD will continue to undergo tumor assessments every 2 months (± 7 days) until PD is noted. All patients will be followed for subsequent anticancer therapy every 2 months (± 7 days) and will also be followed for OS every 2 months (± 7 days) from the date of randomisation to the date of death due to any cause, assessed for approximately 40 months. The patients will be censored on the date of last follow-up visit. See Section 4.2.3 for details of the Follow-up period.

Patients may withdraw from any aspects of the voluntary exploratory research at any time, without prejudice to further treatment and independent of any decision concerning participation in other aspects of the main study. Procedures for withdrawal from the exploratory research are outlined in Section 5.8.7.

Patients who decide to withdraw from the main study will not receive any further study treatment, but will be encouraged to undergo all EOT evaluations, safety assessments, and follow-up assessments detailed in Section 4.2.3. Patients who decide to withdraw from the study may elect to undergo some but not all evaluations (e.g., they may elect to be followed for safety as well as subsequent anticancer therapy and survival every 2 months but not

undergo tumor assessments). As a minimum, patients will be strongly encouraged to allow evaluation of AEs as outlined in Section 6.3.

Unused study drug should be returned by the patient.

3.9.1 Procedures for discontinuation of a subject from investigational product

At any time, subjects are free to discontinue IP or withdraw from the study (i.e., IP and assessments – see Section 3.10), without prejudice to further treatment. A subject that decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator(s). AEs will be followed up (See Section 6); and all study drugs should be returned by the subject.

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

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screening failures are subjects who do not fulfil the eligibility criteria for the study, and therefore must not be randomized. These subjects should have the reason for study withdrawal recorded as ‘Screen failure’ (the potential subject who does not meet one or more criteria required for participation in a trial, this reason for study withdrawal is only valid for not randomized subjects). ‘Failure to meet randomization criteria’ should be selected for an indication that the subject has been unable to fulfil/satisfy the criteria required for assignment into a randomized group (it is only applicable for randomized studies and should be used for subject withdrawal postscreening).

3.10.2 Withdrawal of the informed consent

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

A subject who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The Investigator will follow-up AEs outside of the clinical study.

If a subject withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn subjects will not be replaced.

3.11 Discontinuation of the study

The study may be stopped if, in the judgement of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant

- are assessed as causally related to study drug,
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the case report form (CRF). All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

4 STUDY PLAN AND TIMING OF PROCEDURES

4.1 Dose-escalation and safety cohorts Part A

Treatment schedule for dose-escalation Part A is provided in Table 3.

Table 3 Treatment schedule, dose-escalation Part A

Treatment arm A1, A4, and A6: AZD9150 in combination with MEDI4736 with and without tremelimumab (AZD9150/MEDI4736/tremelimumab; AZD9150/MEDI4736)

	7-day Lead-in							Treatment Cycle 1 (and beyond)																											
								C1 Week 1							C1 Week 2							C1 Week 3							C1 Week 4						
	D -7	D -6	D -5	D -4	D -3	D -2	D -1	D 1							D 8							D 15							D 22						
AZD9150 (2mg/kg or 3 mg/kg IBW IV)	x		x		x			x							x							x							x						
MEDI4736 (20 mg/kg IV)								x																											
[a] Tremelimumab (1 mg/kg) IV								x																											

Treatment arm A2 and A3: AZD5069 in combination with MEDI4736 with and without tremelimumab (AZD5069/MEDI4736/tremelimumab; AZD5069/MEDI4736)

	7-day Lead-in							Treatment Cycle 1 (and beyond)																											
								C1 Week 1							C1 Week 2							C1 Week 3							C1 Week 4						
	D -7	D -6	D -5	D -4	D -3	D -2	D -1	D 1							D 8							D 15							D 22						
AZD5069 (40 mg BID/ 80 mg BID, PO)	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x

MEDI4736 (20 mg/kg IV)								x																							

Abbreviations: BID=twice daily; C=cycle; D=day; IBW=ideal body weight; IV=intravenous; PO=by mouth.
Only applicable to Arm A4 (AZD9150/MEDI4736/tremelimumab) and tremelimumab will be infused only for first 4 cycles.

4.1.1 Screening/Enrolment period

Patients not previously treated with any anti-PD-(L)1 antibodies were assigned to 1 of 2 treatment arms (Arm A1:AZD9150/MEDI4736 or Arm A2:AZD5069/MEDI4736). Currently, patients not previously treated with anti-PD-(L)1 antibodies will now be enrolled in Arm A3 (AZD5069 in alternative dosing schedule in combination with MEDI4736), Arm A4 (AZD9150 in combination with MEDI4736/tremelimumab), and in Arm A6 (safety and dose confirmation cohorts with AZD9150 with MEDI4736 in prostate cancer).

4.1.2 Treatment period

Description of Part A Study Arms

For Arms A1 and A2: DLT evaluable patients were enrolled in the dose-escalation Part A of this study. At the time of protocol amendment 5, the MTDs/RP2D for each of the 2 agents in combination with MEDI4736 (durvalumab) had been identified [AstraZeneca 2016 (a), AstraZeneca 2016 (b)]. In addition, the Arm A3 dose of AZD5069 80 mg twice daily (BID) with alternate dosing schedule was determined to be safe and tolerable. All additional cohorts of Part A enrolled (Arms A4 and A6) patients with advanced solid malignancies refractory to standard therapy or for which no standard of care regimen currently exists. Patients were allocated to treatment in both parts of the study after first considering their history, and any anticipated need to use herbal supplements and/or foods prohibited with concurrent administration of AZD5069. A 14 day washout period will be required for patients who have previously been receiving preparations not compatible with AZD5069. Based on the criteria detailed in Section 3.8.2 the Investigator will then assess whether the patient may be allocated to treatment with AZD5069.

Patients thus excluded by the Investigator from treatment with AZD5069 are allocated to:

- Treatment arm, A4 or A6: AZD9150 in combination with MEDI4736 or MEDI4736/tremelimumab.

Patients thus included by the Investigator for treatment with AZD5069 will be allocated to one of the following treatment arms:

- Treatment arm A4 or A6: AZD9150 in combination with MEDI4736 or MEDI4736/tremelimumab, or
- Treatment arm A3: AZD5069 in combination with MEDI4736.

The starting doses and additional dose levels chosen for each agent in this study are based on the clinical experience with each agent as monotherapy in previous trials and from Arms A1 and A2 of the dose-escalation phase of this trial. Following a 7−day lead-in period, each treatment cycle will span 28 days.

Dosing details of Part A study arms

AZD9150 Arms

For all AZD9150 arms, 3 doses of oligonucleotide are initially administered every other day during a 1-week lead-in period (Day −7 to Day −1). Subsequent cycles of dosing with the addition of antibody drugs (MEDI4736 or tremelimumab) in combination with AZD9150 will begin on Day 1 after the lead-in as described below:

Arm A1: On Day 1 after the lead-in, AZD9150 was administered at a starting dose of 2 mg/kg (IBW) Q1W via a 1-hour IV infusion, followed at least 30 minutes later on the same day by MEDI4736 20 mg/kg IV. AZD9150 was subsequently dosed Q1W, while MEDI4736 was administered every 4 weeks (Q4W). An additional dose level of AZD9150 (3 mg/kg of IBW IV Q1W) was evaluated and determined as RP2D.

Arm A4: For the AZD9150 with MEDI4736 and tremelimumab combination, beginning on Day 1 after the lead-in, AZD9150 will be administered first at 3 mg/kg IV over 1 hour (±10 minutes). The tremelimumab infusion at 1 mg/kg IV will start approximately 1 hour after the end of infusion for AZD9150 and will be administered over approximately 1 hour. One hour after the end of infusion of tremelimumab, MEDI4736 will be infused at 20 mg/kg over a period of 1 hour (±10 minutes). Tremelimumab will be given Q4W for a total of 4 months (up to 4 doses). MEDI4736 and AZD9150 dosing will continue Q4W throughout patient participation in the study. Therefore, the first dose of AZD9150/MEDI4736 (without tremelimumab) will be given 4 weeks after the last dose of tremelimumab.

Arm A6: Upon completion of the lead-in period, AZD9150 will be administered at 3 mg/kg of IBW IV Q1W, in combination with MEDI4736 20 mg/kg IV Q4W as described for Arm A1 above. Again, the infusion of AZD9150 should be completed 30 minutes prior to start of MEDI4736 infusion.

Ideal body weight (IBW) will be determined using the Devine formula (Pai and Paloucek 2000; see Section 7.2.1). 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. During the 7-day lead-in period, AZD9150 will be administered as a loading dose on Days −7, −5, and −3. Starting with Cycle 1, AZD9150 will be administered QW on Days 1, 8, 15, and 22 of each treatment cycle.

AZD5069 Arms

For all AZD5069 arms, BID doses of appropriately sized tablets are initially administered during a 1 week lead-in period (Day −7 to Day 0). Subsequent dosing of additional antibody drugs (MEDI4736 or tremelimumab) in combination with AZD5069 will begin on Day 1 after completion of the lead-in as described below:

Arm A2: Beginning on Day 1 after the lead-in, oral/per os (PO) dosing of AZD5069 continued as before (40 mg PO BID). At least 30 minutes after the morning dose of AZD5069, MEDI4736 was administered at 20 mg/kg IV over 1 hour. Subsequent to this, AZD5069 dosing continued BID while MEDI4736 dosing was repeated Q4W. An additional dose level of AZD5069 (80 mg BID) was also evaluated in combination with MEDI4736 under the same schedule.

Arm A3: AZD5069 will be initially dosed at 80 mg BID with scheduled dose holds and titrations to manage treatment-related reductions in peripheral blood neutrophil counts, as described in Section 5.5. MEDI4736 dosing at 20 mg/kg will begin on Day 1 after the lead-in period as described for Arm A2. At the time of amendment 5, the SRC evaluated 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 and tolerable to be considered as RP2D. In all arms with patients receiving AZD5069, tablets should be administered either 2 hours before or 2 hours after food, with a 2 hour window. Dose should be taken on an empty stomach at approximately the same time each day. Additional dose levels may be tested if deemed necessary to characterise combination tolerability.

Conduct of Part A Study Arms (A3, A4, and A6)

Arm A3: 6 patients were initially assessed. Since these patients progressed through the DLT period with one DLT event of Grade 3 immune hepatitis deemed related to MEDI4736, an additional 6 patients will be added to confirm the dose schedule. The algorithm as determined in Figure 7 and Figure 8 will be followed. Non-evaluable patients may be replaced. In addition to determining DLT in the DLT evaluation period (see Section 5.3.4), the SRC (see Section 5.3.5) will critically review all available data pertaining to safety, tolerability, and IM as well as PK, pharmacodynamic, and anti-tumor activity before deciding on the viability of explored dose and schedule.

For Arm A4: the aim is to conduct a safety run-in of the established dose of AZD9150 and AZD5069 (from Arms A1, A2/A3) in combination with fixed dose of MEDI4736/ tremelimumab in all solid tumor patients. There is no dose-escalation planned for Arm A4. If the dose is not tolerated (≥2 DLT) in this combination of 3 drugs then dose-reductions will be conducted as described in Figure 4, Figure 7, and Figure 8.

For Arm A6: the dose and safety confirmation cohort AZD9150 will be given in combination with MEDI4736 at established doses of AZD9150 (from Arms A1, A2/A3) in combination with a fixed dose of MEDI4736. This will be done in patients with prostate cancer and there will be no intra-patient dose escalation. If the dose is not tolerated in this combination of 2 drugs, then dose-reduction will be conducted as shown in Figure 4, Figure 7, and Figure 8.

Potential subjects who provide written informed consent will be screened; those who are identified as eligible will be enrolled, assessed by the Investigator for treatment with AZD5069, and assigned accordingly to a treatment arm. Following a 7-day lead-in period during which only AZD9150 or AZD5069 will be administered, combination treatment with MEDI4736 and/or tremelimumab starts on Day 1 of Cycle 1. A cycle of study treatment is defined as 28 days.

Each patient will undergo assessments for safety (DLTs, AEs, vital sign measurements, clinical laboratory tests, PS, ECGs, and physical examinations) and other assessments according to the study plan (see Section 5.2).

The DLT evaluation period will be defined as the time from the first dose of AZD9150 or AZD5069 to the end of Cycle 1 (i.e., 35 days total), or until a patient experiences a DLT, whichever occurs first. For patients in treatment arm A4 (AZD9150/MEDI4736/tremelimumab), to be deemed evaluable, a 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 tremelimumab infusion during the DLT evaluation period. Patients who have suffered a DLT during or before Day 35 will also be deemed evaluable. For patients in treatment arm A3 (AZD5069/MEDI4736) to be deemed evaluable, they must have received all doses during the 7-day lead-in period (i.e., 14 doses) and at least 50% of the planned doses of AZD5069.

For Arm A6, the aim is to establish, collect, and confirm safety, tolerability, and PK/pharmacodynamic relations of the RP2D/MT2D for the 2 combinations (i.e., AZD9150/MEDI4736 and AZD5069/MEDI4736) in specific tumor types of prostate cancer at established doses from Arms A1, A2, and A3. Hence, Arm A6 will not be followed for DLTs.

Treatments in Arms A3, A4, and A6 will be administered in 4-week treatment cycles until a patient: has confirmed PD with either clinical deterioration and/or no further benefit from treatment, experiences unacceptable toxicity, or discontinues for any other reason. All patients will be evaluated regularly for response to treatment according to the study plan (see Section 5.2, Table 5). Study treatment will continue between the initial assessment of progression and the confirmation of progression. Patients may continue to receive study treatment beyond confirmed PD in the absence of clinical deterioration and if the Investigator is of the opinion that the patient continues to receive benefit from treatment.

After discontinuation of treatment, patients will continue to be followed for safety, subsequent anticancer therapy, and survival. EOT evaluations, including safety assessments, shall be performed as soon as possible following the decision to discontinue treatment. Safety follow-up for IM will continue for all patients for 90 days (± 7 days) after the last dose of MEDI4736 or until the initiation of subsequent anticancer therapy. Patients who discontinue treatment for reasons other than PD will continue to undergo tumor assessments every 2 months (± 7 days) until PD is noted. All patients will be followed for subsequent anticancer therapy every 2 months (± 7 days) and for OS every 2 months (± 7 days) from the date of randomisation to the date of death due to any cause, assessed for approximately 40 months. The patients will be censored on the date of last follow-up visit. Figure 3 depicts the study scheme.

4.2 Dose-expansion Part B

Treatment schedule for dose-expansion Part B is provided in Table 4.

Table 4 Treatment schedule, dose-expansion Part B

	7-day Lead-in							**Treatment Cycle 1 (and beyond)**																							
								C1 Week 1							**C1 Week 2**							**C1 Week 3**							**C1 Week 4**						
	D -7	D -6	D -5	D -4	D -3	D -2	D -1	D 1							D 8							D 15							D 22						
Treatment arm B5: AZD9150 alone																																			
***AZD9150 (3 mg/kg IBW IV)**	x		x		x			x							x							x							x						
Treatment arm B6: AZD5069 alone																																			
***AZD5069 (40 mg BID, PO)**	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x
Treatment arm B1, B3 and B7: AZD9150 in combination with MEDI4736 (AZD9150/MEDI4736)																																			
AZD9150 (3 mg/kg IBW IV)	x		x		x			x							x							x							x						
MEDI4736 (20 mg/kg IV)								x																											
Treatment arm B2 and B4: AZD5069 in combination with MEDI4736 (AZD5069/MEDI4736)																																			
****AZD5069 (40 mg BID/80 mg BID, PO)**	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x
MEDI4736 (20 mg/kg IV)								x																											

Treatment arm B8 AZD9150 in combination with MEDI4736 (AZD9150/MEDI4736 both flat doses)																																					
AZD9150 (200 mg during lead-in and 400 mg Q2W starting fromC1D1)	x		x		x			x														x															
MEDI4736 (1.5 g IV)								x																													

Abbreviations: BID=twice daily; C=cycle; D=day; IBW=ideal body weight; IV=intravenous; PO=by mouth; Q2W=every 2 weeks.

*Arms B1- B6: In the event of disease progression and after proper approval for the addition of MEDI4736, MEDI4736 will be added to the dosing schedule beginning on Day 1 of the following treatment cycle (i.e., study treatment will follow the same schedule as a patient on a combination therapy arm).

**In the case of the Arm B4 post-interim analysis, the dose of AZD5069 will be 80 mg BID alternate dosing schedule.

4.2.1 Screening/Enrolment period

In Part B of the study, 2L patients will be either allocated or randomly assigned to 1 of the first 6 treatment arms (AZD9150 alone, AZD5069 alone, AZD9150/MEDI4736 with or without prior exposure to an anti PD (L)1 antibody, or AZD5069/MEDI4736 with or without prior exposure to an anti PD (L)1 antibody). Additionally, 2 non-randomized Arms B7 and B8, will enroll patients who have no prior exposure to anti-PD-(L)1 antibody, and who are 1L (no prior systemic treatment for RM SCCHN). Treatments will be administered with 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 derived from treatment, experience unacceptable toxicity, or discontinue for any other reason as per Section 3.9. Patients in the monotherapy arms of Part B with confirmed PD may continue on their current study drug and add MEDI4736 at the discretion of the Investigator with notification to the Medical Monitor (and so long as there is ongoing active enrolment in the treatment combination arms for PD (L)1 naïve patients). In these patients, MEDI4736 will be dosed without a lead-in period. After addition of MEDI4736, these patients will be followed for safety.

4.2.2 Treatment period

Part B of the study will commence once the doses for the combination treatments (AZD9150/MEDI4736 and AZD5069/MEDI4736) have been established in Part A of the study from Arms A1 and A2/A3. In the case of the Arm B4 post-interim analysis, the dose of AZD5069 will be 80 mg BID alternate dosing schedule. If the RP2D combination is established earlier in one arm of Part A than the other, the Sponsor may manually assign patients to a pretreated arm (treatment arm B1/B2 as discussed below) of the determined RP2D combination to obtain safety data (for US sites ONLY). One such patient was manually randomized to Arm B1; this patient will not be included for any efficacy analysis and could be replaced with an actual randomised patient.

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 primary objective of the dose-expansion phase is to evaluate the ORR of AZD9150 and AZD5069 alone or in combination with MEDI4736 in the second-line treatment of patients with RM SCCHN and in patients who are 1L RM SCCHN with no prior systemic treatment.

In the dose-expansion Part B (B1-B6), 155 eligible and efficacy evaluable patients have been enrolled. 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, or B6. Additionally, Arms B7 and B8 will each enroll at least 48 evaluable patients who have not received prior systemic treatment for RM SCCHN. Additionally, based on 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 and detailed in Section 7.2.2 as well as the patient's anticipated need or likelihood to consume such products at any time throughout the study, the Investigator will assess whether the patient may be treated with AZD5069.

ANTI-PD-(L)1 pretreated population

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

- Treatment arm B1: AZD9150 in combination with MEDI4736 (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 randomisation system (IWRS) in a 1:1 ratio to 1 of the following 2 treatment arms:

- Treatment arm B1: AZD9150 in combination with MEDI4736 (anti-PD-(L)1 pretreated population)
- Treatment arm B2: AZD5069 in combination with MEDI4736 (anti-PD-(L)1 pretreated population)

ANTI-PD-(L)1 NAÏVE 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 in combination with MEDI4736 (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 in combination with MEDI4736 (anti-PD-(L)1 naïve population)
- Treatment arm B4: AZD5069 in combination with MEDI4736 (anti-PD-(L)1 naïve population)
- Treatment arm B5: AZD9150 alone (anti-PD-(L)1 naïve population)
- Treatment arm B6: AZD5069 alone (anti-PD-(L)1 naïve population)

- Non-randomized treatment arms B7 and B8: AZD9150 in combination with MEDI4736 (anti-PD-(L)1 [flat dose for B8] naïve population) for patients who have not received prior systemic treatment for RM SCCHN.

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. See Section 8.2.2 for details on sample size, conditions for stopping an arm, and the conduct of an interim analysis.

The dose-expansion Part B is based on efficacy evaluable patients (Section 7.7.8 and Section 8.2.2). Patients identified as not efficacy evaluable will be replaced.

The doses for the combination treatments (AZD9150/MEDI4736 and AZD5069/MEDI4736) will have been established in Part A of the study. In the case of the Arm B4 post-interim analysis, the dose of AZD5069 will be 80 mg BID alternate dosing schedule.

AZD9150 will be administered at the dose determined in Part A of the study via a 1-hour IV infusion (± 10 minutes). During the 7-day lead-in period, AZD9150 will be administered as a loading dose on Days −7, −5, and −3. Starting with Cycle 1, AZD9150 will be administered QW on Days 1, 8, 15, and 22 of each treatment cycle.

The patients allocated to Arm B8 will receive a flat dose of AZD9150 at 400 mg Q2W (200 mg lead-in dose) in combination with MEDI4736 at a 1.5 g flat dose Q4W.

For those patients randomly assigned to treatment arm B1 or B3, AZD9150 will be administered before the infusion of MEDI4736 and should end at least 30 minutes before MEDI4736 infusion starts.

AZD5069 will be administered at the dose determined in Part A of the study PO BID (i.e., in the morning [at least 30 minutes before MEDI4736 infusion starts] and the evening of each day) starting with Day -7 of the 7-day lead-in period for treatment arms B2 and B4. MEDI4736 will be administered Q4W via a 1 hour IV infusion (± 10 minutes). Patients will receive MEDI4736 on Day 1 of each treatment cycle, starting with Cycle 1. MEDI4736 will be infused after the administration of AZD9150 or the morning dose of AZD5069. There should be an interval of at least 30 minutes between the end of the AZD9150 infusion or the taking of the morning dose of AZD5069 and the start of the MEDI4736 infusion.

Each patient will undergo assessments for efficacy and safety as well as other assessments according to the study plan (see Section 5.2, Table 5).

Of the patients randomly assigned to treatment arm B5 and B8, 12 evaluable patients will be asked to provide urine samples for PK assessments in urine. Patients' consent to this evaluation will be mandatory for B8 and voluntary for B5.

Patients participating in Part B of the study will be administered study drug(s) following the 7-day lead-in period in 4-week treatment cycles for as long as they are continuing to show clinical benefit, as judged by the Investigator, unless a patient has confirmed PD with either clinical deterioration and/or no further benefit from treatment, experiences unacceptable toxicity, or discontinues for any other reason.

Patients in the monotherapy arms of Part B (i.e., Arm B5 or B6) with confirmed PD may continue on their current study drug and add MEDI4736 at the discretion of the Investigator with notification to the Medical Monitor (and so long as there is active enrolment ongoing in the treatment combination arms for PD-(L)1 naïve patients). In these patients, MEDI4736 will be added to the schedule beginning on Day 1 of the following treatment cycle with AZD9150 and MEDI4736 (i.e., study treatment will be dosed on the same schedule as a patient on a combination therapy arm starting on Day 1 of the following Cycle; see Table 4 for dosing schedule). After addition of MEDI4736, these patients will be followed for safety but censored from the efficacy analysis. When the addition of MEDI4736 (durvalumab) occurs, the first safety reassessment for the combination of treatment in these patients is to take place 45 days after the first administration (of combination treatment) and every 8 weeks thereafter.

All patients will be evaluated according to the study plan (see Section 5.2, Table 5) and their clinical status classified according to the RECIST guidelines version 1.1 (Eisenhauer et al 2009) with modifications to account for the unique response kinetics, which have been observed in some patients where responses to immunotherapy may occur after PD is assessed (Wolchok et al 2009). Specifically, RECIST criteria will be modified so that PD in the absence of clinical deterioration must be confirmed at least 4 weeks after the initial assessment of PD. Study treatment will continue between the initial assessment of progression and the confirmation for progression. Patients may continue to receive study treatment beyond confirmed PD in the absence of clinical deterioration and if the Investigator is of the opinion that the patient continues to receive benefit from treatment.

Following a 7-day lead-in period, each treatment cycle will span 28 days. Table 4 provides an overview of the treatment schedule in the dose-expansion Part B of the study.

After discontinuation of treatment, patients will continue to be followed for safety, subsequent anticancer therapy, and survival. During this time, all patients will be followed for safety (including concomitant medication) for 28 days (± 7 days) after the last dose of study drug or until the initiation of a subsequent anticancer therapy. In addition, patients who received MEDI4736 as part of their combination treatment will be followed for IM for 90 days (±7 days) after the last dose of MEDI4736 or until the initiation of alternative anticancer therapy. Patients who discontinued treatment for reasons other than PD will continue to undergo tumor assessments every 2 months (± 7 days) until PD is noted. All patients will be followed for subsequent anticancer therapy every 2 months (± 7 days) and will also be

followed for OS every 2 months (± 7 days) from the date of randomisation to the date of death due to any cause, assessed for approximately 40 months. The patients will be censored on the date of last follow-up visit. Figure 3 depicts the Part B study scheme.

4.2.3 End-of-treatment evaluations and follow-up

EOT evaluations, including safety and tumor assessments, shall be performed as soon as possible following the decision to discontinue treatment (see the study event overview, Table 5).

In addition, patients should be followed up for at least 28 days (+7 days) after the last dose of study treatment for any new reports of AEs, SAEs, and concomitant medications.

Safety follow-up for IM will continue for all patients treated with MEDI4736 for 90 days (±7 days) after the last dose of MEDI4736 or until the initiation of subsequent anticancer therapy.

Patients who discontinued treatment for reasons other than PD will continue to undergo tumor assessments every 2 months (± 7 days) until PD is noted. All patients will be followed for subsequent anticancer therapy every 2 months (± 7 days) and will also be followed for OS every 2 months (± 7 days) from the date of randomisation to the date of death due to any cause, assessed for approximately 40 months. The patients will be censored on the date of last follow-up visit.

The status of "ongoing," "withdrawn from the study," and "lost to follow-up" for patients at the time of an OS analysis should be obtained by the site personnel through checking the patient notes, hospital records, contacting the patient's general practitioner, and checking publicly available death registries. If the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

5 STUDY ASSESSMENTS

5.1 Recording of data

Web-based data capture (WBDC) will be used for data collection and query handling. The Investigator will ensure that data are recorded in the electronic CRFs (eCRFs) as specified in the CSP and in accordance with the instructions provided.

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

For details of data and study management see Appendix E, "Data and Study Management" of this CSP.

5.2 Study plan and event overview

Procedures and assessments during study entry, as well as subsequent safety and tumor assessments are similar in Part A and Part B of the study; an overview of these study events is provided in the Study Plan in Table 5.

Pharmacokinetic, pharmacodynamic, and IM assessments, however, differ between Part A and Part B; Table 6 provides an overview of these assessments for Part A, Table 7 for Arms B1 to B7, and Table 8 for B8.

Details of the various procedures and assessments are provided in the footnotes to the figures and in the subsequent CSP sections.

Table 5 Study plan for study entry, treatment, safety, and tumor assessments

Assessments	**Screening**	**Lead-in (-7 to -1)**			**Cycle 1 and all subsequent cycles, unless noted**								**Even cycles only**	**End-of-Treatment[a]**	**Follow-up[b]**
					Week 1		**Week 2**		**Week 3**		**Week 4**				
Day:	**-21 to -8**	**-7**	**-5**	**-3**	**1**	**2-7**	**8**	**9-14**	**15**	**16-21**	**22**	**23-28**			
Informed consent	x														
Demography, baseline characteristics, medical, and surgical history	x														
Previous tumor-related tx	x														
Selection criteria	x	x													
Complete physical exam[c]	x	x			x									x	
Targeted physical exam[c]									x						
ECOG performance status	x	x			x									x	
Vital signs[q]	x	x			x		x		x		x			x	
Height	x														
Weight[c,d]	x	x			x									x	
12-Lead ECG in triplicate[e]	x				x[e]									x	
Laboratory safety tests (haematology, serum chemistry)[c,f]	x	x			x		x[f]		x		x[f]			x	
Laboratory safety tests (coagulation)[c,g]	x	x			x				x[g]					x	
Urinalysis[c,h]	x	x			x				x[h]					x	
Thyroid function tests[c,i]	x	x			x									x	
HIV, HBV, HCV serology	x														

Assessments	**Screening**	**Lead-in (-7 to -1)**			**Cycle 1 and all subsequent cycles, unless noted**								**Even cycles only**	**End-of-Treatment[a]**	**Follow-up[b]**
					Week 1		**Week 2**		**Week 3**		**Week 4**				
Day:	**-21 to -8**	**-7**	**-5**	**-3**	**1**	**2-7**	**8**	**9-14**	**15**	**16-21**	**22**	**23-28**			
HPV status	x														
Pregnancy test[j]	x	x			x									x	
Tumor assessments[k]	x[k]												x[k]	x	x[k]
Concomitant medications[l]	x	←										→		x	x
AE[l]	x	←										→		x	x
AZD9150[m]		x	x	x	x		x		x		x				
AZD9150[m] (Arm B8 only)		x	x	x	x				x						
AZD5069 (combination therapy or monotheapy) (BID)[n]		← x →			x x	x x	x x	x x	x x	x x	x x	x x			
tremelimumab[p]					x										
MEDI4736[o]					x										
MEDI4736[o] (1.5g flat dose for Arm B8 only)					x										

[a] An EOT visit shall occur as soon as possible following the decision to discontinue treatment.

[b] Patients are to be followed up for 28 (+7) days after the last dose of study treatment for any new reports of AEs, SAEs, and concomitant medications. Safety follow-up for IM will continue for all patients treated with MEDI4736 for 90 days (± 7 days) after the last dose of MEDI4736 or until the initiation of subsequent anticancer therapy. Patients who discontinued treatment for reasons other than PD will continue to undergo tumor assessments every 2 months (± 7 days) until PD is noted. All patients will be followed for subsequent anticancer therapy every 2 months (± 7 days) and will also be followed for overall survival every 2 months (± 7 days) from the date of randomisation to the date of death due to any cause, assessed for approximately 40 months. The patients will be censored on the date of last follow-up visit.

[c] To facilitate scheduling of predose assessments, a window of −2 days is allowed to obtain the following procedures prior to dosing a patient: complete and targeted physical exam, weight, laboratory safety tests (haematology, serum chemistry, and coagulation), urinalysis, and thyroid function tests.

[d] Weight (in kilograms) will be obtained at screening, before dosing on Day −7 of the lead-in, before dosing on Day 1 of each cycle, and at the EOT visit. Weight obtained on Day −7 of the lead-in will be used to calculate the weight-related doses of AZD9150 for the lead-in. Weight obtained on Day 1 of each cycle will be used to calculate the weight-related doses of AZD9150 and MEDI4736 for each cycle..

[e] For patients treated with AZD5069, 12-lead resting ECGs in triplicate will be obtained at screening, throughout the treatment, and at the EOT visit. On Day 1 of Cycle 1, 12-lead ECGs should be recorded at 2 hours after the morning dose of AZD5069, and for patients treated with MEDI4736, again 2 hours after end of the MEDI4736 infusion. On Day 1 of Cycle 2 and of all subsequent odd-numbered cycles (to match PK assessments), 12-lead ECGs should be recorded at the end of infusion and 2 hours after the morning dose of AZD5069. The timing and number of ECGs may be adjusted by the SRC in response to the emerging PK and safety profile. For patients not treated with AZD5069, 12-lead resting ECGs in triplicate will be obtained at screening, on Day 1 of Cycle 1 (2 hours after the end of the AZD9150 infusion, and for patients treated with MEDI4736, again 2 hours after end of the MEDI4736 infusion), and at the EOT visit. For B8, digital triplicate ECGs should be taken at predose, 1 hour after the start of the AZD9150 infusion (end of AZD9150 infusion) and 2 hours after the start of infusion on lead-in Day -7, Day 1 of Cycle 1, 2, and at subsequent PK time points. Refer to Section 5.4.3 for additional details.

[f] Blood samples for routine haematology and serum chemistry safety assessments will be obtained at screening; before dosing on Day −7 of the lead-in; before dosing on Days 1, 8, 15, and 22 of Cycle 1; before dosing on Days 1 and 15 of all subsequent cycles; and at the EOT visit. To shorten the time between the blood draw and the decision if dosing may proceed, blood samples for routine haematology and serum chemistry safety assessments are to be drawn and split into 2 samples. One portion of the sample is to be analysed locally to determine toxicity prior to dosing and the second portion of the sample is to be sent to the designated central laboratory. Samples are not to be split on days where no study drug administration is scheduled. Haematology parameters include haemoglobin, haematocrit, RBC count, mean corpuscular volume, mean corpuscular haemoglobin concentration, WBC count with differential (absolute and %), and platelet count. Serum chemistry parameters include sodium, potassium, chloride, bicarbonate, magnesium, calcium, phosphate, blood urea nitrogen, uric acid, creatinine, glucose (random), TBL, indirect bilirubin, LDH, total protein, albumin, ALP, ALT, AST, GGT, creatine phosphokinase, C-reactive protein, cholesterol, and triglycerides. Refer to Section 5.4.1, for details.

[g] Blood samples for routine coagulation assessments will be obtained at screening; before dosing on Day −7 of the lead-in; before dosing on Days 1 and 15 of Cycle 1; before dosing on Day 1 of all subsequent cycles; and at the EOT visit. Tests include prothrombin time, partial thromboplastin time, fibrinogen, haptoglobin, and international normalised ratio. Refer to Section 5.4.1, for details.

[h] Urine samples for routine urinalysis will be obtained at screening; before dosing on Day −7 of the lead-in; before dosing on Days 1 and 15 of Cycle 1; before dosing on Day 1 of all subsequent cycles, and at the EOT visit. Urinalysis parameters include colour, appearance, specific gravity, pH, protein, glucose, ketones, blood, bilirubin, and microscopic evaluation of WBC/HPF, and RBC/HPF. Refer to Section 5.4.1, for details.

[i] Thyroid function tests are required at screening, before dosing on Day −7 of the lead-in, before dosing on Day 1 of each cycle, and at the EOT visit. Thyroid function tests include TSH, and free T3 and T4.

[j] For women of childbearing potential, defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause): A blood sample to determine serum β hCG is required at screening; this sample will be analysed at the central laboratory for the study. Additionally, urine samples for a urine-based pregnancy test will be collected before dosing on Day −7 of the lead-in, before dosing on Day 1 of each cycle, and at the EOT visit. Urine-based pregnancy tests will be performed at the study centres.

[k] Tumor assessments to be performed at screening, on Day 15 of Cycle 2 (i.e., at the beginning of Week 7), at the beginning of each subsequent even-numbered cycle, and at the EOT visit. Patients who are on study treatment for more than 24 months may have the frequency of tumor assessment reduced to every 12 to 16 weeks at the discretion of the Investigator. Patients who discontinue treatment for reasons other than PD will continue to undergo tumor assessments every 2 months (± 7 days) until PD is noted. To facilitate scheduling of tumor assessments, a window of ±7 days is allowed. For the additional 48 patients to be enrolled in first-line in Arms B7 and B8, a central imaging read will be done in addition to the local site RECIST evaluation. See Section 5.3.1 for additional details.

[l] The reporting period for AEs and concomitant medication starts immediately following the time that written informed consent is obtained and ends 28 (+7) days after the last dose of study drug or until the initiation of subsequent anticancer therapy. For patients dose-reduced to levels −1 or −2 of AZD9150 in Arms B1, B3, or B7 who are experiencing treatment-related AEs of Grade 2 or lower, visits on Day 8 and Day 22 of each cycle (no AZD9150 dosing) may be considered optional, unless, in the Investigator's estimation, more frequent individual evaluations are appropriate.

[m] During the 7-day lead-in period, AZD9150 will be infused on Days −7, −5, and −3. A window of +1 day per loading dose is allowed. Doses should not be given on back-to-back days. Starting with Cycle 1, AZD9150 will be administered every week on Days 1, 8, 15, and 22 of each treatment cycle; doses have a ±2 day dosing window. When given in combination with MEDI4736, AZD9150 will be administered before the infusion of MEDI4736 and must be completed at least 30 minutes before the start of MEDI4736 infusion. When given in combination with tremelimumab, AZD9150 will be administered before the infusion of MEDI4736 and must be completed at least 1 hour before the start of MEDI4736 infusion. For treatment Arm B8, AZD9150 will be administered at 200 mg on lead-in Days −7, −5, and −3 and 400 mg every 2 weeks starting in Cycle 1.

[n] In combination therapy arms, patients will receive AZD5069 BID (i.e., in the morning at least 30 minutes before MEDI4736 infusion or tremelimumab infusion [as applicable] and in the evening) starting with Day −7 of the lead-in cycle. The morning dose of AZD5069 on Day −7 of the lead-in period and on any subsequent day when blood samples before the morning dose are required must be administered at the study centre and the precise time noted. All other doses may be self-administered by the patient; self-administration of AZD5069 will be recorded in the Patient Diary. Subsequently, AZD5069 will be administered BID (i.e., in the morning and in the evening) starting with Day 1 of Cycle 1. The morning dose of AZD5069 in the lead-in period and on any subsequent day when blood samples before the morning dose are required must be administered at the study centre and the precise time noted. All other doses may be self-administered by the patient; self-administration of AZD5069 will be recorded in the Patient Diary.

[o] For MEDI4736, a window of ±2 days is allowed for dosing days. Patients will receive MEDI4738 Q4W on Day 1 of each cycle. When given in combination with tremelimumab, the infusion of MEDI4736 will be 1 hour after the end of the tremelimumab infusion. Patients should be observed after administration of MEDI4736 for a minimum of 2 hours for the appearance of any acute drug reactions. In the event of an acute reaction, in order to help understand the potential drug relatedness of such a reaction, a blood sample should be drawn during the event for possible additional ADA testing. Serum tryptase or other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at the discretion of the Investigator. For patients on monotherapy in Arms B5 and B6: In the event of disease progression and after proper approval for the addition of MEDI4736— MEDI4736 will be added to the dosing schedule beginning on Day 1 of the following treatment cycle (i.e., study treatment will follow the same schedule as a patient on a combination therapy arm, [see Table 4 for dosing schedule]). After addition of MEDI4736, these patients will be followed for safety; the first safety reassessment for the combination of treatment in these patients is to take place 45 days after the first administration (of combination treatment) and every 8 weeks thereafter. See Section 5.4 for details on safety assessments. MEDI4736 will be administered as a 1.5g flat dose Q4W for treatment Arm B8. If body weight decreases to less than 30 kg, weight-based dosing (20 mg/kg Q4W) will be implemented.

[p] (Applicable only for Arm A4) Tremelimumab will be given only for 4 cycles (once a month on Day 1 of every cycle for up to 4 months), and will be infused after AZD9150 and AZD5069, and prior to MEDI4736 infusions in Arm A4 (AZD9150/MEDI4736/tremelimumab).

[q] Vital signs for patients on AZD5069 will not be required for Day 8 and Day 22 visits beyond Cycle 2 as there are no dosing visits scheduled for these patients on these days. Vital signs for patients in Arm B8 will not be required for Day 8 and Day 22 (all cycles) as there are no dosing visits scheduled for these patients on these days.

Abbreviations: ADA=antidrug antibody; AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; β hCG=beta human chorionic gonadotropin; BID=twice daily; CT=computerised tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End-of-Treatment; GGT=gamma-glutamyl transpeptidase; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HPF=high-power field; IM=immunogenicity; kg=kilogram; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; PD=progression of disease; PK=pharmacokinetic(s); PS=performance status; Q4W=every 4 weeks; RBC=red blood cell(s); SRC= Safety Review Committee; T3=triiodothyronine; T4=thyroxine; TBL=total bilirubin; TSH=thyroid-stimulating hormone; tx=treatment; WBC=white blood cells

Table 6 Study plan for pharmacokinetic, pharmacodynamic, immunogenicity, and pharmacogenetic assessments in Part A

Assessments	Screening	Lead-in (-7 to -1)				Cycles															EOT [a]	FU
						C1			C2		C3	C4	C5	C6	C7	C8	C9	C10	C11	*C12		
Day:	-21 to -8	-7	-5	-4	-3	1	8	15	1	15	1	1	1	1	1	1	1	1	1	1		
Blood samples for pharmacokinetic assessments																						
AZD9150[b]		x	x			x			x		x		x		x		x		x			
AZD5069[c]		x		x		x			x		x		x		x		x		x			
MEDI4736[d]						x				x		x		x		x[d]		x		x		x
Tremelimumab[l]						x				x		x										
Blood samples for pharmacodynamic assessments																						
PDRNA[e]	x	x				x	x		x		x	x	x	x	x	x	x	x	x	x	x	
sPD-L1[f]						x				x		x		x		x		x		x		x
MDSCs[g]	x	x				x			x		x		x								x	
Blood samples for IM assessments																						
ADA[h]						x				x		x		x		x		x		x		x
Anti-AZD9150 Ab[i]						x			x			x		x		x		x		x		
Blood samples for exploratory blood-borne biomarkers[j]																						
Serum sample[j]	x	x		x		x	x	x	x		x		x		x		x		x		x	
Plasma sample[j]	x	x				x	x	x	x		x		x		x		x		x		x	
PBMC[j]	x	x				x	x	x			x			x			x				x	
sPSA [m]	x					x				x		x		x		x		x			x	
cfDNA blood sample[o]	x	x							x		x	x		x		x		x		x	x	

Other																					
Collection of archival tumor samples[n]	x																				
Optional																					
Pharmacogenetics[j]		x																			
Tumor biopsy[k]	x																				

* In order to ensure all samples required for sample point collection are accurately collected, the cycles beyond Cycle 12 should mimic Cycle 9, 10, 11, and 12 in a repeated pattern through to Cycle 40, except where noted in the footnotes below (eg, PBMC collection).

An EOT visit shall occur as soon as possible following the decision to discontinue treatment.

[a] For patients treated with AZD9150 (Arm A1, A4 and A6), PK blood samples for AZD9150 (2 mL) will be collected relative to the AZD9150 infusion as follows; a window of 10% of the nominal time point is acceptable:

Lead in, Day −7: Predose and at 0.5 hour (±3 min), 1 hour (end of infusion; ±6 min), 2 hours (±12 min), 4 hours (±24 min), and 6 hours (±36 min) after the start of the infusion

Lead in, Day −5: At 48 (±4) hours after the start of the first infusion (on Day −7) and before the second infusion (on Day −5)

Cycle 1, Day 1: Predose

Cycle 2, Day 1: Predose and at 0.5 hour (±3 min), 1 hour (end of infusion; ±6 min), 2 hours (±12 min), 4 hours (±24 min), and 6 hours (±36 min) after the start of the infusion

Cycle 3 and all subsequent odd-numbered cycles, Day 1: Predose

[b] For patients treated with AZD5069 (**PRIOR TO DETERMINATION OF RP2D, Arms A2 and A3**), PK blood samples for AZD5069 and its metabolite AZ13587715 (2 mL total) will be collected as follows; a window of 10% of the nominal time point is acceptable:

Lead-in, Day −7: Before the first morning dose and at 0.5 hour (±3 min), 1 hour (±6 min), 2 hours (±12 min), 4 hours (±24 min), 6 (±36 min), 8 (±48 min), and 10 hours (±60 min) (when possible) after the first morning dose

Cycle 1, Day 1: Before the morning dose and at 2 hours (±12 min) after the morning dose

Cycle 2, Day 1: Before the morning dose and at 0.5 hour (±3 min), 1 hour (±6 min), 2 hours (±12 min), 4 hours (±24 min), 6 (±36 min), 8 (±48 min), and 10 hours (±60 min) (when possible) after the morning dose

Cycle 3 and all subsequent odd-numbered cycles, Day 1: Before the morning dose and at 2 hours (±12 min) after the morning dose

The morning dose of AZD5069 on Day −7 of the lead-in period and on any subsequent day where blood samples before the morning dose are required must be administered at the study centre and the precise time noted. Failure to obtain the 10-hour samples will not be considered a protocol deviation.

[c] For all patients, PK blood samples for MEDI4736 (3.5 mL) will be collected relative to the MEDI4736 infusion as follows; a window of 10% of the nominal time point is acceptable:

Cycle 1, Day 1: Predose and 1 hour (±6 min) after the start of the infusion (end of infusion)

Cycle 2, Day 15: Any time

Cycle 4 and all subsequent even-numbered cycles, Day 1: Predose

Cycle 8, Day 1: In addition to the predose sample, a sample at 1 hour (±6 min) after the start of the infusion (end of infusion)

Follow-up: For patients who discontinue MEDI4736, a sample will be drawn 90 days after their last dose of MEDI4736 (coinciding with an IM [ADA] sample)

[d] For all patients, 2 blood samples (2.5 mL each) for pharmacodynamic RNA (PDRNA) will be collected predose at each specified time point to assess pharmacodynamic response in blood for AZD9150 (STAT3 knockdown) and exploratory blood-borne biomarkers that may correlate to treatment or response (gene expression changes or modification of genomic DNA): At screening; on Day −7 of the lead-in period; on Day 1 and Day 8 of Cycle 1; on Day 1 of subsequent; and at the EOT visit. The revised sample collection for PDRNA samples is applicable to newly enrolled patients only (under protocol amendment 5, dated 10 May 2017, and onwards), existing patients will have samples collected up to Cycle 5, Day 1. New patients will be required to have samples collected beyond Cycle 5.

[e] For all patients (except for patients in Arms A3, A4, and A6), a single blood sample (3.5 mL) will be collected predose at each specified time point to assess the pharmacodynamic response in blood for MEDI4736 (sPD-L1): Day 1 of Cycle 1, Day 15 of Cycle 2, and 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.

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

[g] For all patients, blood samples for IM (5 mL) will be collected predose on Day 1 of Cycle 1, on Day 15 of Cycle 2, and on Day 1 of each subsequent even-numbered cycle. For patients who discontinue MEDI4736, a blood sample will also be collected during follow-up at 90 days after the last dose of MEDI4736.

[h] For patients treated with AZD9150, blood samples for IM (2 mL) will be collected relative to AZD9150 infusion as follows: Cycle 1, Day 1: Predose; Cycle 2, Day 1: Predose; and Cycle 4 and all subsequent even-numbered cycles, Day 1: Predose.

[i] For all patients, at the time points specified, a single 2 mL blood sample for serum, a single 10 mL blood sample for plasma, and two 6 mL blood samples for PBMC will be collected predose for the assessment of exploratory biomarkers.

The 2 mL blood sample for serum will be obtained at screening; on Days −7 and −3 of the lead-in period; on Days 1, 8, and 15 of Cycle 1; on Day 1 of Cycle 2; on Day 1 of all subsequent odd-numbered cycles; and at the EOT visit.

The 10 mL blood sample for plasma will be obtained at screening; on Day −7 of the lead-in period; on Days 1, 8, and 15 of Cycle 1; on Day 1 of Cycle 2; on Day 1 of all subsequent odd-numbered cycles; and at the EOT visit.

The two 6 mL blood samples for PBMC will be obtained at screening; on Day −7 of the lead-in period; on Days 1, 8, and 15 of Cycle 1; on Day 1 of cycles 3, 6, and 9; and at the EOT visit.

[j] If a patient agrees to participate in the host pharmacogenetics research component of the study and signs a separate informed consent for genetic research, a saliva sample will be collected. The saliva sample for genetic research will ideally be obtained from the patients immediately prior to dosing on Day 1. If for any reason, the sample is not obtained prior to dosing, it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient for genetics during the study. See Section 6.8.2 for details.

[k] If a patient in treatment Arm A6 agrees to provide a screening tumor biopsy, this will be documented via an optional ICF.

[l] For all patients in treatment Arms A4 and A5, PK blood samples for tremelimumab (3.5 mL) will be collected relative to the tremelimumab infusion as follows: a window of 10% of the nominal time point is acceptable:

Cycle 1, Day 1: Predose and 1 hour (±6 min) after the start of the infusion (end of infusion)

Cycle 2, Day 15: any time

Cycle 4, Day 1: Predose

[m] For all prostate cancer patients in treatment Arm A6, 2.5 mL of blood will be collected at screening, Cycle 1 Day 1, at all response assessment visits and EOT.

[n] Archival tumor biopsy is mandatory if available. If the archival tumor sample is not available it will not impact the patient's right to participate in the trial.

[o] The collection of cfDNA samples is only required to be obtained for newly enrolled patients consented (under protocol amendment 5, dated 10 May 2017 and onwards). It is not a requirement to collect cfDNA samples for patients enrolled prior to the implementation of protocol amendment 5, dated 10 May 2017.

Abbreviations: Ab=antibody; ADA=antidrug antibody; cfDNA=circulating-free DNA; EOT=End-of-Treatment; FU=follow-up; ICF=informed consent form; IM=immunogenicity; MDSC1=myeloid-derived suppressor cells; PBMC=peripheral blood mononuclear cell(s); PK=pharmacokinetic; PDRNA=pharmacodynamic RNA (samples for STAT3 RNA and other exploratory analyses); sPD-L1=soluble programmed death-ligand 1; sPSA=serum prostate-specific antigen.

Table 7 Study plan for pharmacokinetic, pharmacodynamic, immunogenicity, and pharmacogenetic assessments in Part B (Arms B1-B7)

Assessments	Screening	Lead-in (-7 to -1)			Cycles															EOT[a]	FU
					C1			C2		C3	C4	C5	C6	C7	C8	C9	C10	C11	*C12		
Day:	-21 to -8	-7	-5	-3	1	8	15	1	15	1	1	1	1	1	1	1	1	1	1		
Blood samples for pharmacokinetic assessments																					
AZD9150[b]																					
First 10 pts[b]		x	x		x			x		x		x		x		x		x			
Subsequent pts & B7[b]								x		x		x		x		x		x			
AZD5069 (monotherapy arm)[c]								x		x		x		x		x		x			
AZD5069 (combination therapy arms)[d]																					
First 10 pts[d]		x			x			x		x		x		x		x		x			
Subsequent pts[d]								x		x		x		x		x		x			
MEDI4736[e]					x				x		x		x		x[e]		x		x		x
Urine samples for pharmacokinetic assessments (optional consent)																					
AZD9150[f]		x	x		x																
Blood samples for pharmacodynamic assessments																					
PDRNA[g]	x	x			x	x		x		x	x	x	x	x	x	x	x	x	x	x	
sPD-L1[h]					x				x		x		x		x		x		x		x
MDSCs[i]	x	x			x			x		x		x								x	
Blood samples for immunogenicity assessments																					
ADA[j]					x				x		x		x		x		x		x		x

Assessments	Screening	Lead-in (-7 to -1)			Cycles															EOT [a]	FU
					C1			C2		C3	C4	C5	C6	C7	C8	C9	C10	C11	*C12		
Day:	-21 to -8	-7	-5	-3	1	8	15	1	15	1	1	1	1	1	1	1	1	1	1		
Anti-AZD9150 Ab[k]					x			x			x		x		x		x		x		
Blood samples for exploratory blood-borne biomarkers[l]																					
Serum sample[l]	x	x		x	x	x	x	x		x		x		x		x		x		x	
Plasma sample[l]	x	x			x	x	x	x		x		x		x		x		x		x	
PBMC[l]	x	x			x	x	x			x			x			x				x	
cfDNA blood sample[o]	x	x						x			x		x		x		x		x	x	
Other																					
Collection of archival tumor samples	x																				
Tumor biopsy[m]	x							x												x[m]	
Optional																					
Pharmacogenetics[n]		x																			

[a] *In order to ensure all samples required for sample point collection are accurately collected, the cycles beyond Cycle 12 should mimic Cycle 9, 10, 11 and 12 in a repeated pattern through to Cycle 40, except where noted in the footnotes below (e.g., PBMC collection). An EOT visit shall occur as soon as possible following the decision to discontinue treatment.

[b] In the first 10 patients randomized to treatment with AZD9150 alone or in combination with MEDI4736 (i.e., treatment arm B1, B3, or B5), PK blood samples for AZD9150 (2 mL) will be taken as follows; a window of 10% of the nominal time point is acceptable:

Lead-in, Day −7: Predose and at 0.5 hour (±3 min), 1 (end of infusion; ±6 min), 2 (±12 min), 4 (±24 min), and 6 hours (±36 min) after the start of the infusion

Lead-in, Day −5: At 48 (±4) hours after the start of the first infusion (on Day −7) and before the second infusion (on Day −5)

Cycle 1, Day 1: Predose

Cycle 2, Day 1: Predose and at 0.5 hour (±3 min), 1 (end of infusion; ±6 min), 2 (±12 min), 4 (±24 min), and 6 hours (±36 min) after the start of the infusion

Cycle 3 and all subsequent odd-numbered cycles, Day 1: Predose

In patients following the first 10 patients randomised to treatment with AZD9150 alone or in combination with MEDI4736 (i.e., treatment arm B1, B3, or B5) and Arm B7, a predose and a 2-hour (±12 min) sample will be collected on Day 1 of Cycle 2 and subsequent odd-numbered cycles.

[c] In patients randomized to treatment with AZD5069 monotherapy (arm B6), PK blood samples for AZD5069 and its metabolite AZ13587715 (2 mL total) will be collected as follows; a window of 10% of the nominal time point is acceptable:

Cycle 2, Day 1: Before the morning dose

Cycle 3 and all subsequent odd-numbered cycles, Day 1: Before the morning dose

The morning dose of AZD5069 on any day where blood samples before the morning dose are required must be administered at the study centre and the precise time noted.

[d] In the first 10 patients randomised to treatment with AZD5069 combination therapy (i.e., treatment arm B2 or B4), PK blood samples for AZD5069 and its metabolite AZ13587715 (2 mL total) will be collected as follows; a window of 10% of the nominal time point is acceptable:

Lead-in, Day −7: Before the morning dose and at 0.5 hour (±3 min), 1 hour (±6 min), 2 hours (±12 min), 4 hours (±24 min), 6 hours (±36 min), and 8 hours (±48 min), and 10 hours (±60 min) (when possible) after the first morning dose

Cycle 1, Day 1: Before the morning dose and at 2 hours (±12 min) after the morning dose

Cycle 2, Day 1: Before the morning dose and at 0.5 hour (±3 min), 1 hours (±6 min), 2 hours (±12 min), 4 hours (±24 min), 6 hours (±36 min), and 8 hours (±48 min), and 10 hours (±60 min) (when possible) after the morning dose

Cycle 3 and all subsequent odd-numbered cycles, Day 1: Before the morning dose and 2 hours (±12 min) after the morning dose

Failure to obtain the 10-hour samples will not be considered a protocol deviation.

In patients following the first 10 patients randomised to treatment with AZD5069 in combination with MEDI4736 (i.e., treatment arm B2 or B4), a predose and a 2 hour (±12 min) sample will be collected on Day 1 of Cycle 2 and subsequent odd-numbered cycles. The morning dose of AZD5069 on Day −7 of the lead-in period and on any subsequent day where blood samples before the morning dose are required must be administered at the study centre and the precise time noted. Failure to obtain 10 and 12 hour samples will not be considered as protocol deviation.

[e] In patients randomized to receive MEDI4736 (i.e., treatment arm B1, B2, B3, B4, or B7), PK blood samples for MEDI4736 (3.5 mL) will be collected relative to the MEDI4736 infusion as follows; a window of 10% of the nominal time point is acceptable:

Cycle 1, Day 1: Predose and 1 hour (±6 min) after the start of the infusion (end of infusion)

Cycle 2, Day 15: Predose

Cycle 4 and all subsequent even-numbered cycles, Day 1: Predose

Cycle 8, Day 1: In addition to the predose sample, a sample at 1 hour (±6 min) after the start of the infusion (end of infusion)

Follow-up: For patients who discontinue MEDI4736, a sample will be drawn 90 days after their last dose of MEDI4736 (coinciding with an IM (ADA) sample

[f] In patients randomized to AZD9150 alone (treatment arm B5) and first 12 patients for the Arm B7, who optionally consented to urine PK sampling, urine PK samples (20 to 40 mL) will be collected from the total urine samples provided during each of the following collection intervals; a window of 10% of the nominal time point is acceptable:

Lead-in, Day −7: 0 to 1, 1 to 6, and 6 to 24 hours after start time of AZD9150 infusion

Lead-in, Day −6 to −5: 24 to 48 hours after the start time of the first AZD9150 infusion

Cycle 1, Day 1: 0 to 1, 1 to 6, and 6 to 24 hours after start time of AZD9150 infusion

[g] Note: Instructions will be provided to patients to collect these samples, as applicable, at home.For all patients, 2 blood samples (2.5 mL each) for PDRNA will be collected predose at each specified time point to assess pharmacodynamic response in blood for AZD9150 (STAT3 knockdown) and exploratory blood-borne biomarkers that may correlate to treatment or response (gene expression changes or modification of genomic DNA): At screening, Day −7 of the lead-in period, Day 1 and Day 8 of Cycle 1, Day 1of subsequent Cycles and at the EOT visit. The revised sample collection for PDRNA samples is applicable to newly enrolled patients only under protocol amendment 5, dated 10 May 2017 and onwards; existing patients will have samples collected up to Cycle 5, Day 1. New patients will be required to have samples collected beyond Cycle 5.

[h] In patients randomized to receive MEDI4736 (i.e., treatment arms B1, B2, B3 and B4), a single blood sample (3.5 mL) will be collected predose at each specified time point to assess the pharmacodynamic response in blood for MEDI4736 (sPD-L1): Day 1 of Cycle 1, Day 15 of Cycle 2, 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. sPDL samples will NOT be collected for the following patients: patients in B1, B2 and B4 post first 20 patients and patients in Arm B7

[i] For all patients, blood samples for MDSC (5 mL), will be collected predose 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. MDSC samples will NOT be collected for the following patients: patients in B1, B2 and B4 post first 20 patients and patients in Arm B7.

[j] In patients randomised to receive MEDI4736 (i.e., treatment arms B1, B2, B3, B4, and B7), blood samples for IM (5 mL) will be collected predose on Day 1 of Cycle 1, on Day 15 of Cycle 2, and on Day 1 of each subsequent even-numbered cycle. For patients who discontinue MEDI4736, a blood sample will also be collected during follow-up at 90 days after the last dose of MEDI4736.

[k] For patients treated with AZD9150, blood samples for IM (2 mL) will be collected relative to AZD9150 infusion as follows: Cycle 1, Day 1: Predose; Cycle 2, Day 1: Predose; and Cycle 4 and all subsequent even-numbered cycles, Day 1: Predose.

[l] For all patients, at the time points specified, a single 2 mL blood sample for serum, a single 10 mL blood sample for plasma, and two 6 mL blood samples for PBMC will be collected predose for the assessment of exploratory biomarkers.

The 2 mL blood sample for serum will be obtained at screening, on Days −7 and −3 of the lead-in period, Days 1, 8, and 15 of Cycle 1, on Day 1 of Cycle 2, on Day 1 of all subsequent odd-numbered cycles, and at the EOT visit.

The 10 mL blood sample for plasma will be obtained at screening, on Day −7 of the lead-in period, Days 1, 8, and 15 of Cycle 1, on Day 1 of Cycle 2, on Day 1 of all subsequent odd-numbered cycles, and at the EOT visit.

The two 6 mL blood samples for PBMC will be obtained at screening, on Day −7 of the lead-in period, on Days 1, 8, and 15 of Cycle 1, on Day 1 of cycles 3, 6, and 9, and at the EOT visit.

[m] To be eligible, patients must have at least 1 SCCHN lesion amenable to biopsy and must be medically fit and willing to undergo a mandatory biopsy during screening and, unless clinically contraindicated, again at the end of Cycle 1 (designated as Cycle 2 Day 1 in the table above). Lesions used for biopsy should not be those used as RECIST lesions, unless there are no other lesions suitable for biopsy (in which case, the lesion must be ≥2 cm in longest diameter). In the event of disease progression, biopsies at the EOT are optional but encouraged. On-treatment biopsy timing may be refined with emerging PK and/or pharmacodynamic data during the course of the trial, and the collection of on-treatment tumor samples may be stopped at the Sponsor's discretion. Screening biopsy sample: if patient has a biopsy report and sample from fewer than 45 days prior to start of treatment (Day -7), it would be considered acceptable. On-treatment biopsy: there is a ± 1 week window for collection of this biopsy sample.

[n] If a patient agrees to participate in the host pharmacogenetics research component of the study and signs a separate ICF for genetic research, a saliva sample will be collected. The saliva sample for genetic research will ideally be obtained from the patients immediately prior to dosing on Day 1. If for any reason, the sample is not obtained prior to dosing, it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient for genetics during the study. See Section 5.8.2 for details.

[o] The collection of cfDNA samples is only required to be obtained for newly enrolled patients consented under protocol amendment 5, dated 10 May 2017 and onwards. It is not a requirement to collect cfDNA samples for patients enrolled prior the implementation of protocol amendment 5, dated 10 May 2017.

Abbreviations: ADA=antidrug antibody; cfDNA=circulating-free DNA; EOT=End-of-Treatment; FU=follow-up; IM=immunogenicity; MDSC=myeloid-derived suppressor cells; PBMC=peripheral blood mononuclear cell(s); PK=pharmacokinetic; PDRNA=pharmacodynamic RNA (samples for STAT3 RNA and other exploratory analyses); pts=patients; RECIST=Response and Evaluation Criteria for the Evaluation of Solid Tumors; SCCHN=squamous cell carcinoma of the head and neck; sPD-L1=soluble programmed death-ligand 1.

Table 8 Study plan for pharmacokinetic, pharmacodynamic, immunogenicity, and pharmacogenetic assessments in Part B (B8)

Assessments	Screening	Lead-in (-7 to -1)			Cycles															EOT[a]	FU
					C1			C2		C3	C4	C5	C6	C7	C8	C9	C10	C11	*C12		
Day:	-21 to -8	-7	-5	-3	1	8	15	1	15	1	1	1	1	1	1	1	1	1	1		
Blood samples for pharmacokinetic assessments																					
AZD9150[b]		x			x			x		x		x		x		x		x			
MEDI4736[c]					x				x		x		x		x		x		x		x[d]
Urine samples for pharmacokinetic assessments (mandatory for up to 12 patients and then optional consent thereafter – USA only)																					
AZD9150[e]		x	x		x																
Blood samples for pharmacodynamic assessments																					
PDRNA	x	x			x		x	x		x	x	x	x	x	x	x	x	x	x	x	
Blood samples for immunogenicity assessments																					
ADA[f]					x				x		x		x		x		x		x		x
Anti-AZD9150 Ab[g]		x			x			x			x		x		x		x		x		x
Blood samples for exploratory blood-borne biomarkers[h]																					
Serum sample[h]	x	x		x	x		x	x		x		x		x		x		x		x	
Plasma sample[h]	x	x			x		x	x		x		x		x		x		x		x	
PBMC[h]	x	x			x		x			x			x			x				x	
cfDNA blood sample	x	x						x		x	x		x		x		x		x	x	
Other																					
Collection of archival tumor samples	x																				

Assessments Day:	**Screening**	**Lead-in (-7 to -1)**			**Cycles**															**EOT**[a]	**FU**
					C1			**C2**		**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**	**C11**	***C12**		
	-21 to -8	**-7**	**-5**	**-3**	**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**		
Tumor biopsy[i]	x							x												x	
Optional																					
Pharmacogenetics[j]		x																			

[a] *In order to ensure all samples required for sample point collection are accurately collected, the cycles beyond Cycle 12 should mimic Cycle 9, 10, 11 and 12 in a repeated pattern through to Cycle 40, except where noted in the footnotes below (eg, PBMC collection). An EOT visit shall occur as soon as possible following the decision to discontinue treatment.

[b] AZD9150 PK samples are required at predose, 1 hour (end of infusion) and 2 hours (±12 min) on lead-in Day −7, Day 1 of Cycle 1, Cycle 2, Cycle 3, Cycle 5, Cycle 7, Cycle 9, and Cycle 11 in the first year and then every 6 cycles.

[c] PK blood samples for MEDI4736 (3.5 mL) will be collected relative to the MEDI4736 infusion as follows; a window of 10% of the nominal time point is acceptable:

Cycle 1, Day 1: Predose and 1 hour (±6 min) after the start of the infusion (end of infusion)

Cycle 2, Day 15: Predose

Cycle 4 and all subsequent even-numbered cycles, Day 1: Predose

Cycle 8, Day 1: In addition to the predose sample, a sample at 1 hour (±6 min) after the start of the infusion (end of infusion)

[d] Follow-up: For patients who discontinue MEDI4736, a sample will be drawn 90 days after their last dose of MEDI4736 (coinciding with an IM (ADA) sample or prior to the initiation of a subsequent anticancer therapy.

[e] USA only: For up to 12 patients enrolled into this cohort, it will be mandatory to obtain urine PK sampling; for subsequent patients in B8, these samples will be optional. Urine PK samples (20 to 40 mL) will be collected from the total urine samples provided during each of the following collection intervals; a window of 10% of the nominal time point is acceptable:

Lead-in, Day −7: 0 to 1, 1 to 6, and 6 to 24 hours after start time of AZD9150 infusion

Lead-in, Day −6 to −5: 24 to 48 hours after the start time of the first AZD9150 infusionCycle 1, Day 1: 0 to 1 and 1 to 6 hours after start time of AZD9150 infusion.

Note: Instructions will be provided to patients to collect these samples, as applicable, at home.

[f] MEDI4736 blood samples for IM (5 mL) will be collected predose on Day 1 of Cycle 1, on Day 15 of Cycle 2, and on Day 1 of each subsequent even-numbered cycle. For patients who discontinue MEDI4736, a blood sample will also be collected during follow-up at 90 days after the last dose of MEDI4736.

[g] AZD9150 blood samples for IM (2 mL) will be collected relative to AZD9150 infusion as follows: Day -7, Day 1 of Cycle 1, on Day 1 of Cycle 2, and on Day 1 of each subsequent even-numbered cycle. For patients who discontinue AZD9150, a blood sample will also be collected during follow-up at 90 days after the last dose of AZD9150.

[h] For all patients, at the time points specified, a single 2 mL blood sample for serum, a single 10 mL blood sample for plasma, and two 6 mL blood samples for PBMC will be collected predose for the assessment of exploratory biomarkers.

The 2 mL blood sample for serum will be obtained at screening, on Days −7 and −3 of the lead-in period, Days 1 and 15 of Cycle 1, on Day 1 of Cycle 2, on Day 1 of all subsequent odd-numbered cycles, and at the EOT visit.

The 10 mL blood sample for plasma will be obtained at screening, on Day −7 of the lead-in period, Days 1 and 15 of Cycle 1, on Day 1 of Cycle 2, on Day 1 of all subsequent odd-numbered cycles, and at the EOT visit.

The two 6 mL blood samples for PBMC will be obtained at screening, on Day −7 of the lead-in period, Days 1 and 15 of Cycle 1, on Day 1 of Cycles 3, 6, and 9, and at the EOT visit.

[i] To be eligible, patients must have at least 1 SCCHN lesion amenable to biopsy and must be medically fit and willing to undergo a mandatory biopsy during screening and, unless clinically contraindicated, again at the end of Cycle 1 (designated as Cycle 2 Day 1 in the table above). Lesions used for biopsy should not be those used as RECIST lesions, unless there are no other lesions suitable for biopsy (in which case, the lesion must be ≥2 cm in longest diameter). In the event of disease progression, biopsies at the EOT are optional but encouraged. On-treatment biopsy timing may be refined with emerging PK and/or pharmacodynamic data during the course of the trial, and the collection of on-treatment tumor samples may be stopped at the Sponsor's discretion. Screening biopsy sample: if patient has a biopsy report and sample from fewer than 45 days prior to start of treatment (Day -7), it would be considered acceptable. On-treatment biopsy: there is a ± 1 week window for collection of this biopsy sample.

[j] If a patient agrees to participate in the host pharmacogenetics research component of the study and signs a separate ICF for genetic research, a saliva sample will be collected. The saliva sample for genetic research will ideally be obtained from the patients immediately prior to dosing on Day 1. If for any reason, the sample is not obtained prior to dosing, it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient for genetics during the study. See Section 5.8.2 for details.

Abbreviations: ADA=antidrug antibody; cfDNA=circulating-free DNA; EOT=End-of-Treatment; FU=follow-up; IM=immunogenicity; MDSC=myeloid-derived suppressor cells; PBMC=peripheral blood mononuclear cell(s); PK=pharmacokinetic; PDRNA=pharmacodynamic RNA (samples for STAT3 RNA and other exploratory analyses); pts=patients; RECIST=Response and Evaluation Criteria for the Evaluation of Solid Tumors; SCCHN=squamous cell carcinoma of the head and neck; sPD-L1=soluble programmed death-ligand 1.

5.3 Efficacy assessments

5.3.1 Tumor assessments

Tumor assessments will be performed at screening, on Day 15 of Cycle 2, at the beginning of Week 7, at the beginning of each subsequent even-numbered cycle, and at the EOT visit. Patients who are on study treatment for more than 24 months may have the frequency of tumor assessment reduced to every 12 to 16 weeks at the discretion of the Investigator. Patients who discontinue treatment for reasons other than PD will continue to undergo tumor assessments every 2 months (±7 days) until PD is noted.

It is important to follow the assessment schedule as closely as possible. To facilitate scheduling of tumor assessments, a window of ±7 days is allowed.

Baseline tumor assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Baseline assessments should be performed no more than 21 days before the start of study treatment and ideally should be performed as close as possible to the start of study treatment. Tumor assessments 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.

Tumor assessments may include the following evaluations: Physical examination (with photograph and measurement of skin lesions as applicable); CT or MRI scan of the chest, abdomen, and pelvis; and CT or MRI scan of the brain. CT or MRI scan of the brain will be performed only at screening or if the patient is neurologically symptomatic. The preferred method of disease assessment is CT with contrast. If CT with contrast is contraindicated, CT without contrast is preferred over MRI. The methods of assessment used at baseline should be used at each subsequent follow-up assessment. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform subsequent assessments at the scheduled visits while the patient remains on study treatment.

Sites will be required to store electronic copies of all scans, and the study Sponsor may arrange for possible centralized storage of all imaging data. The centralized storage of imaging data would be for possible independent centralized review of disease assessments.

5.3.1.1 Response assessment

All patients will be evaluated according to the study plan (see Section 5.2, Table 5) and their clinical status classified according to the revised RECIST guidelines version 1.1 (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 PD is assessed (Wolchok et al 2009). Specifically, RECIST version 1.1 has 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, TLs, and nontarget lesions (NTLs) and the objective tumor response criteria are presented in Appendix F "Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 (Response Evaluation Criteria in Solid Tumors)" of this CSP.

If the Investigator is in doubt as to whether progression has occurred, particularly with response to NTLs or the appearance of a new lesion, it is advisable to continue treatment and reassess the patient's status at the next scheduled assessment or sooner if clinically indicated.

To achieve "unequivocal progression" on the basis of nontarget disease, there must be an overall level of substantial worsening in nontarget disease such that, even in the presence of stable disease (SD) or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of 1 or more NTLs is usually not sufficient to qualify for unequivocal disease progression status.

5.4 Safety assessments

At each clinic visit, the Investigator will be responsible for reviewing all available safety data, including vital sign measurements and ECG recordings, and assessing the patient for signs of tumor progression. To facilitate scheduling of predose assessments, a window of -2 days is allowed to obtain the following procedures prior to dosing a patient: Complete and targeted physical exam, weight, laboratory safety tests (haematology, serum chemistry, and coagulation), urinalysis, and thyroid function tests.

5.4.1 Laboratory safety assessments

All blood samples will be analyzed at the central laboratory for the study on behalf of AstraZeneca. On days of study drug administration, to shorten the time between the blood draw and the decision if dosing may proceed, blood samples for routine haematology and serum chemistry safety assessments are to be drawn and split into 2 samples: one portion of the sample is to be analysed locally to determine toxicity prior to dosing, and the second portion of the sample is to be sent to the designated central laboratory.

Samples are not to be split on days where no study drug administration is scheduled. See Study Plan (Section 5.2, Table 5) for details.

Blood samples for routine haematology and serum chemistry safety assessments will be obtained at screening; before dosing on Day −7 of the lead-in; before dosing on Days 1, 8, 15, and 22 of Cycle 1; before dosing on Days 1 and 15 of all subsequent cycles; and at the EOT visit.

Blood samples for routine coagulation assessments will be obtained at screening; before dosing on Day −7 of the lead-in; before dosing on Days 1 and 15 of Cycle 1; before dosing on Day 1 of all subsequent cycles; and at the EOT visit.

Urine samples for routine urinalysis will be obtained at screening; before dosing on Day −7 of the lead-in; before dosing on Days 1 and 15 of Cycle 1; before dosing on Day 1 of all subsequent cycles; and at the EOT visit.

The study plan shown in Table 9 lists the variables that will be measured for routine haematology, serum chemistry, coagulation, and urinalysis.

In addition, thyroid function tests are required at screening, before dosing on Day −7 of the lead-in, before dosing on Day 1 of each cycle, and at the EOT visit. Thyroid function tests include thyroid-stimulating hormone and free T3 and T4.

Blood samples for HIV, HBV, and HCV serology are required at screening. The eligibility of patients who have active infection for HIV, HBV, and/or HCV is at the discretion of the Investigator. HIV screening will be based on an FDA-approved antigen/antibody combination immunoassay; HBV screening will include HBsAg, anti-HBc, and anti-HBs, and HCV screening will be based on anti-HCV. HPV status will be collected at screening visit.

For women of childbearing potential (see Section 3.8.1), negative pregnancy tests are required before entering the study and while on study. A blood sample to determine serum β-human chorionic gonadotropin (β hCG) is required at screening; this sample will be analysed at the central laboratory for the study. Additionally, urine samples for a urine-based pregnancy test will be collected before dosing on Day −7 of the lead-in, before dosing on Day 1 of each cycle, and at the EOT visit. Urine-based pregnancy tests will be performed at the study centres.

On Day −7 of the lead-in, laboratory safety assessments do not need to be repeated if the screening assessments were performed no more than 3 days before. The date of each collection will be recorded in the appropriate eCRF.

The timing of blood samples may be altered depending on the emerging PK and safety profile. Additional sampling times may be added if indicated by the emerging data.

Laboratory values that meet the criteria for CTCAE grade 3 or have changed significantly from baseline and are considered to be of clinical concern should be repeated/confirmed within 7 days and followed up as appropriate.

Importantly, in case a patient's AST, ALT, or TBL test results show an AST or ALT ≥3 × ULN or TBL ≥2 × ULN, please refer to Appendix G of this CSP "Actions Required in Cases of Increases of Liver Biochemistry and Evaluation of Hy's Law" for further instructions.

For blood volume, see Section 5.8.3.

The following laboratory variables will be measured:

Table 9 Laboratory Safety Variables

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.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

5.4.2 Physical examination

A complete physical examination will be performed at screening, before dosing on Day −7 of the lead-in, before dosing on Day 1 of each cycle, and at the EOT visit. A targeted physical

examination as directed by disease, signs and symptoms is required before dosing on Day 15 of each cycle.

5.4.3 ECG

Electrocardiograms will be obtained at screening, throughout the treatment, and at the EOT visit. On days when ECGs and PK samples are drawn, ECG must always be taken prior to the PK blood draw.

- For patients treated with AZD5069: On Day 1 of Cycle 1, 12-lead ECGs should be recorded 2 hours after the morning dose of AZD5069 and for patients treated with MEDI4736, again 2 hours after end of the MEDI4736 infusion. On Day 1 of Cycle 2 and of all subsequent odd-numbered cycles (to match PK assessments), 12 lead ECGs should be recorded 2 hours after the morning dose of AZD5069. The timing and number of ECGs may be adjusted by the SRC in response to the emerging PK and safety profile.
- For patients not treated with AZD5069, 12-lead ECGs will be obtained at screening, on Day 1 of Cycle 1 (2 hours after the end of the AZD9150 infusion, and for patients treated with MEDI4736, again 2 hours after end of the MEDI4736 infusion), and at the EOT visit.
- For B8, 12-lead ECGs will be obtained at screening, Day −7, Day 1 of Cycles 1, 2, and 3, and subsequent odd-numbered cycles for first year: pre-dose and 1 hour after the start of AZD9150 infusion (end of AZD9150 infusion) and 2 hours after the start of infusion, every 6 cycles after 1 year, and at the EOT visit.

5.4.3.1 Resting 12-lead ECG

Twelve-lead ECGs will be obtained after the patient has been resting semi-supine for at least 10 minutes. All ECGs should be recorded with the patient in the same physical position. A standardised ECG machine should be used and the patient should be examined using the same machine throughout the study, where feasible. For Arm B8, central digital ECGs will be used.

For each time point, 3 ECG recordings should be taken within a 5 minute interval, but a window of up to -30 minutes is acceptable (as all the ECGs are triplicate). The mean QTcF interval from all 3 ECGs at any given time point should be considered for evaluation of eligibility and toxicity.

After paper ECGs have been recorded, the Investigator or designated physician will review each of the ECGs and may refer to a local cardiologist if appropriate. A paper copy should be filed in the patient's medical records. If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the Investigator, it should be reported as a concurrent condition. For all ECGs, details of rhythm, PR, R-R, QRS, and QTc intervals and an overall evaluation will be recorded.

5.4.4 Vital signs

Vital signs including resting pulse, supine blood pressure (BP), respiratory rate, and body temperature measured in degrees Celsius, should be assessed at screening; before dosing on Day −7 of the lead-in; before dosing on Days 1, 8, 15, and 22 of each cycle; and at the EOT visit. Measurements should be taken in a supine position following at least 10 minutes of rest.

Vital signs for patients on AZD5069 will not be required for Day 8 and Day 22 visits beyond Cycle 2 as there are no dosing visits scheduled for patients on these days. Vital signs for patients in Arm B8 will not be required for Day 8 and Day 22 (all cycles) as there are no dosing visits scheduled for these patients on these days.

Height (in centimetres) will be obtained at screening.

Weight (in kilograms) will be obtained at screening, before dosing on Day −7 of the lead-in, before dosing on Day 1 of each cycle, and at the EOT visit. Weight obtained on Day −7 of the lead-in will be used to calculate the weight-related doses of AZD9150 (with the exception of Arm B8) for the lead-in. Weight obtained on Day 1 of each cycle will be used to calculate the weight-related dose of AZD9150 for each cycle.. In Arm B8, a flat dose for AZD9150 and MEDI4736 will be administered. MEDI4736 will be administered as 1.5g flat dose Q4W. If body weight decreases to less than 30 kg, weight-based dosing (20 mg/kg Q4W) will be implemented from that cycle onwards.

The Investigator should assess any abnormal changes (i.e., changes that are out of range) in vital sign measurements for their clinical significance and determine if they require to be recorded as an AE.

5.4.5 Eastern Cooperative Oncology Group performance status (Other safety assessments)

Eastern Cooperative Oncology Group PS will be assessed at screening, before dosing on Day -7 of the lead-in, before dosing on Day 1 of each cycle, and at the EOT visit. The ECOG PS will be used to assess how a patient's disease is progressing, assess how the disease affects the patient's daily activities, and help the Investigator determine the appropriate treatment and progress. The ECOG scales and criteria are defined as follows:

0 = Fully active, able to carry out all predisease activities without restrictions

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

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

3 = Capable of only limited self-care confined to bed or chair more than 50% of waking hours

4 = Completely disabled; cannot carry on self-care; totally confined to bed or chair

5 = Death

5.5 Pharmacokinetics

5.5.1 Collection of samples

Venous blood samples for analysis of AZD9150, AZD5069 and its metabolite AZ13587715, tremelimumab, and MEDI4736 will be obtained to determine the plasma concentrations of each of the various agents under investigation (see Table 6 for the dose-escalation Part A and Table 7 for the dose-expansion Part B of the study). The date and time of collection of each sample will be recorded. A window of 10% of the nominal time point is acceptable (e.g., ±3 minutes for a 30-minute timepoint, ±6 minutes for a 60-minute time point, etc.).

- For patients treated with **AZD9150** in Part A, PK blood samples for AZD9150 (Arms A1, A4 and A6) (2 mL) will be collected relative to the AZD9150 infusion as follows:
    - Lead-in, Day −7: Predose and at 0.5 hour (±3 min), 1 (end of infusion; ±6 min), 2 hours (±12 min), 4 hours (±24 min), and 6 hours (±36 min) after the start of the infusion
    - Lead-in, Day −5: At 48 (±4) hours after the start of the first infusion (on Day −7) and before the second infusion (on Day − 5)
    - Cycle 1, Day 1: Predose
    - Cycle 2, Day 1: Predose and at 0.5 hour (±3 min), 1 (end of infusion; ±6 min), 2 hours (±12 min), 4 hours (±24 min), and 6 hours (±36 min) after the start of the infusion
    - Cycle 3 and all subsequent odd-numbered cycles, Day 1: Predose
    - In Part B, only the first 10 patients randomised to treatment with AZD9150 alone or in combination with MEDI4736 (i.e., treatment arm B1, B3 or B5), will follow the schedule as in Part A. In patients following the first 10 patients randomised to treatment with AZD9150 alone or in combination with MEDI4736 (i.e., treatment arm B1 or B3) and in Arms B7 and B8, a predose and a 2 hour (±12 min) sample will be collected on Day 1 of Cycle 2 and subsequent odd-numbered cycles.

- For patients treated with **AZD5069** (Arms A2 and A3) in Part A (**PRIOR TO DETERMINATION OF RP2D**), PK blood samples for AZD5069 and its metabolite AZ13587715 (2 mL total) will be collected as follows:
    - Lead-in, Day −7: Before the first morning dose and at 0.5 hour (±3 min), 1 hour (±6 min), 2 hours (±12 min), 4 hours (±24 min), 6 hours (±36 min), 8 hours (±48 min), and 10 hours (±60 min) (when possible, if optional consent is provided) after the first morning dose
    - Cycle 1, Day 1: Before the morning dose and at 2 hours (±12 min) after the morning dose
    - Cycle 2, Day 1: Before the morning dose and at 0.5 hour (±3 min), 1 hour (±6 min), 2 hours (±12 min), 4 hours (±24 min), 6 hours (±36 min), 8 hours (±48 min), and 10 hours (±60 min) (when possible, if optional consent is provided) after the morning dose
    - Cycle 3 and all subsequent odd-numbered cycles, Day 1: Before the morning dose and at 2 hours (±12 min) after the morning dose
    - Failure to obtain the 10 hour (±60 min) samples will not be considered a protocol deviation

      The morning dose of AZD5069 on Day −7 of the lead-in period and on any subsequent day where blood samples before the morning dose are required must be administered at the study centre and the precise time noted.

- In Part B, only the first 10 patients randomised to treatment **AZD5069** in combination with MEDI4736 (i.e., treatment arm B2 or B4), will follow the schedule as in Part A. In patients following the first 10 patients randomised to treatment with AZD5069 in combination with MEDI4736 (i.e., treatment arm B2 or B4), a predose and a 2 hour (±12 min) sample will be collected on Day 1 of Cycle 2, and subsequent odd-numbered cycles.
    - Failure to obtain the 10-hour samples will not be considered a protocol deviation
    - The morning dose of AZD5069 on any day where blood samples before the morning dose are required must be administered at the study centre and the precise time noted.

- For patients treated with **AZD5069** monotherapy in Part B (i.e., treatment arm B6) PK blood samples for **AZD5069** and its metabolite AZ13587715 (2 mL total) will be collected as follows:
    - Cycle 2, Day 1: Before the morning dose

  - Cycle 3 and all subsequent odd-numbered cycles, Day 1: Before the morning dose

  - The morning dose of AZD5069 on any day where blood samples before the morning dose are required must be administered at the study centre and the precise time noted.

- For all patients in Part A and for patients randomised to receive **MEDI4736** in Part B (i.e., treatment arm B1, B2, B3, B4, or B7), PK blood samples for **MEDI4736** (3.5 mL) will be collected relative to the MEDI4736 infusion as follows:
  - Cycle 1, Day 1: Predose and 1 hour (±6 min) after the start of the infusion (end of infusion)

  - Cycle 2, Day 15: Any time

  - Cycle 4 and all subsequent even-numbered cycles, Day 1: Predose

  - Cycle 8, Day 1: In addition to the predose sample, a sample at 1 hour (±6 min) after the start of the infusion (end of infusion)

  - Follow-up: For patients who discontinue MEDI4736, a sample will be drawn 90 days after their last dose of MEDI4736 (coinciding with an IM [antidrug antibody (ADA)] sample)

- For all patients in treatment arm A4 in Part A, PK blood samples for tremelimumab (3.5 mL) will be collected relative to the tremelimumab infusion as follows:
  - Cycle 1, Day 1: Predose and 1 hour (±6 min) after the start of the infusion (end of infusion)

  - Cycle 2, Day 15: Any time

  - Cycle 4, Day 1: Predose

Of the patients randomly assigned to treatment with AZD9150 alone in the dose-expansion Part B (treatment arm B5) and the first 12 patients for arm B7 will be asked to provide urine samples for AZD9150 PK assessments in urine (see Table 7). For Arm B8, up to 12 patients enrolled will be required to provide consent for urine samples for PK assessments (mandatory, USA only). For the subsequent patients enrolled in this arm, consent will be optional (see Table 8). Patients' consent to this evaluation will be documented on a separate ICF for urine sample collection. The date and time of collection and the weight of each urine collection will be recorded.

- For patients randomised to **AZD9150** alone (treatment arm B5) and first 12 patients for the Arm B7 who optionally consented to urine PK sampling and up to 12 patients of Arm B8 (mandatory, USA only)(or if optional consent was provided), urine PK samples (20 to 40 mL) will be collected from the total urine samples provided during each of the following collection intervals:
    - Lead-in, Day −7: 0 to 1, 1 to 6, and 6 to 24 hours after start time of AZD9150 infusion
    - Lead-in, Day −6 to −5: 24 to 48 hours after the start time of the first AZD9150 infusion
    - Cycle 1, Day 1: 0 to 1, 1 to 6, and 6 to 24 hours after start time of AZD9150 infusion. Note: The Cycle 1, Day 1, 6 to 24 hour time point is not required for treatment arm B8.

  Note: Instructions will be provided to patients to collect these samples, as applicable, at home.

- For patients enrolled in treatment arm B8 to receive **AZD9150** 400 mg Q2W (200 mg in lead-in period) in combination with **MEDI4736** 1.5 g, PK blood samples for AZD9150 will be collected relative to the **AZD9150** infusion as follows:
    - Predose, 1 hour and 2 hours (±12 min) on: Lead-in Day −7, and Day 1 of Cycle 1, Cycle 2, Cycle 3, Cycle 5, Cycle 7, Cycle 9, and Cycle 11 and then every 6 cycles

- For patients enrolled in treatment arm B8 to receive **AZD9150** 400 mg Q2W (200 mg in lead-in period) in combination with **MEDI4736** 1.5 g, PK blood samples for MEDI4736 (3.5 mL) will be collected relative to the **MEDI4736** infusion as follows:
    - Cycle 1, Day 1: Predose and 1 hour (±6 min) after the start of the infusion (end of infusion)
    - Cycle 2, Day 15: Predose
    - Cycle 4 and all subsequent even-numbered cycles, Day 1: Predose
    - Cycle 8, Day 1: In addition to the predose sample, a sample at 1 hour (±6 min) after the start of the infusion (end of infusion)
    - Follow-up: For patients who discontinue MEDI4736, a sample will be drawn 90 days after their last dose of MEDI4736 (coinciding with an IM [ADA] sample or prior to the initiation of a subsequent anticancer therapy).

The timing of the PK samples may be adjusted during the study, dependent on emerging data, in order to ensure appropriate characterisation of the plasma concentration-time profiles. The

total number of samples and the total volume of blood taken from each patient will not exceed those presented in Table 10, Section 5.8.3.

If a patient misses any doses of AZD9150 or AZD5069 within 3 days of PK sampling, please contact the AstraZeneca PK representative via the Medical Monitor [redacted] (see Section 6.10 for contact information) to inquire if changes in the timing of the PK assessments are required. (Note: All other assessments, including laboratory safety assessments, vital signs, and RECIST should continue to be performed as per study plan, relative to baseline assessments.)

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

Any residual sample remaining after PK analysis has been performed may be used for exploratory biomarker research and characterisation of metabolites, if consent for this exploratory research has been obtained.

5.5.2 Determination of drug concentration

Samples for determination of AZD9150, AZD5069 and its metabolite AZ13587715, tremelimumab, and MEDI4736 will be analysed, using appropriate bioanalytical methods. Full details of the analytical method used will be described in a separate bioanalytical report.

All samples still within the known stability of the analytes of interest at the time of receipt by the bioanalytical laboratory will be analysed by a central laboratory on behalf of AstraZeneca.

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

5.5.3 Storage and destruction of pharmacokinetic samples

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

Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the Clinical Study Report (CSR).

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

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

5.6 Pharmacodynamics and patient selection biomarkers

Any sample collections listed in this Section may be discontinued at any time during the study at the Sponsor's discretion. See Table 6 for the dose-escalation Part A and Table 7 for the dose-expansion Part B of the study.

5.6.1 Collection of blood samples for pharmacodynamics assessments

In both the dose-escalation and safety cohorts Part A and dose-expansion Part B of the study, blood samples (2.5 mL) for evaluation of STAT3 RNA knockdown (secondary objective) and associated gene expression changes (exploratory objective)/pharmacodynamic RNA (AZD9150) will be collected from patients at screening; on Day −7 of the lead-in period; on Day 1 and Day 8 of Cycle 1; on Day 1 of all subsequent cycles; and at the EOT visit. The revised sample collection for pharmacodynamic RNA samples is applicable to newly enrolled patients only under protocol amendment 5, dated 10 May 2017 and onwards, existing patients will have samples collected up to Cycle 5, Day 1. New patients will be required to have samples collected beyond Cycle 5.

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 sPD-L1 samples will not be collected after the first 20 patients. The sPD-L1 samples will also not be collected for Arms B7 and B8.

Details of pharmacodynamic blood sample collection, processing, shipping, and storage will be described in the Laboratory Manual.

5.6.2 Collection of blood for myeloid-derived suppressor cells

In both the dose-escalation Part A and dose-expansion Part B of the study, blood sample (5 mL for MDSC) will be collected: At screening, Day −7 of the lead-in period, Day 1 of Cycles 1, 2, 3, 5, and at the EOT visit. Samples will be used for quantification of MDSCs by flow cytometry using a multicolour panel of cell surface markers. Myeloid-derived suppressor cell levels at baseline and/or effect of treatment on MDSCs may predict clinical responses. 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 B7 and B8.

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

5.6.3 Collection of tumor biopsies for evaluation of STAT3 and PD-L1 expression

In Part B of the study, eligibility criteria require a patient to have at least 1 SCCHN lesion (TL) amenable for a biopsy and to be medically fit and willing to undergo a biopsy during screening and, unless clinically contraindicated, at the end of Cycle 1. Lesions used for biopsy should not be those used as RECIST lesions, unless there are no other lesions suitable for biopsy. If a RECIST TL is used for biopsy, the lesion must be ≥2 cm in the longest diameter.

A baseline biopsy is mandatory, and an on-treatment biopsy at the end of Cycle 1 is mandatory and will be performed when clinically feasible (i.e., unless clinically contraindicated or the patient has withdrawn consent); a biopsy collection upon disease progression is optional but encouraged when feasible. Failure to obtain sufficient on treatment tumor samples after making best efforts to biopsy the tumor will not be considered a protocol deviation. Also biopsy reports and samples of biopsy done fewer than 45 days prior to start of treatment (Day -7) on the trial would be an acceptable substitute to baseline biopsy.

On-treatment biopsy timing may be refined with emerging PK and/or pharmacodynamic data during the course of the trial, and the collection of on-treatment tumor samples may be stopped at the Sponsor's discretion. There is a ± 1 week window for on treatment biopsy collection.

Baseline and on-treatment biopsies will be used to assess tumor STAT3 pharmacodynamics in tumor and immune infiltrating cells by immunohistochemistry and/or gene expression analysis.

Baseline biopsies will be used to assess PD-L1 as a potential patient selection biomarker by examining its expression level and localisation on tumor and immune infiltrating cells by immunohistochemistry.

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

5.6.4 Storage, re-use and destruction of pharmacodynamic samples

Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. The results of any investigation will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

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

5.7 Immunogenicity

In all patients treated with MEDI4736, venous blood samples for IM assessments will be obtained. This applies to all patients in the dose-escalation Part A and patients randomised to receive MEDI4736 in the dose-expansion Part B (i.e., treatment arms B1, B2, B3, B4, B7, and B8). The date and time of collection of each sample will be recorded.

Blood samples for IM (5 mL) will be collected predose on Day 1 of Cycle 1, on Day 15 of Cycle 2, and on Day 1 of each subsequent even-numbered cycle. For patients who discontinue MEDI4736, a blood sample will also be collected during follow-up at 90 days after the last dose of MEDI4736.

Blood samples for IM determination of a potential anti-AZD9150 antibody (2 mL) will be collected predose from all patients treated with AZD9150 on Day -7 (B8 only), Day 1 of Cycle 1, Day 1 of Cycle 2, and Day 1 of each subsequent even-numbered cycle.

Samples will be measured for the presence of ADA using a validated bridging immunoassay. Tiered analysis will be performed to include screening, confirmatory, and titre assay components and positive-negative cut points will be employed that were statistically determined from drug naïve validation samples.

Samples will be stored for assessing the neutralisation capacity in the future.

5.8 Exploratory research

5.8.1 Exploratory biomarker research

Participation in the exploratory biomarker research component of the study is mandatory. Biological samples (e.g., plasma, serum, PBMCs, PDRNA, archival tumor samples, and tumor biopsy sections remaining after secondary biomarker assessments) will be collected and analysed for exploratory biomarkers to assess correlations with disease activity, effects of study drug and clinical outcomes.

These samples serve as a source of protein, DNA, RNA, or other products of biological processes that can be used to analyse, e.g., immunogenomics (gene sequences associated with patients' immune responses), gene expression immune cell abundance by immunohistochemistry or based on gene expression, genetic alterations, alternative pathway activation, or other emerging biomarkers.

Additional biomarker-related information (for example, gene mutations, cytogenetic abnormalities, etc.) may be collected directly from the clinical sites for exploratory analyses based on emerging science and available data.

Exploratory biomarker analysis will be as described in a biomarker plan separate from the CSP.

The results of this exploratory biomarker research will be reported separately and will not form part of the CSR.

The results of this exploratory biomarker research may be pooled with biomarker data from other studies with the study drugs to generate hypotheses to be tested in future studies.

5.8.1.1 Collection of exploratory blood-borne biomarkers

In both the dose-escalation Part A and dose-expansion Part B of the study, blood samples for exploratory biomarkers will be taken pretreatment and at multiple time points on-treatment:

- The 2 mL blood sample for serum will be obtained at screening; on Days −7 and −3 of the lead-in period; on Days 1, 8 (not B8), and 15 of Cycle 1; on Day 1 of Cycle 2; on Day 1 of all subsequent odd-numbered cycles; and at the EOT visit.
- The 10 mL blood sample for plasma will be obtained at screening; on Day −7 of the lead-in period; on Days 1, 8 (not B8), and 15 of Cycle 1; on Day 1 of Cycle 2; on Day 1 of all subsequent odd-numbered cycles; and at the EOT visit.
- The 10 mL blood sample for double-spun plasma (cfDNA sample) will be obtained at screening; on Day -7 of the lead-in period, and on Day 1 of all even-numbered cycles; Day 1 of Cycle 3 (B8 only) and at the EOT visit. The collection of cfDNA samples are only required to be obtained for new patients consented under protocol amendment 5, dated 10 May 2017 and onwards (B3, B7, and B8 as well as Part A). It is not a requirement to collect cfDNA samples for all other existing patients.
- The 6 mL blood samples for PBMC will be obtained at screening; on Day −7 of the lead-in period; on Days 1, 8 (not B8), and 15 of Cycle 1; on Day 1 of Cycles 3, 6, and 9; and at the EOT visit.

Serum and/or plasma samples may be analysed for changes in factors associated with drug treatment. These include but are not limited to cytokines (e.g., IL-8, GRO-α, interferon gamma, IL 6, IL 8, TIMP1, CXCL9, CXCL10, tumor necrosis factor α) or other soluble factors (e.g., CRP, ARG1) or metabolites/small molecules (e.g., arginine). Plasma samples may also be used to evaluate circulating tumor or free DNA (cfDNA), or exosomes, or cell-free RNA for correlation with treatment effects or clinical responses. Double-spun plasma samples ("cfDNA" samples) will be prioritized for evaluation of circulating tumor DNA but may also be used for other analyses. Peripheral blood mononuclear cell samples may be analysed for changes in activated or proliferating T cells or changes in diversity of T cell receptor expression that correlate with treatment or clinical responses, or as a source of protein, DNA, RNA or other cellular product to analyze emerging biomarkers associated with response to treatment or clinical response.

Additional details on exploratory research blood sample processing, handling, shipment, and storage will be provided in the Laboratory Manual.

5.8.1.2 Collection of exploratory tumor biomarkers

In addition to secondary biomarkers outlined in Section 5.6.3, mandatory (archival tissue and baseline and on-treatment tumor biopsies, and optional disease progression tumor biopsies will be used for exploratory research as indicated in Section 5.8.1.1 above and used for investigating potential mechanisms and markers of response or resistance by evaluating immunogenomics (gene sequences associated with patients' immune responses), gene expression, immune cell infiltrate, genetic alterations, or alternative pathway activation. Other analyses may be conducted based on emerging data in the scientific literature.

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

5.8.1.3 Collection of archival tumor samples

Formalin fixed tumor tissue embedded in paraffin blocks will be retrieved for all patients if available. The archival samples will be preferably from the primary tumor and/or metastatic site. Freshly prepared unstained slides (minimum of 3, but preferably 10 to 20) from the archival tumor block will be accepted if tumor blocks cannot be submitted. Because uncontrolled oxidation processes affect tumor sections, tumor tissue blocks are preferred. From submitted archival tumor blocks, 2 cores may be removed in order to construct tissue microarrays for later biomarker analysis. The remaining part of the tumor block will be returned to the institution.

Details of archival tumor sample collection, processing, shipping, and storage will be described in the Laboratory Manual.

5.8.2 Pharmacogenetics

If a patient agrees to participate in the host pharmacogenetics research component of the study and signs a separate ICF for genetic research, a saliva sample will be collected. The results of this pharmacogenetic research will be reported separately and will not form part of the CSR.

The saliva sample for genetic research will ideally be obtained from the patients immediately prior to dosing on Day 1. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an AE. Such patients would be important to include in any genetic analysis. If for any reason, the sample is not obtained prior to dosing it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient for genetics during the study.

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

Each sample for exploratory research will be identified with the study number and patient enrolment number. In this way, exploratory biomarker and genetic data may be correlated

with clinical data. Samples will be destroyed in the case of withdrawal of consent and regulatory audit enabled.

Where genetic analysis will be undertaken, the processes adopted for the coding and storage of samples will be more stringent in order to maintain patient confidentiality. As an added precaution, irrespective of the type of sample, the DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number will be used to identify the sample and corresponding data at the AstraZeneca genetics laboratories or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff) working with the DNA.

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment code and the DNA number will be maintained and stored in a secure environment, with restricted access within the Clinical Genotyping Group Laboratory Information Management System at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, to facilitate correlation of genotypic results with clinical data, to allow regulatory audit, and to trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analysed.

5.8.3 Volume of blood

The volume of blood that will be drawn from each patient in this study during the lead-in period and during the first cycle of treatment for Parts A and B is shown in Table 10.

Table 10 Volume of blood to be drawn from each patient during screening, lead-in period, and Cycle 1 of Part A and Part B

Test Type	Name	Sample volume (mL)	Number of samples	Total volume (mL)
Safety	Clinical chemistry/pregnancy test	5 (Screening only)	1	17.5
		2.5	5	
	Haematology	2	6	12
	Coagulation	1.8	4	7.2
	Thyroid panel	3.5	3	10.5
	Hepatitis B and C	3.5	1	3.5
	HIV	2.5	1	2.5
Pharmacokinetics	AZD9150	2	9	18
	OR			
	AZD5069 and its metabolite AZ13587715 (combination therapy, Part A)	2	10	20
	OR			
	AZD5069 and its metabolite AZ13587715 (combination therapy, Part B)	2	9	18
	OR			
	AZD5069 and its metabolite AZ13587715 (food effect, Part A)	2	18	36
	MEDI4736 (combination therapy arms only)	3.5	2	7
	Tremelimumab (part A Arms A4 and A5)	3.5	4	14
Immunogenicity	Anti-drug antibody	5	1	5
	Anti-AZD9150 antibody (AZD9150-treated arms only)	2	1	2
		2 (required for Arm B8)	2	4
Pharmacodynamics	PDRNA	5	4	20
	sPD-L1	3.5	2	7
	MDSCs	2	2	4

Test Type	Name	Sample volume (mL)	Number of samples	Total volume (mL)
	sPSA	2.5 (Part A only)	3	7.5
Exploratory biomarker research	Serum	2	6	12
	Plasma	10	5	50
	PBMC	12	5	60
	cfDNA	10	2	20
MAXIMUM TOTAL[a]				**357.7**

[a] Note that for pharmacokinetic sampling in the Part B combination therapy arms a reduced sampling schedule will only occur after the first 10 patients. In addition, sPDL and MDSC samples will not be collected for the following patients: patients in B1, B2 and B4 post first 20 patients and patients in Arms B7 and B8.

Abbreviations: cfDNA=circulating-free DNA; HIV=human immunodeficiency virus; MDSCs=myeloid-derived suppressor cells; PBMC=peripheral blood mononuclear cells; PDRNA=pharmacodynamic RNA (samples for STAT3 RNA and other exploratory analyses); sPD-L1=soluble programmed death-ligand 1; sPSA=serum prostate-specific antigen.

In all subsequent cycles past Cycle 1, a maximum total of 76.5 mL of blood will be taken per cycle. The number and timing of samples taken, as well as the volume required for each analysis, may be changed during the study as emerging PK, pharmacodynamic, or safety data on the study drugs become available.

5.8.4 Handling, storage, and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use as described below.

Any PK sample remaining after analysis for AZD9150, AZD5069 (and AZ13587715, the metabolite of AZD5069), tremelimumab, or MEDI4736 may be used for biomarker analyses. These analyses are for AstraZeneca use only, and results will not be included in the CSR. Biological samples for future research can be retained on behalf of AstraZeneca for a maximum of 15 years following the last patient's last visit in the study. The results from future analysis will not be reported in the CSR but separately in a CSR addendum/scientific report or scientific publication. No personal details identifying the individual will be available to AstraZeneca or designated organizations working with the DNA

5.8.4.1 Pharmacokinetic samples

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples and reported in a separate bioanalytical report.

5.8.4.2 Samples for exploratory research

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

Each sample for exploratory research will be identified with the study number and patient enrolment number. In this way exploratory biomarker data may be correlated with clinical data, samples destroyed in the case of withdrawal of consent and regulatory audit enabled.

5.8.5 Labelling and shipment of biological samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document.'

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the subject unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

All archival tumor samples should be shipped at ambient temperature as per the Laboratory Manual to the AstraZeneca designated central Contract Research Organisation.

5.8.6 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator, at each centre, keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

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

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

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

5.8.7 Withdrawal of Informed Consent for donated biological samples

If a subject withdraws consent to the use of voluntarily donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

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

The Principal Investigator:

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

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

5.9 Patient reported outcomes

There will be no patient reported outcomes assessed in this study.

6 SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

An AE is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g., an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and nonserious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

6.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-subject hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of an SAE, see Appendix A to the CSP.

6.3 Definitions of adverse events of special interest

AEs of special interest (AESIs) are events of scientific and medical interest for the further understanding of the AZD9150, AZD5069, tremelimumab, and MEDI4736 safety profiles and require close monitoring and rapid communication by the Investigator to AstraZeneca. Such AESIs may be serious or non-serious. The rapid reporting of these AESIs allows ongoing analysis of these events in order to characterise and understand them in association with the use of these IPs.

MEDI4736, an anti-PD-L1 antibody, binds with high affinity and specificity to PD-L1 and blocks its binding to PD-1 (CD279) and B7-1 (CD80) molecules, thus promoting anti-tumor immunity and tumor cell killing. Potential risks based on these mechanisms of action include immune-mediated reactions such as enterocolitis, dermatitis, hepatotoxicity or hepatitis, endocrinopathy, neuropathy or neurologic events, pancreatitis, and pneumonitis. More specific guidelines for their evaluation, reporting, and treatment are described in detail for MEDI4736 in Annex 1. Further information on these risks (e.g., presenting symptoms) can also be found in the current edition of the MEDI4736 (durvalumab) IB.

AZD5069, an inhibitor of CXCR2, acts by modulating neutrophil migration and has been shown to weakly bind the hERG receptor. Therefore, effects on neutrophil count, including reduction in their number (neutropenia), infections (especially requiring the administration of outpatient oral or IV antibiotics) are deemed of special interest, as are ECG abnormalities arising after the beginning of treatment with this agent.

At present, there are no AESIs for AZD9150.

6.4 Recording of adverse events

6.4.1 Time period for collection of adverse events

AEs and concomitant medications will be collected and reported throughout the study. The reporting period for AEs and concomitant medication starts immediately following the time that written informed consent is obtained and ends 28 days (+7 days) after the last dose of

study drug or until the initiation of subsequent anticancer therapy. SAEs occurring in the follow-up period should be reported to AstraZeneca in the usual manner (see Section 6.5).

Safety follow-up for IM continues for all patients for 90 days (±2 days) after the last dose of MEDI4736 or until the initiation of subsequent anticancer therapy.

SAEs will be recorded from the time of informed consent.

6.4.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

If an Investigator learns of any SAEs, including death, at any time after a patient has completed the study and he/she considers there is a reasonable possibility that the event is related to study treatment the Investigator should notify AstraZeneca.

6.4.3 Variables

The following variables will be collect for each AE;

- AE diagnosis/description (verbatim)
- The date when the AE started and stopped
- CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- Outcome.

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

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication

- Description of AE.

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

The grading scales found in the current CTCAE version 4.03 (14 June 2010) will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the current CTCAE version can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

6.4.4 Causality collection

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

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

A guide to the interpretation of the causality question is found in Appendix B “Additional Safety Information” of this CSP.

6.4.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study site staff: “Have you/the child had any health problems since the previous visit/you were last asked?”, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms; However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.4.6 Adverse events based on examinations and tests

The results from the CSP mandated laboratory tests and vital signs, ECGs, and other safety assessments will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated parameters should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

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

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

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

6.4.7 Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN may need to be reported as SAEs. Please refer to Appendix G for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.4.8 Serious bleeding events with combination drug MEDI4736 (durvalumab) in squamous cell carcinoma of the head and neck patients

Reports of bleeding, including fatal reports, have been received from patients with RM SCCHN (Arms B1 to B8) enrolled in AstraZeneca clinical trials with MEDI4736 (durvalumab) as monotherapy or in combination (with any of the other study drugs). While it is not yet conclusively known whether the risk of bleeding would be higher or lower with the experimental treatment than with standard chemotherapy, an interim internal safety analysis conducted by the Sponsor concluded that a reasonable possibility of a causal relationship between bleeding complications in SCCHN patients and treatment with durvalumab, either alone or in combination with tremelimumab, could not be established.

6.4.9 Investigators should carefully assess the risk in relation to benefit of using anticoagulation or other medications that might exacerbate bleeding during study participation. Investigators should consider discontinuation of these agents if the clinical scenario permits it unless discontinuation would be clinically contraindicated. Disease progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new or progression of existing metastasis to the primary cancer under study should be considered

as disease progression and not an AE. **Events, which are unequivocally due to disease progression, should not be reported as an AE during the study**.

6.4.10 New cancers

The development of a new cancer should be regarded as an AE and will generally meet at least 1 of the serious criteria. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

6.4.11 Handling of deaths

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

- Death that is unequivocally due to disease progression should be communicated to the study monitor at the next monitoring visit and should be documented in the eCRF module but should not be reported as an SAE during the study.
- Where death is not clearly due to disease progression of the disease under study the AE causing the death should be reported as an SAE within 24 hours. The report should contain a comment regarding the coinvolvement of PD, if appropriate, and should assign a single primary cause of death with any contributory causes.
- Deaths with an unknown cause should always be reported as an SAE but every effort should be made to establish a cause of death. A postmortem may be helpful in the assessment of the cause of death, and, if performed, a copy of the postmortem results (with translation of important parts into English) should be reported in an expedited fashion within the usual timeframes.

6.4.12 Disease under Study (DUS)

Symptoms of DUS are those which might be expected to occur as a direct result of solid tumors (Arms A1 to A4), prostate cancer (Arm A6), and RM SCCHN (Arms B1 to B8). Events that are unequivocally due to disease under study should not be reported as AEs during the study unless they meet SAE criteria or lead to discontinuation of the IP.

6.5 Reporting of serious adverse events

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

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

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

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

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

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

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

The reference document for definition of expectedness/listedness is the IBs for each of the 3 study drugs.

6.6 Overdose

Use of AZD5069, MEDI4736, or tremelimumab in doses in excess of those specified in the CSP is considered to be an overdose. For AZD9150, administration in doses significantly exceeding those specified in the CSP (>10% above the recommended dose) may be considered to be an overdose. In all cases, Investigators should be advised that any patient who receives a higher dose than that intended should be monitored closely, managed with appropriate supportive care, and followed up expectantly. There is currently no specific treatment in the event of overdose of MEDI4736 or tremelimumab, and possible symptoms of overdose are not established. See Section 6.6.3 for details. **Exception**: Overdose in an amount of ≤10% of the specified dose does not need to be reported for AZD9150 if there are no associated AEs**.**

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

- An overdose without associated symptoms is only reported on the Overdose CRF module.

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site. For each case of overdose, study sites are required to record the overdose as a protocol deviation within the clinical database.

For overdoses associated with an SAE, the standard reporting timelines apply (see Section 6.5). For other overdoses, reporting must occur within 30 days.

6.6.1 AZD9150

Overdose with an injectable drug can take 2 forms. The first is the acute type where either a dose contains more drug than intended or the appropriate dose was IV infused in a substantially shorter time (e.g., 1000 mg infused in 30 minutes instead of 3 hours). Depending on the extent of the overdose, both of these events will lead to higher plasma concentrations (both C_{max} and AUC) than planned for an ASO. Greater prolongation of aPTT and prothrombin time and increased international normalised ratio is a likely outcome. Complement pathway activation is a possible outcome. Clinical signs and symptoms for both should be monitored and appropriate supportive care and necessary countermeasures should be undertaken if clinical evidence suggests either has occurred. Since the distribution concentration half-life ($t_{1/2}$) of ASO in plasma is 1 to 2 hours, the 2 side effects are expected to be transient.

The second type of overdose is repeated administration of a substantially higher dose (e.g., repeated administration of 1000 mg by 3-hour IV infusion instead of 600 mg). In addition to the potential acute effects described above, this type of overdose will also result in the accumulation of higher tissue levels of ASO than planned. Patients should be monitored closely for target organ toxicity (kidney and liver). If effects are suspected, appropriate supportive care and necessary countermeasures should be instituted. Based on measurements in monkey, the tissue $t_{1/2}$ of AZD9150 is approximately 3 to 4 weeks.

There are no known occurrences of adverse outcomes related to AZD9150 overdose in man.

6.6.2 AZD5069

The maximum single dose so far given to human subjects is 200 mg. This dose was well tolerated. A single overdose higher than this is expected to cause a drop in blood neutrophil

counts but it is not known what other signs or symptoms may occur. Neutrophil counts should be monitored until they return to normal.

There is no experience of overdose and no known antidote to AZD5069. In cases of known or suspected overdose, symptomatic treatment and monitoring of vital functions should be performed according to routine clinical practice. If there is a prolonged, profound reduction in blood neutrophil counts administration of G-CSF may be considered as this has been shown in a healthy volunteer study (D3550C00017) to produce a sustained increase in blood neutrophil count during treatment with AZD5069 at a relatively high dose (100 mg BID).

6.6.3 MEDI4736

There has been no experience with overdose in the ongoing clinical studies of MEDI4736. There are no recommended specific treatments for an overdose with MEDI4736, and the Investigator is advised to use clinical judgement to treat such an event.

6.6.4 Tremelimumab

There has been no experience with overdose in the ongoing clinical studies of tremelimumab. There are no recommended specific treatments for an overdose with tremelimumab, and the Investigator is advised to use clinical judgement to treat such an event.

6.7 Pregnancy

All pregnancies and their subsequent outcomes (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) of pregnancy should be reported to AstraZeneca using the appropriate forms except for:

- If the pregnancy is discovered before the study subject has received any study drug.

6.7.1 Maternal exposure

If a subject becomes pregnant during the course of the study, IP must be discontinued immediately.

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

If any pregnancy occurs during exposure to IP or in the 28 days after discontinuing IP, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.5) and within 28 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.7.2 Paternal exposure

Pregnancy of a patient's partner should not be considered an AE. However, the outcome of all pregnancies occurring from the date of dosing until 16 weeks after the last dose of study drug should, if possible, be followed up, documented, and reported to AstraZeneca and documented in the Pregnancy report Form. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

6.8 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the subject or has the potential to cause harm to the subject.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or subject.

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the subject received the drug
- did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, e.g., medication prepared incorrectly, even if it was not actually given to the subject
- Drug not administered as indicated, e.g., wrong route or wrong site of administration
- Drug not taken as indicated, e.g., tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, e.g., kept in the fridge when it should be at room temperature

- Wrong subject received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to subject (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Subject accidentally missed drug dose(s), e.g., forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Subject failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AstraZenca product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 6.5) and within 30 days for all other medication errors.

6.9 Management of IP related toxicities

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab and tremelimumab are provided in the durvalumab/tremelimumab Toxicity Management Guidelines (TMGs). Please see Annex 1. The most current version of the TMGs is also available through the following link: https://tmg.azirae.com. In addition a version of the current TMGs is maintained within the Site Master File. Please contact your clinical trial associate for information on how to gain access to this website.

Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the immune-mediated AEs (imAE). Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

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

Following the first dose of IP, subsequent administration of tremelimumab can be modified based on toxicities observed as described in the TMGs. These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgement in treating these types of toxicities. These guidelines apply to AEs considered causally related to tremelimumab by the reporting Investigator.

6.9.1 Dose modifications

If a patient experiences a clinically significant and/or unacceptable toxicity with the IP, dosing will be interrupted or the dose reduced and supportive therapy administered as required. Because of the long tissue $t_{1/2}$ of AZD9150 and MEDI4736, a 21-day (unless otherwise specified) recovery period has been allowed. If the toxicity resolves or reverts to a lower CTCAE grade within 21 days of onset and the patient is showing clinical benefit, study treatment may be restarted using the rules below for dose modifications (see Table 11 and Table 12).

If the toxicity does not resolve to CTCAE grade 2 (grade 1 for liver function tests) after 21 days, study treatment should be permanently discontinued (unless otherwise specified) and the patient should be followed up for safety (see Section 4.2.3 for details).

A maximum of 2 dose-reductions (Figure 4, Figure 5, Figure 7, and Figure 8) will be allowed for an individual patient. If the second dose-reduction is not tolerated, study treatment should be permanently discontinued and the patient should be followed up for safety (see Section 4.2.3 for details). The lowest doses that may be administered are:

- AZD9150: 2 mg/kg IBW Q2W (200 mg Q2W for Arm B8)
- AZD5069: 20 mg BID
- MEDI4736: flat dose administration of 10 mg/kg Q4W (MEDI4736 dose-reductions are not permitted for Arm B8)
- Tremelimumab: 1 mg/kg

If a patient experiences a clinically significant and/or unacceptable toxicity at these dose levels, study treatment should be permanently discontinued and the patient should be followed up for safety (see Section 5.9 for details).

Table 11 Dose modifications for toxicity (excluding liver function tests and in case of neutropenia for AZD5069 alternate dosing schedule arms)

Toxicity	Recovery	Re-dosing	Notes
Grade 3	G2[a] ≤21 days	Restart at dose level -1	If second dose interruption, decrease to dose level -2

	G2[a] >21 days	Discontinue study drug treatment	
Grade 4	G2[a] ≤21 days	Restart at dose level -2	If second grade 4 toxicity, discontinue study drug treatment
	G2[a] >21 days	Discontinue study drug treatment	

[a] Patients starting with an abnormal baseline may restart when the lab/AE returns to pretreatment status. If thrombocytopenia is accompanied by bleeding, discontinue study drug treatment. Neutropenia when on AZD5069 alternate dosing schedule should be managed as in Figure 7 and Figure 8

Abbreviation: G=grade.

If in the Investigator's clinical judgement, the thrombocytopenia events with patients on AZD9150 monotherapy or in combination with MEDI4736 (durvalumab) needs to be managed in a way different from the one proposed above in the Table 11, it will warrant discussion with the Sponsor Study Team Physician and the Study Investigator and the Sponsor Study Team Physician approval/waiver on the alternate management.

Table 12 Dose modifications for elevations in liver function tests

Toxicity	Recovery	Re-dosing	Notes
Grade 3	G1[a] ≤21 days	Restart at dose level -1	If second dose interruption, decrease to dose level -2
	G1[a] >21 days	Discontinue study drug treatment	
Grade 4 – and assessed by the Investigator as related to study treatment		Discontinue study drug treatment	

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

Abbreviation: G=grade.

All dose-reductions must be discussed case-by-case by the Investigator and the Sponsor Study Team Physician (see Section 6.10 for contact information). Until this discussion occurs, dosing of study treatment must be interrupted temporarily. Dose-reductions are defined as doses below the dose at which the toxicity occurred and they may only include dose levels tested during the dose escalation. In combination treatments, a dose-reduction may involve 1 or both of the 2 agents. All decisions regarding dose-reductions will be presented to the SRC at the next scheduled meeting.

6.9.2 Infusion reactions

In order to help understand the potential drug relatedness of any acute reaction, a blood sample should be drawn during the event for possible additional ADA testing. Serum tryptase or other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at the discretion of the Investigator.

In the event of a grade 2 infusion related reaction as determined by the Investigator, the infusion should be interrupted and restarted at the same rate as the original infusion after symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, and IV fluids) and resolution of the reaction.

In the event of a grade 3 infusion related reaction, the infusion should be interrupted and restarted at half the rate after symptomatic treatment and resolution of the reaction. If the infusion reaction returns to grade 3 or greater, the patient should discontinue the study treatment permanently.

In the event of a grade 4 infusion-related reaction, the patient should discontinue the study treatment permanently.

6.9.3 Hypersensitivity reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti PD-(L)1 therapy (Brahmer et al 2012). Although MEDI4736 is a human anti-PD-L1 mAb, as with any antibody, allergic reactions following the infusion are possible and can be caused by various mechanisms, including acute anaphylactic (IgE-mediated) and anaphylactoid reactions against the mAb, and serum sickness.

Severe hypersensitivity reactions should be managed according to standard clinical practice. At all sites, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognise and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

In order to help understand the potential drug relatedness of any acute reaction, a blood sample should be drawn during the event for possible additional ADA testing. Serum tryptase or other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at the discretion of the Investigator.

6.9.4 Differential diagnosis: Infusion-related reaction versus anaphylaxis

Anaphylaxis and infusion-related reactions have some common manifestations and may be difficult to distinguish from each other. The Investigator is advised to carefully examine symptoms of adverse reactions observed during or shortly after exposure to study drug,

especially MEDI4736, and to consider the following guidance prior to making a final diagnosis.

Infusion-related reactions are commonly observed during or shortly after the first exposure to therapeutic mAbs delivered through IV infusion. These reactions are less common following subsequent exposures. Unlike infusion-related reactions, anaphylaxis is a rare event, usually occurring after subsequent exposure to an antigen, and it is most commonly accompanied by severe systemic skin and or mucosal reactions.

Reactions occurring at the time of or shortly after subsequent infusions of IP(s) are to be judged by the Investigator at his/her own discretion. The following guidance for anaphylaxis diagnosis, based on the 2006 National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network symposium (Sampson et al 2006), is provided guidance for is provided for the Investigator's convenience and in order to facilitate consistency in judgements.

National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognise 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to >95% of all cases of anaphylaxis (for all 3 categories).

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalised hives, pruritus or flushing, swollen lips-tongue-uvula), AND AT LEAST 1 OF THE FOLLOWING:

   – Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory function, hypoxemia), and/or
   – Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence).

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   – Involvement of the skin-mucosal tissue (e.g., generalised hives, itch-flush, swollen lips-tongue-uvula),
   – Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory function, hypoxemia),
   – Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence), and/or
   – Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting).

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   - Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP,
   - Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline.

6.9.5 Liver chemistry tests

If the conditions for dose interruption or dose discontinuation (see above) are fulfilled, retest of liver chemistries (ALT, AST, alkaline phosphatase [ALP], international normalised ratio, and indirect and TBL) should occur at least once weekly until levels stabilise or begin to recover. Further investigation may include the following:

- Obtain a more detailed history of symptoms and prior and concurrent diseases
- Obtain further history for concomitant drug use (including nonprescription medication, herbal, and dietary supplement preparations), alcohol use, recreational drug use, and special diets
- Obtain a history for exposure to environmental chemical agents and travel
- Scan for liver metastasis as appropriate
- Serology for viral hepatitis (hepatitis A virus IgM, hepatitis B surface antigen, HCV antibody, cytomegalovirus IgM, and Epstein Barr virus antibody panel)
- Serology for autoimmune hepatitis (e.g., antinuclear antibody)

For any combined increases of aminotransferases and bilirubin, please refer to Appendix G "Actions Required in Cases of Increases of Liver Biochemistry and Evaluation of Hy's Law" of this CSP.

6.9.6 Potential immune-related adverse events

Based on the mechanism of action of MEDI4736 leading to T cell activation and proliferation, there is the possibility of observing irAEs during the conduct of this study. Potential irAEs may be similar to those seen with the use of ipilimumab (YERVOY®) and nivolumab (OPDIVO®) and may include irAE such as enterocolitis, dermatitis, hepatotoxicity, endocrinopathy, pneumonitis, neuropathy, and the development of serious infection (Hodi et al 2010, Brahmer et al 2012). For tremelimumab, identified risks include: diarrhoea, rash, and pruritus, and important potential risks are immune-mediated gastrointestinal events including colitis, intestinal perforation, abdominal pain, dehydration, nausea and vomiting, and decreased appetite (anorexia); immune-mediated dermatitis including urticaria, skin exfoliation, and dry skin; immune-mediated endocrinopathies including hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism; immune-mediated hepatitis including autoimmune hepatitis, and increased serum ALT and AST; immune-mediated pancreatitis

including autoimmune pancreatitis, and lipase and amylase elevation; immune-mediated respiratory tract events including pneumonitis and interstitial lung disease; immune-mediated nervous system events including encephalitis, peripheral motor and sensory neuropathies, and Guillain-Barre syndrome; immune-mediated cytopenias including thrombocytopenia, anemia and neutropenia; infusion-related reactions, anaphylaxis, and serious allergic reactions; and headache, fatigue, and pyrexia.

Potential risks are associated with MEDI4736 and tremelimumab given their mechanism of action, which involves immune system activation, as well as data from studies of relevant or similar therapies. The occurrence of irAEs that are either overlapping or greater than when each of these drugs is/are used as monotherapy is possible. For information on all identified and potential risks with MEDI4736 and tremelimumab, always refer to the current editions of the respective IBs.

AEs of Special Interest (AESIs) for durvalumab ± tremelimumab include, but are not limited to, events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy.

An immune-mediated AE (imAE) is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate aetiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the Investigator has any questions in regards to an event being an imAE, the Investigator should promptly contact the Study Physician.

AESIs observed with durvalumab ± tremelimumab include:

- Diarrhoea / Colitis and intestinal perforation
- Pneumonitis / ILD
- ALT/AST increases / hepatitis / transaminase increases / hepatotoxicity
- Neuropathy / neuromuscular toxicity (e.g., Guillain-Barré and myasthenia gravis)
- Endocrinopathies (i.e., events of hypophysitis/ hypopituitarism, adrenal insufficiency, diabetes insipidus, hyperthyroidism, hypothyroidism, and type I diabetes mellitus)
- Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis / serum (or labs suggestive of pancreatitis - increased serum lipase and , increased serum amylase increases)

- Myocarditis
- Myositis / Polymyositis
- Neuropathy / neuromuscular toxicity (e.g., Guillain-Barré, and myasthenia gravis)
- Other inflammatory responses that are rare/less frequent with a potential immune-mediated aetiology include, but are not limited to, myocarditis, pericarditis, sarcoidosis, and uveitis and other events involving the eye, skin, haematological and rheumatological events.

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

Further information on these risks (e.g., presenting symptoms) can be found in the current edition(s) of the durvalumab and tremelimumab IBs. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (see Annex 1). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgement in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting Investigator.

Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or PD), an immune-related aetiology should be considered for signs or symptoms of enterocolitis, dermatitis, hepatotoxicity, endocrinopathy, pneumonitis, or neuropathy. In addition to the dose-reductions described in Section 5.5.1 above, management of irAEs should generally be consistent with the guidelines previously outlined for ipilimumab (Weber et al 2012), which recommend the following:

1. Patients should be evaluated to identify any alternative aetiology.
2. In the absence of clear alternative aetiology, all events of an inflammatory nature should be considered to be immune related.
3. Symptomatic and topical therapy should be considered for low-grade events.
4. Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.
5. More potent immunosuppressives should be considered for events not responding to systemic steroids (e.g., infliximab, mycophenolate).

More specific recommendations concerning the diagnosis and management of irAEs related to MEDI4736 are provided in Annex 1 (MEDI4736 Adverse Events of Special Interest) and Annex 1 (Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion-related, and Non–immune-mediated Reactions [MEDI4736 Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy]). Because the side effects of AZD9150 and MEDI4736 are to some degree overlapping (possible ALT/AST elevations, thrombocytopenia, and neutropenia), ascertaining the cause of any toxicity to

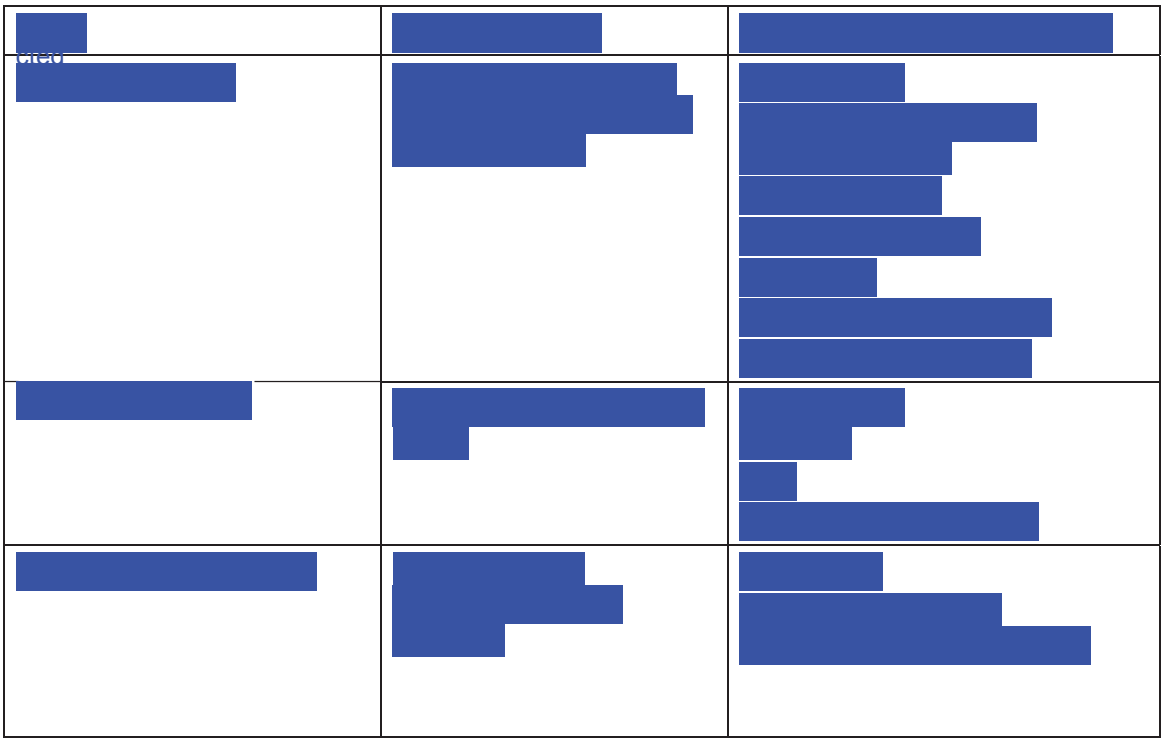
involved organ systems will require careful consideration in patients receiving both drugs simultaneously. If the Investigator has any questions in regards to an AE being an AE, the Investigator should immediately contact the Medical Monitor [redacted] (see Section 6.10 for contact information).

6.10 Study team contacts for emergencies

The Principal Investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such** (see Section 6.5).

In the case of a medical emergency, the Investigator may contact the Medical Monitor [redacted]. If the Medical Monitor [redacted] is not available, contact the Sponsor Study Team Physician.

In case of nonmedical emergencies, please contact either the Operational Lead [redacted] or the Operational Lead at AstraZeneca. If neither is available, contact the Medical Monitor [redacted].



6.11 Duration of treatment

Patients participating in either part of the study will be administered study drug(s) following a 7-day lead-in period in 4-week treatment cycles. This may continue for as long as they are continuing to show clinical benefit, as judged by the Investigator, unless a patient has confirmed PD with either clinical deterioration and/or no further benefit from treatment, experiences unacceptable toxicity, or discontinues for any other reason.

If a patient on either monotherapy arm (treatment arms B5 or B6) has confirmed PD, they may, at Investigators' discretion and with notification to the Medical Monitor, add MEDI4736 to their treatment regimen. These patients, after the addition of MEDI4736 to the monotherapy treatment, will continue to be part of the safety analysis but will be censored from the efficacy analysis.

After discontinuation of treatment, all patients will continue to be followed for safety, subsequent anticancer therapy, and survival. During this time, all patients will be followed for safety (including concomitant medication) for 28 days (+7 days) after the last dose of study drug or until the initiation of a subsequent anticancer therapy. In addition, patients who received MEDI4736 as part of their combination treatment will be followed for IM for 90 days (±7 days) after the last dose of MEDI4736 or until the initiation of alternative anticancer therapy. Patients who discontinued treatment for reasons other than PD will continue to undergo tumor assessments every 2 months (±7 days) until PD is noted. All patients will be followed for subsequent anticancer therapy every 2 months (±7 days) and will also be followed for OS every 2 months (±7 days) from the date of randomisation to the date

of death due to any cause, assessed for approximately 40 months. The patients will be censored on the date of last follow-up visit.

6.12 Expected start and end of study

The study started on 05 Aug 2015 (first patient screening visit). The data cut-off for the primary endpoint will be the 28 Feb 2020 (6 months + 90 days follow up after the last patient recruited and started IP). Data analysis will be performed, and a CSR will be written based on this data cut-off.

Any patients still receiving IP at the time of this data cut-off will be able to continue to receive IPs within the current study, through a continued treatment period, while they are in the Investigator's opinion, deriving clinical benefit and not fulfilling discontinuation criteria. During this continued treatment period, assessments will revert to the standard of care for each individual site. Data will not be entered into the clinical study database after the data cut-off date. During this continued treatment period, patients will continue to be monitored for all SAEs up to 28 days after the last dose of IP. Paper based SAE reporting will be used for any SAEs identified after the data cut-off. SAE data will be entered in to the AstraZeneca's global safety database. All SAEs, overdoses and pregnancies will be reported until 28 days after last dose. The IVRS system will be closed following the data cut-off, and sites will manually order IP. The IP dispensation and reconciliation will be handled by the study site at each patient's visit. The IP accountability information must still be collected until all patients have completed treatment. After the data cut-off for the CSR, individual study sites will be closed once their final patient completes the 28-day follow-up visit. The continued treatment period will remain available to patients until the last patient completes treatment and has his or her 28-day safety follow-up visit. The Last Subject Last Visit is defined as the date of the last patient's 28-day safety follow-up visit.

6.13 Study suspension or early termination

The Sponsor reserves the right to temporarily suspend or terminate this study at any time. The reasons for temporarily suspending or terminating the study early may include, but are not limited to, the following:

1. The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
2. Patient enrolment is unsatisfactory
3. Noncompliance that might significantly jeopardise the validity or integrity of the study
4. Sponsor decision to terminate development
5. Sponsor decision to terminate the study based on a planned futility analysis

If the Sponsor determines that temporary suspension or early termination of the study is required, the Sponsor will discuss the reasons for taking such action with all participating

Investigators. When feasible, the Sponsor will provide advance notice to all participating Investigators of the impending action.

If the study is suspended or terminated early for safety reasons, the Sponsor will promptly inform all Investigators. The Sponsor will also promptly inform the relevant regulatory authorities of the suspension/early termination along with the reasons for such action. Where required by applicable regulations, the Investigator must inform the site's Institutional Review Board (IRB)/Independent Ethics Committee (IEC) promptly and in writing of the suspension/early termination along with the reasons for such action and send a copy of the notification to the Sponsor.

If the study is suspended for safety reasons and it is deemed appropriate by the Sponsor to resume the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study.

7 INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

AstraZeneca's Pharmaceutical Development, R&D Supply Chain will supply the IPs shown in Table 13.

Table 13 Dosage form and strength of the investigational products

Investigational product	Dosage form and strength
AZD9150	2 mL vial, 50 mg/mL concentrate for solution for infusion
AZD5069 capsules[a]	20 mg hard gelatine brown capsules for oral use
AZD5069 tablets	10 mg beige tablets for oral use
AZD5069 tablets	40 mg beige tablets for oral use
MEDI4736	10 mL vial, 50 mg/mL concentrate for solution for infusion
tremelimumab	Formulated at a nominal concentration of 20 mg/mL in 20 mM histidine/histidine HCl, 222 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, and 0.27 mM EDTA, pH 5.5.

[a] Capsule formulation was used in Part A in the dose-escalation Arm A2 for first cohort.

7.2 Dose and treatment regimens

7.2.1 Administration of AZD9150

AZD9150: Arms A1, A4, A6, B1, B3, B5, B7, and B8: Patients will receive loading dose of AZD9150 (Days −7, −5, and −3) at the defined dose in each treatment arm as described in the study design. Following loading dose, patients will receive QW dosing of AZD9150 (except in Cohort 2 of Arm A4, and Arm B8 where the schedule of AZD9150 is Q2W). AZD9150 will be administered as a 1-hour (± 10 minutes) infusion. In all cases, infusion of AZD9150 is planned to be completed at least 30 minutes (in subsequent cycles if no infusion reaction in first cycle) before the start of the MEDI4736 infusion on days that both drugs are administered.

For Arm A4 specifically, the sequence of dosing for first 4 cycles would be AZD9150 infused over 1 hour (± 10 minutes), followed by tremelimumab infused over 1 hour (± 10 minutes) followed by MEDI4736 infused over 1 hour (± 10 minutes). Ideal body weight will be used to calculate the administered dose in all arms where AZD9150 is to be infused except Arm B8 where flat dose AZD9150 is to be administered, i.e. 200 mg as lead-in doses on Days −7, −5, and −1 and 400 mg Q2W thereafter in a 28-day cycle.

AZD9150 will be administered on an mg/kg IBW basis via a 1-hour IV infusion (a window of ±10 minutes will be allowed). However, the patients allocated in B8 will be administered on a flat dosing regimen. As described in Section 1, the infusion time for AZD9150 has been shortened from 3 hours in previous studies to a 1 hour infusion. The SRC will continue to monitor patients dosed with AZD9150 for any toxicities possibly associated with the shortened infusion time and may recommend modifying the length of infusion if any toxicities associated with C_{max} are observed.

Ideal body weight is used for the administration of AZD9150 as the apparent volume of distribution for oligonucleotides does not increase proportionately to body weight in obese patients or patients who weigh substantially less than their IBW (Dorr et al 1999). Ideal body weight will be determined using the Devine formula (Pai and Paloucek 2000):

Men (kg) = 50+2.3kg*inch over 5 feet

= 50+2.3kg*((actual height (cm)–152.4) * 0.4)

Women (kg) = 45.5+2.3kg*inch over 5 feet

= 45.5+2.3kg*((actual height (cm)–152.4) * 0.4)

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 dose.

Weight obtained on Day −7 of the lead-in will be used to calculate the weight-related doses of AZD9150 for the lead-in. Weight obtained on Day 1 of each cycle will be used to calculate the weight-related dose of AZD9150 for each cycle.

During the 7-day lead-in period, AZD9150 will be administered as a loading dose on Days −7, −5, and −3. A window of +1 day per loading dose is allowed. Doses should not be given on back-to-back days. Starting with Cycle 1, AZD9150 will be administered QW on Days 1, 8, 15, and 22 of each treatment cycle; doses have a ±2 day dosing window.

7.2.2 Administration of AZD5069

When given in combination with MEDI4736 (Arms A2, A3, A7, B2, B4, and B6): AZD5069 will be administered as 40 mg BID starting with Day −7 of the 7-day lead-in period at the defined dose in each treatment Arm as described in the study design. Following the lead-in period, patients will receive BID dosing of AZD5069 daily for a 28-day cycle. On days when both AZD5069 and MEDI4736 are given, the morning dose of AZD5069 is administered at least 30 minutes before starting infusion of MEDI4736. For Arm A5 specifically, the sequence of dosing for first 4 cycles would be AZD5069 followed 30 minutes later by tremelimumab infused over 1 hour (± 10 minutes) followed by MEDI4736 infused over 1 hour (+/− 10 minutes). As discussed in the study design, Arms A5, A7, and food effect substudy will not open for enrolment. In all cases, AZD5069 should be administered either 2 hours before or 2 hours after (with ± 2 hours window) food consumption at approximately the same time each day.

Tremelimumab will be administered at 1mg/kg (once Q4W), and the infusion duration will be approximately 1 hour. The MEDI4736 infusion at 20 mg/kg (once Q4W), will start approximately 1 hour after the end of infusion of tremelimumab, and the infusion will be administered over approximately 1 hour (a window of ±10 minutes will be allowed). The dose of AZD5069 will be 80 mg BID alternate dosing schedule. Tremelimumab will be infused for a total of 4 months (up to 4 doses). After completion of the initial 4 doses of tremelimumab, patients will continue to receive AZD5069/MEDI4736 as in Arm A2. The first AZD5069/MEDI4736 dose will be given 1 day after the last received dose of AZD5069 of a cycle (Week 4 dose) with MEDI4736 and tremelimumab combination therapy. In the case of the Arm B4 post-interim analysis, the dose of AZD5069 will be 80 mg BID alternate dosing schedule.

When given alone (treatment arm B6 in Part B): AZD5069 will be administered as a fixed PO at flat doses PO BID starting with Day −7 of the 7-day lead-in period. AZD5069 should be administered either 2 hours before, or 2 hours after food (± 2 hours). Dose should be taken on an empty stomach (unless specified for a particular visit for monotherapy arm patients) at approximately the same time each day.

In the fasted condition, patients will be fasted for ≥10 hours before AZD5069 dosing, until 4 hours postdose. Patients may have glucose (sugar tablets) and/or juice (except for grapefruit juices or juices containing grapefruit or Seville oranges) if they have signs or symptoms of hypoglycaemia after they have received AZD5069 in the fasted state. Water will be restricted from 1 hour predose until 1 hour postdose, except for the water administered with AZD5069. After review of the PK data, if it is agreed that the data support no clinically relevant impact of food on the PK of AZD5069 and so recommended by the SRC and AstraZeneca, the AZD5069 fasting/administration instructions may be removed.

The morning dose of AZD5069 taken during the lead-in period and on any subsequent day when blood samples before the morning dose are required must be administered at the study centre and the precise time noted. All other doses may be self-administered by the patient; self-administration of AZD5069 will be recorded in the Patient Diary.

As part of the pharmaceutical development of the AZD5069 formulation, a new tablet formulation has been developed to meet manufacturability concerns and the strengths for oncology studies and will be used in Part A enrolment in Arms A3, A5, and A7 and in Part B of the trial.

7.2.3 Administration of MEDI4736

MEDI4736 will be administered on an mg/kg (with the exception of Arm B8) basis Q4W via a 1-hour IV infusion.

MEDI4736: Arms (A1 to A7, B1 to B4, B7): Patients will receive MEDI4736 starting Day 1 of Cycle 1 administered as a 20 mg/kg infusion over 1 hour Q4W in a 28-day cycle. In addition to the above arms, patients in monotherapy arms (B5 and B6) who develop confirmed disease progression may have MEDI4736 added, at the discretion of the Investigator and after notifying the Medical Monitor. MEDI4736 will be added to the dosing schedule beginning on Day 1 of the following treatment cycle. Thereafter, all study treatment will follow the same schedule as for a patient on a combination therapy arm.

For patients in B8, a 1.5 g flat dose will be administered via infusion starting Day 1 of Cycle 1 over 1 hour Q4W in a 28-day cycle. If body weight decreases to less than 30 kg, weight-based dosing (20 mg/kg Q4W) will be implemented.

Patients will receive MEDI4736 on Day 1 of each treatment cycle, starting with Cycle 1; doses have a ±2 day dosing window. Weight obtained on Day 1 of each cycle will be used to calculate the weight-related dose of MEDI4736 for each cycle.

Patients should be observed after administration of MEDI4736 for a minimum of 2 hours for the appearance of any acute drug reactions. In the event of an acute reaction, in order to help understand the potential drug relatedness of such a reaction, a blood sample should be drawn

during the event for possible additional ADA testing. Serum tryptase or other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at the discretion of the Investigator.

7.2.4 Administration of tremelimumab

Tremelimumab will be administered in Arm A4 as 1 mg/kg IV infusion over 1 hour Q4W in a 28-day cycle, starting on Day 1 of Cycle 1 with a ± 2 days window and given Q4W for a total of 4 cycles (up to 4 doses). Weight obtained on Day 1 of each cycle will be used to calculate the dose of tremelimumab for each cycle.

The dose will be calculated using the following formula:

$$\text{Dose (mL)} = \frac{[\text{patient weight (kg)} \times \text{tremelimumab dose level (mg/kg)}]}{20 \text{ mg/mL}}$$

where 20 mg/mL is tremelimumab concentration.

The corresponding volume of tremelimumab should be rounded to the nearest 0.1 mL. If no institutional standard on dose calculations exists, then dose adjustments for each cycle are only needed for a greater than 10% change in weight.

Tremelimumab will be infused after AZD9150 and AZD5069 and prior to MEDI4736 infusions in Arm A4.

7.3 Labelling

Labelling of the IP will be carried out by AstraZeneca or designee in accordance with Annex 13 and current Good Manufacturing Practice and regulatory requirements of each country participating in the study. The labels will be translated into local languages where applicable as required by local regulations.

The patient's emergency contact details and patient's dosing instructions will not be on the labels but can be found in the ICF and the Patient Information Card. For emergency purposes, the patient must be in possession of the emergency contact details at all times.

Additional information about the 4 IPs may be found in the respective IBs.

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The IP label on the vial/bottle specifies the appropriate storage.

AZD9150 and MEDI4736 are to be stored at the study centre in a secured facility with limited access and controlled temperature (2ºC to 8ºC). The temperature should be monitored on daily

basis and documented in the temperature monitoring log according to the study drug handling instructions.

AZD5069 (capsules and tablets) is to be stored at the study centre in ambient temperature in a secured facility with limited access. The temperature should be monitored on a daily basis and documented in the temperature monitoring log according to the study drug handling instructions.

Tremelimumab is to be stored with investigational site pharmacy at 2°C to 8°C (36°F to 46°F). Do not freeze.

The IPs must be kept in the original outer container and under conditions specified on the labels.

In the following cases, the centre staff should not use affected study drug and should immediately contact AstraZeneca representative for further guidance:

- Temperature excursion upon receipt or during storage at the study
- Damaged kit upon receipt
- Damaged vial/bottle

Damaged study drug should be documented according to the instructions provided by AstraZeneca representative.

7.5 Distribution of AZD5069 to the patient

A description of how AZD5069 will be packaged for distribution to the patient and detailed instructions how to dispense AZD5069 to the patient will be provided in writing to the study centres before or at the time of site initiation.

7.6 Treatment compliance and accountability

The study drug provided for this study will be used only as directed in the CSP.

The study site staff will account for all study drugs received at the centre, for unused study drugs, and for appropriate destruction (according to local procedures). Certificates of delivery, destruction, and/or return should be signed.

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

AZD9150, tremelimumab, and MEDI4736 will be administered IV at the study centre on treatment visits and within visit windows as specified in Section 5.2, Table 5.

AZD5069 will be administered orally by patients at times at the study centre but more often at home as specified in Section 5.2, Table 5. Self-administration of AZD5069 will be recorded in the Patient Diary, which will be used as a measure of compliance. Patients will be asked to return all unused medication and empty containers to the study centre on each treatment visit. The patient's compliance will be assessed by the Investigator and recorded in the eCRF. A capsule/tablet count should be performed at the patient level and recorded in the eCRF as well as in a dispensing log by the study centre personnel.

7.7 Dose-escalation and safety cohorts: Part A and Part B

In the dose-escalation part of the study, 31 evaluable patients were enrolled. At the time of protocol amendment 5, the MTDs/RP2D for each of the 2 agents in combination with MEDI4736 (durvalumab) had been identified [AstraZeneca 2016 (a), AstraZeneca 2016 (b)]. Based upon the safety data gathered from 6 evaluable patients enrolled in Arm A3, the SRC determined on 29 March 2017, that the 80 mg BID alternate dosing schedule for AZD5069 was also a safe and tolerable dose.

All cohorts of Part A will enroll patients with advanced solid malignancies refractory to standard therapy or for which no standard of care regimen currently exists. Following enrolment, based on 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 and detailed in Section 3.8.2, as well as the patient's anticipated need or likelihood to consume such products at any time throughout the study, the Investigator will then assess whether the patient may be allocated to treatment with AZD5069.

Patients thus excluded by the Investigator from treatment with AZD5069 will be allocated to:

- Treatment arm A4 or A6: AZD9150 in combination with MEDI4736 (AZD9150/MEDI4736/tremelimumab or AZD9150/MEDI4736).

Patients thus included by the Investigator for treatment with AZD5069 will be allocated sequentially to 1 of the following 2 treatment arms:

- Treatment arm A4 or A6: AZD9150 in combination with MEDI4736 (AZD9150/MEDI4736/tremelimumab or AZD9150/MEDI4736), or
- Treatment arm A3: AZD5069 in combination with MEDI4736.

7.7.1 Starting dose and dose-escalation scheme

The starting doses and additional dose levels chosen for each agent in this study were based on the clinical experience with each agent as monotherapy in previous trials.

In Arm A1, AZD9150 was administered at a starting dose of 2 mg/kg IBW. Additional dose level up to 3 mg/kg IBW was evaluated and determined as RP2D. Lower dose selection is

based on PD (STAT3 protein expression) analysis of peripheral blood and tumor biopsy specimens from patients with DLBCL treated in a ISIS Phase 1/2 clinical trial (Clinical study ISIS 481464-CS1, see Section 1.2). The upper limit of 3 mg/kg IBW is based on MTD determination for patients in the same study.

In Arm 2, AZD5069 was administered at a starting dose of 40 mg PO BID (i.e., daily dose of 80 mg). Additional dose level up to 80 mg BID (for a maximum total daily dose of 160 mg) was evaluated. The 40 mg BID dose was considered as the MTD based on initial safety assessment, but based on maturing safety data it was better understood that the DLTs of neutropenia occurring in patients treated with AZD5069 are due to mechanism of AZD5069 (myelokathexis) and are hence functional. The SRC determined to enroll an additional cohort at 80 mg BID dose of AZD5069 with a different dose schedule involving drug holds to manage treatment-related functional toxicities (Arm A3 as described below). The outcome of this cohort has been determined and it concludes 80 mg BID alternate dosing schedule as a viable RP2D. The lowest dose is based on PD (CD11b expression) analysis of peripheral blood cells from healthy volunteers treated in a single ascending dose Phase 1 study (D3550C00001). Arm A3: 6 patients will be initially dosed. If tolerating the dosing schedule well, an additional 6 patients will be added to confirm the dose schedule. If ≥2 patients do not tolerate the dose (i.e., meet DLT criteria), the dose will be reduced back to 40 mg BID of AZD5069 (Figure 7 and Figure 8). Non-evaluable patients may be replaced.

For Arm A4, the aim is to conduct a safety run-in of the established dose of AZD9150 (from Arms A1, A2/A3) in combination with a fixed dose of MEDI4736/ tremelimumab in all solid tumor patients. No dose-escalation is planned for Arm A4. If the dose is not tolerated (i.e., patient meets DLT criteria) in this combination of 3 drugs, then dose-reductions will be conducted as described in Figure 4, Figure 7, and Figure 8.

For Arm A6, the dose and safety confirmation cohort, AZD9150 will be given at the established dose of AZD9150 (from Arms A1, A2/A3) in combination with fixed dose of MEDI4736. This will be done in patients with prostate cancer, and there is no intent to do any intra-patient dose escalation. If the dose is not tolerated in this combination of 2 drugs, then dose-reduction will be conducted as in Figure 4, Figure 7, and Figure 8.

MEDI4736 was administered at a dose of 20 mg/kg Q4W.

Tremelimumab was administered at a dose of 1 mg/kg Q4W.

For the definition of DLT, see Section 7.7.3.

In Arms A1 and A2, dose-escalation for the 2 combination treatments (i.e., AZD9150/MEDI4736 and AZD5069/MEDI4736) advanced independent of each other. In addition to determining DLT in the DLT Evaluation period, the SRC critically reviewed all

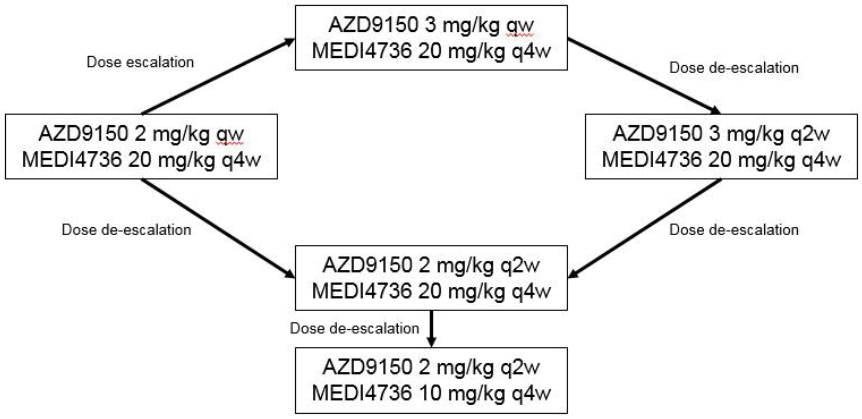
available data pertaining to safety, tolerability, and IM as well as PK, pharmacodynamic, and anti-tumor activity before deciding on the next dose levels/schedules to be explored. Dose-escalation in each arm was considered completed once 1 of the following criteria was met:

- The MTD (for definition of MTD see Section 7.7.4) 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 (i.e., AZD9150 3 mg/kg IBW, AZD5069 120 mg BID [for a maximum total daily dose of 240 mg], and MEDI4736 20 mg/kg)

See Figure 4 for the for the possible dose combinations for study Arms A1, A4, A6 and dose-reduction levels for Part B, and Figure 5 for the possible dose combinations for study Arm A2 and dose-reduction levels for Part B. All potential dose-escalation and de-escalation levels after the starting doses will be determined by the SRC in light of emerging safety, tolerability, and/or PK data (see Section 7.7.6).

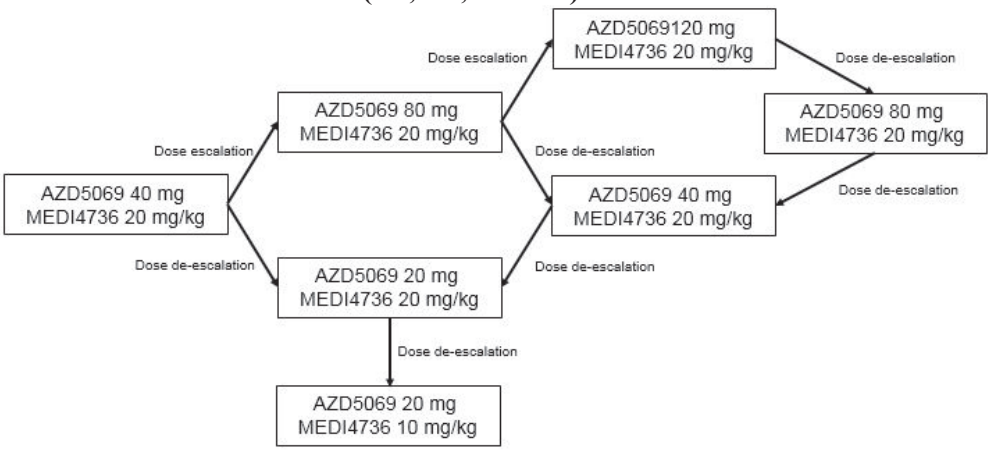
There will be no intra-patient dose escalations.

Figure 4 Dose-escalation and de-escalation Arms A1, A4, A6 and dose-reduction levels for Part B (B1, B3, B5, and B7)



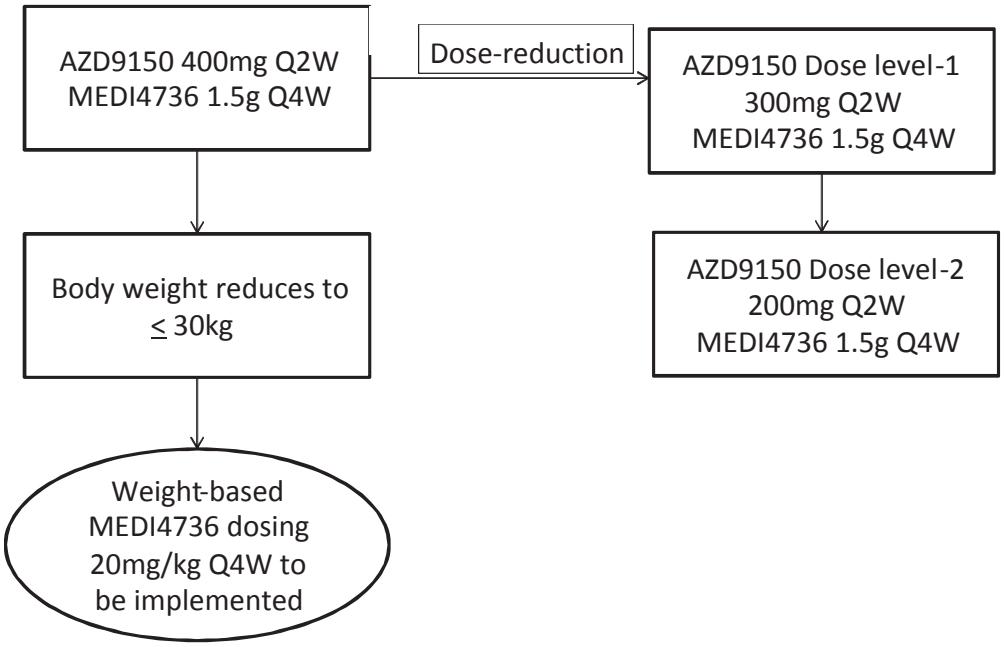
Additional dose combinations not listed in the table may be explored based on emerging safety, tolerability, and/or PK data. All dose combinations will be determined by the SRC. For Part B, AZD9150 will be administered at 3 mg/kg QW.

Figure 5 Dose-escalation and de-escalation Arm A2 and dose-reductions levels for Part B (B2, B4, and B6)



Additional dose combinations not listed in the table may be explored based on emerging safety, tolerability, and/or pharmacokinetic data. All dose combinations will be determined by the SRC. Figure 7, and Figure 8 provide dosing guidelines for Arms A in Part A and for Arm B2 (post first 20 patients) and Arm B4 (post-interim analysis) in Part B. For Part B, AZD5069 will be administered at 40 mg BID.

Figure 6 Dose-reduction levels for treatment Arm B8



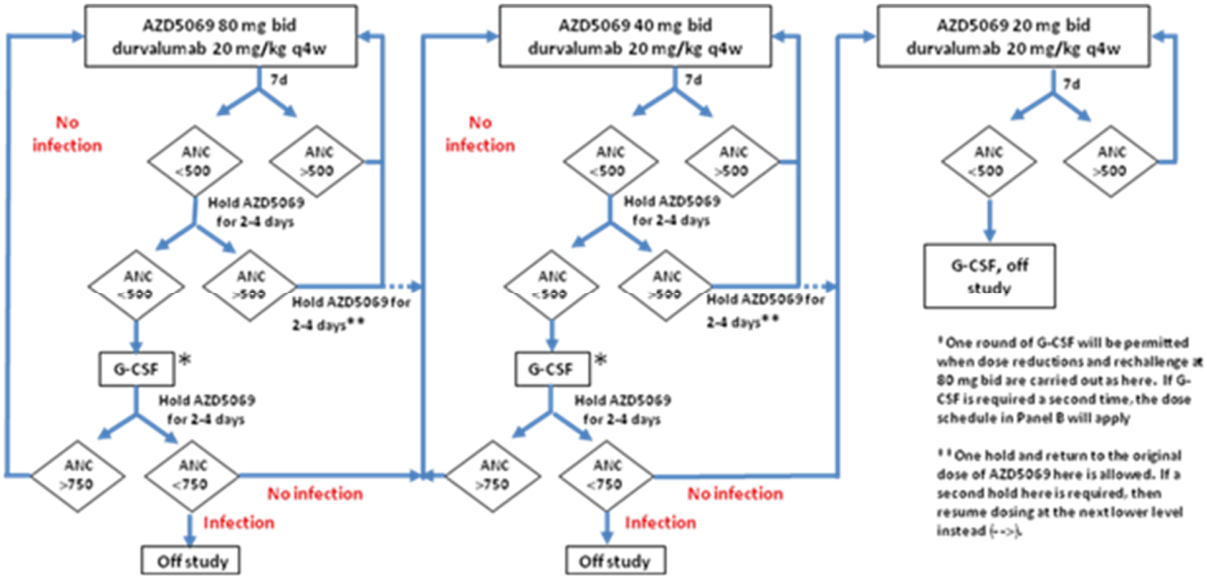
If body weight decreases to less than 30 kg, weight-based MEDI4736 dosing (20 mg/kg Q4W) will be implemented. No other dose-reductions will be permitted for MEDI4736 for B8.

- AZD9150 Dose level -1: 300 mg Q2W
- AZD9150 Dose level -2: 200 mg Q2W

7.7.2 Management of causally related infusion events

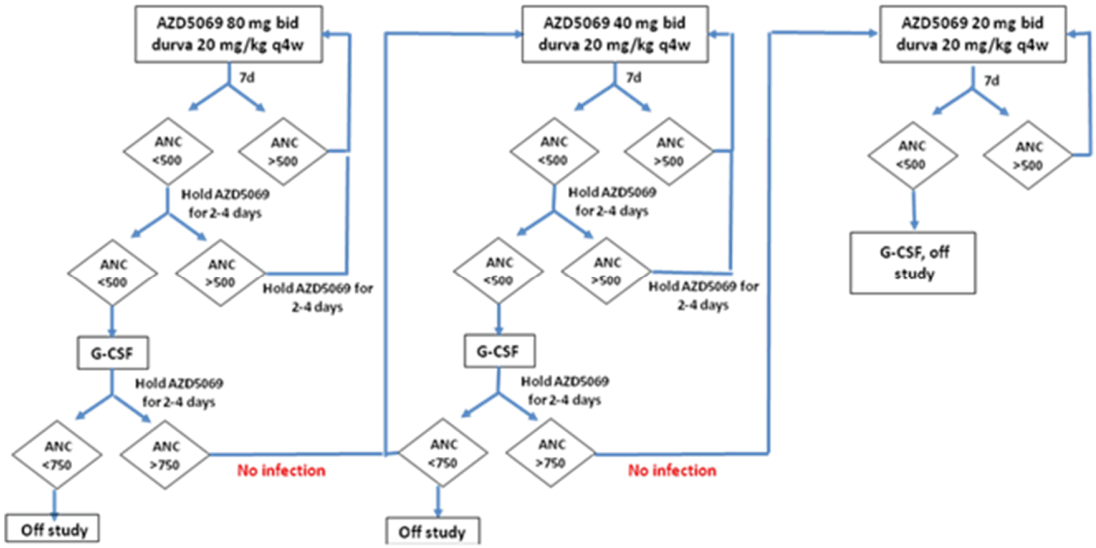
For events deemed causally related to infusion of MEDI4736 or tremelimumab refer to Annex 1.

Figure 7 **Alternative dose schedule, titration and dose-reduction for Arms A3 and B4 (post-interim analysis)**



One round of granulocyte-colony stimulating factor will be permitted when dose-reductions are done in the manner prescribed above. If granulocyte-colony stimulating factor is required for second time, the alternative dose schedule and titration as described in Figure 8 will be followed.

Figure 8 **Alternative dose schedule, dose titration and dose-reduction for Arms A3 and B4 (post-interim analysis)**



7.7.3 Definition of dose-limiting toxicity

The DLT evaluation period will be defined in Part A of the study as the time from the first dose of AZD9150 or AZD5069 to the end of Cycle 1 (i.e., 35 days total) or until a patient experiences a DLT, whichever occurs first.

A DLT is defined as any AE that occurs from the first dose of study treatment up to the end the DLT evaluation period, that is judged by the Investigator to be drug-related (i.e., unrelated to PD, intercurrent illness, or concomitant medications), and that is assessed as grade 3 or worse according to the NCI CTCAE, with the following exceptions:

- Increases in transaminase levels (serum glutamic oxaloacetic transaminase [SGOT]/AST and serum glutamic-pyruvic transaminase [SGPT]/ALT) are DLT if:
  - SGOT/AST and/or SGPT/ALT increase to >15 × ULN at any time, and/or
  - SGOT/AST and/or SGPT/ALT increase to >10× to 15 × ULN over a span of 14 consecutive days, and/or
  - SGOT/AST and/or SGPT/ALT increase to >ULN, and 1 or more of the following conditions is met and not explained by other causes:
    (a) TBL increased to >2 × ULN
    (b) New appearance of eosinophilia (>5%)
    (c) Clinical signs of functional liver impairment
- Nausea, vomiting, and diarrhoea will be considered a DLT only if assessed as grade 3 or worse after optimal prophylactic or treatment measures have been prescribed.
- Fatigue will not be considered a DLT.
- Neutropenia will be considered a DLT only:
  - If in the context of grade 3 febrile neutropenia (i.e., absolute neutrophil count [ANC] <1,000 mm^3 with a single temperature of more than 38.3ºC (101ºF) or a sustained temperature of at least 38ºC (100.4ºF) for more than 1 hour;
  - If in the context of grade 4 febrile neutropenia (i.e., ANC <1,000 mm^3 with life-threatening consequences that indicate urgent intervention);
  - If assessed as grade 3 or worse (i.e., ANC <1,000 mm^3) and associated with an infection that is clinically severe, associated with sepsis or requiring hospitalization. Grade 3 non febrile neutropenia with clinically minor (as judged by the Investigator) infection need not be regarded as DLT; or
  - If assessed as grade 4 (i.e., ANC <500 mm^3) for more than 5 days.

- Thrombocytopenia will be considered a DLT only:
  - If assessed as grade 3 or worse (i.e., platelet count <50,000 mm^3) and associated with bleeding, or
  - If assessed as grade 4 i.e., platelet count <25,000 mm^3).

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

Any toxicity judged by the Investigator to be drug-related (i.e., causality rated as possible or greater) that requires study treatment to be discontinued for more than 10 consecutive days will be considered a DLT.

7.7.4 Definition of maximum tolerated dose

A dose will be considered non-tolerated and dose-escalation will cease if ≥33% of patients on that dose experience a DLT. Once the non-tolerated dose is defined, the MTD will be confirmed at a dose level below the non-tolerated dose or a dose between the non-tolerated dose and the last tolerated dose may be investigated. At least 6 evaluable patients are required to determine the MTD.

7.7.5 Definition of dose-limiting toxicity evaluable patient

For patients in treatment arms A1 and A4 (AZD9150/MEDI4736 or AZD9150/MEDI4736/tremelimumab), to be deemed evaluable for dose-escalation purposes, a 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 tremelimumab infusion during the DLT Evaluation period or have suffered a DLT within the first 35 days of treatment.

For patients in treatment arm A2 or A3 (AZD5069/MEDI4736 or AZD5069/MEDI4736/tremelimumab), to be deemed evaluable for dose-escalation purposes, a patient must have received all doses during the 7-day lead-in period (i.e., 14 doses) and at least 42 additional doses of AZD5069 or 50% of planned doses during the DLT Evaluation period) as well as the MEDI4736 infusion and remained active on trial at the end of Day 35 of the study.

7.7.6 Safety Review Committee

The SRC will be chaired by the Sponsor Study Team Physician (or delegate) and include the Investigator (or delegate) from each of the investigational sites. In addition, other physicians such as the Global Safety Physician (or delegate) or a senior physician from the same or another project, as well as the Clinical Pharmacology Scientist, Study Statistician, Patient Safety Scientist, Associate Director Study Management, and others may be invited as

appropriate. Further internal or external experts may be consulted by the SRC as necessary. The Global Safety Physician or delegate should always be present at the SRC if there are safety issues for discussion. The SRC Remit document for this study will define the exact membership and who should be present for decisions to be made.

The SRC will review and assess all available safety data from the cohort, with available PK and pharmacodynamics data to determine the dose for the next cohort of patients. Any dose interruptions and reductions (see Section 5.5 for dose modifications) will be taken into account.

Once a DLT has been observed, SRC may decide to:

1. Expand the cohort to include additional patients
2. De-escalate the dose either to a previous lower dose level (up to a maximum of 6 evaluable patients) or to an intermediate lower dose level
3. Stop the arm enrolment

When there are other patients ongoing at the time of this review, the SRC may decide to defer their decision until these further patients become evaluable.

Any patient started on treatment in error (e.g., he/she failed to comply with all of the selection criteria) who meets the criteria of a DLT evaluable patient will be reviewed on a case-by-case basis by the SRC to determine if the patient's data should be included or excluded in the decision for dose escalation.

The decisions and decision-making of the SRC on the next dose level will be documented and provided to the Investigators before dosing any new patients.

7.7.7 Confirmation of the presumed recommended dose

Once the MTDs for each of the 2 agents in combination with MEDI4736 and/or MEDI4736/tremelimumab have been identified or the maximum doses of each of the 2 agents in combination with MEDI4736 and/or MEDI4736/tremelimumab have been reached, the SRC may decide to enroll 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.

Dose-expansion Part B

Once the doses for AZD9150 and AZD5069 in combination with MEDI4736 have been established in Part A of the study as detailed in Section 5.3, the dose-expansion Part B will begin. If the RP2D combination is established earlier in one arm of Part A than the other, the Sponsor may manually assign patients to a pretreated arm (treatment arm B1/B2 as discussed below) of the determined RP2D combination to get safety data (for US sites ONLY). One

such patient was manually randomized to Arm B1; this patient will not be included for any efficacy analysis and could be replaced with an actual randomized patient. 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.

In the dose-expansion Part B, based on the patient's history of treatment with any anti-PD-(L) 1 antibody, the Investigator will assess whether the patient will be assigned treatment in 1 of the anti-PD-(L)1 pretreated arms or naïve treatment arms. Additionally, Arms B7 and B8 will enroll patients who are PD-(L)-1 treatment naïve and have not received any prior systemic treatment for recurrent metastatic SCCHN. Also additionally, based on 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 and detailed in Section 5.1.2 as well as the patient's anticipated need or likelihood to consume such products at any time throughout the study, the Investigator will further assess each patient enrolled in the study to determine if the patient may be treated with AZD5069. Details regarding study arms for Part B can be found in Section 4.2.

The dose-expansion Part B will use an adaptive approach to sample size based on Bayesian statistical methodology and so the number of actively enrolling treatment arms may decrease as the study continues. See Section 8.2.2 for details on sample size, conditions for stopping an arm, and the conduct of an interim analysis.

7.7.8 Definition of efficacy evaluable patient

As described in Section 8.2.2, the dose-expansion Part B is based on efficacy evaluable patients. Patients identified as not efficacy evaluable will be replaced.

An efficacy evaluable patient is defined as a patient with unidimensional measurable disease at baseline as per the RECIST v1.1 criteria, meeting all eligibility criteria, and who received at least 1 dose of study treatment. For combination arm patients this population will hence include all patients who have received at least one dose of combination.

7.8 Concomitant and other treatments

Information on any treatment in the 30 days before starting study treatment and all concomitant treatments given during the study, including start and stop dates as well as the reasons for the treatment, will be recorded in the eCRF. If medically feasible, patients taking regular medication, with the exception of medications restricted during the course of the study (see Table 2 above) or herbal supplements, should be maintained on these medications throughout the study period.

Other anticancer agents, investigational agents, and radiotherapy should not be given while the patient receiving study treatment, although radiation for palliation at focal sites is permitted.

Blood and blood product transfusions, including platelet infusions are allowed at any time during the study.

Patients already receiving erythropoietin at the time of screening for the study may continue the erythropoietin providing they have been receiving it for more than 1 month at the time study treatment is started. Prophylactic erythropoietin should not be started during the 7-day lead-in period and Cycle 1 in Part A (i.e., the DLT Evaluation period) but may be started during Cycle 2 or after at the discretion of the Investigator. There are no restrictions on the use of erythropoietin in Part B of the study.

Antiemetic premedication for nausea and granulocyte colony stimulating factors are permitted for use at the discretion of the Investigator. The use of either prophylactic antiemetic premedication for nausea or granulocyte colony stimulating factors is not permitted during the 7-day lead-in period and Cycle 1 in Part A (i.e., the DLT Evaluation period); it may be started during Cycle 2 or after at the discretion of the Investigator. There are no restrictions on the use of antiemetic premedication for nausea and granulocyte colony stimulating factors in Part B of the study.

Patients may receive treatment with megestrol acetate when prescribed for appetite stimulation.

Patients may receive treatment with corticosteroids and/or bisphosphonates for the treatment of bone metastases.

Patients may take low molecular weight dextran. The use of Coumadin (warfarin) is not permitted in patients treated with AZD5069 but allowed for all other patients. It is recommended that patients treated with an anticoagulant should have their anticoagulation monitored carefully and dose adjusted accordingly.

Patients allocated to treatment with MEDI4736 may not receive live attenuated vaccines during the study and for 30 days after the last dose of MEDI4736. Non-clinical studies have demonstrated that MEDI4736 partially suppressed the primary antibody response to a T cell dependent antigen (keyhole limpet haemocyanin). Secondary antibody responses to this antigen were normal. The relevance of this finding with respect to a human immune response is theoretical; a reduction in humoral immunity may result in a reduced response to vaccination and increased risk of infection.

As described in the previous section, patients treated with AZD5069, coadministration of drugs that are known potent or moderate CYP3A4 inhibitors, potent or moderate CYP3A4 inducers, P-gp substrates with narrow therapeutic index, sensitive CYP2B6 substrates, warfarin or any other coumarin derivatives, BCRP-substrates that reduce blood neutrophils, and any herbal medications should be avoided. See Section 3.8.2 for details and Table 2 for a list of prohibited medications for patients administered AZD5069. Any questions regarding concomitant treatments in these patients should be referred to the Medical Monitor [redacted] (see Section 6.10 for contact information).

With the exceptions noted above, other medication that is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and will be recorded in the appropriate sections of the eCRF.

Patients should abstain from donating blood and plasma during the study.

Investigators should carefully assess the risk in relation to benefit of using anticoagulation or other medications that might exacerbate bleeding during study participation. Investigators should consider discontinuation of these agents if the clinical scenario permits it unless discontinuation would be clinically contraindicated. For example, if the clinical condition for which anticoagulation/nonsteroidal anti-inflammatory drugs/aspirin is/are being used may be managed with an alternate agent/s that has a lower risk of bleeding, a substitution should be considered.

7.8.1 Other concomitant treatment

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

8 STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

- Analyses will be performed by AstraZeneca or its representatives.
- Refer to Statistical Analysis Plan (SAP) for further details.
- For open-label studies, and if there is a regulatory requirement to submit SAP to regulatory agencies with the CSP, the SAP should be signed off before enrolment of the first subject. For all other studies, the SAP will be signed off before review of any potential treatment-revealing data is undertaken (this includes blinded delivery reviews and data monitoring committee reviews). For all situations, a full draft of the SAP should be available to ensure sufficient time to prepare for any blinded or unblinded data review.

8.2 Sample size estimate

8.2.1 Dose-escalation 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 dose 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 MTD in 21.8%

of simulated trials. On average, the number of patients treated at each of the 4 dose levels is 5.7, 4.8, 3.0, and 1.3. The average number of DLTs at each of the 4 doses is 0.7, 1.5, 1.7, and 1.0.

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 MTD. 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 0.2, 1.2, 5.5, 4.5, 0.8, and 2.9. The average number of DLTs at each of the 6 dose levels is 0.0, 0.0, 0.6, 1.4, 0.45, and 2.3.

In Arm 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 tremelimumab (Arm A4).

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

8.2.2 Dose-expansion Part B

The dose-expansion Part B will use an adaptive approach to sample size based on Bayesian statistical methodology (Figure 9).

Anti-PD-(L)1 naïve patients

For the 2 combination arms in the anti-PD-(L)1 naïve patients (B3 and B4), once 12 efficacy outcomes have been observed in the first 12 efficacy evaluable patients in each arm, a predictive power 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 power is based on a parameter free approach to predictive power as it applies to variables that follow a binomial distribution (Jennison and Turnbull 2000). Predictive power (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 and the 1L RM SCCHN patients in Arm B7. The 2 monotherapy arms will continue recruiting until 12 efficacy evaluable patients have been enrolled in each arm.

Anti-PD-(L)1 pretreated patients

For the 2 combination arms in the anti-PD-(L)1 pretreated patients (B1 and B2), 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 20 of 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.

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.

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.

An efficacy evaluable patient is defined as a patient with unidimensional measurable disease at baseline as per the RECIST 1.1 criteria who received at least 1 dose of study treatment.

Simulation methods (10,000 simulated trials) were used to estimate the operating characteristics of the dose-expansion studies. The expected sample size for a series of true ORR values for the combination therapy arms are presented in Table 14 below. These simulation data show that between 207 and approximately 255 patients are expected to be treated in all 8 randomized arms of the dose-expansion Part B (B1 to B8).

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 non-informative prior.

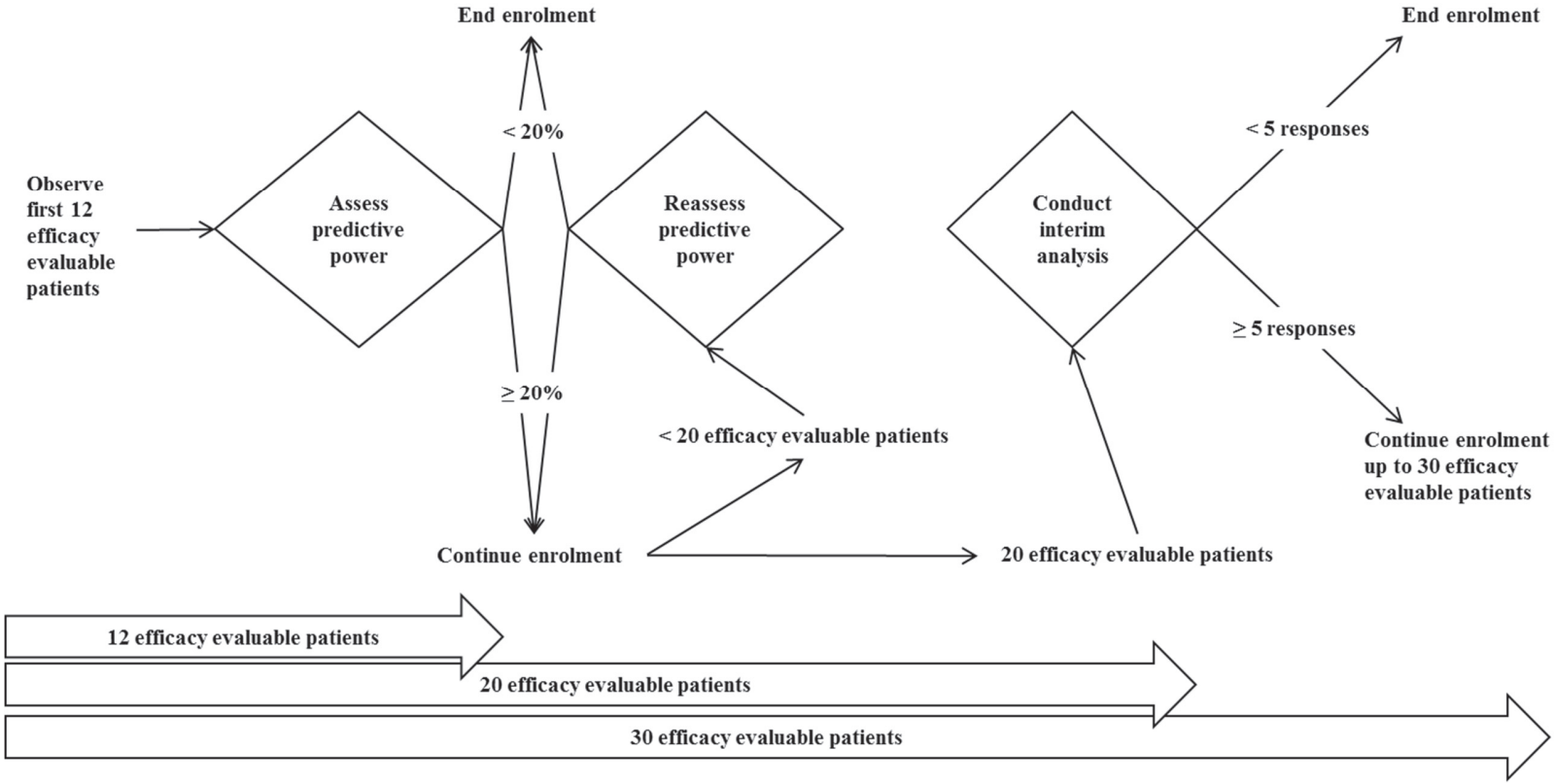
Table 14 Expected sample sizes for a series of true objective response rates for combination therapy in anti-PD-(L)1 naïve and anti-PD-(L)1 pretreated patients

True objective response rate of combination therapy		Expected sample size[a]
Naïve	Pretreated	
0.25	0.15	121.3
0.25	0.05	121.5
0.25	0.025	121.3
0.15	0.15	114.9
0.15	0.05	115
0.15	0.025	115
0.05	0.15	103.9
0.05	0.05	103.8
0.05	0.025	103.7

[a] The results are averaged over the corresponding set of naïve and pretreated values. The expected sample size includes 12 patients in each of the 2 monotherapy arms.

Thus, with the study design and interim assessments as described above, the chance to stop a combination arm in anti-PD-(L)1 naïve patients given an optimistic true ORR value (0.45 for naïve and 0.31 for pretreated patients) is approximately 19.3%. The chance to stop a combination arm in anti-PD-(L)1 pretreated patients is approximately 11.7%. If the true ORR performance of the combination arms is low (i.e., approximately 10% for naïve, 5% for pretreated), the chance that any combination will stop before fully recruiting is >98% for naïve and >94% for pretreated.

Figure 9 Adaptive approach to sample size Part B (B1-B6)



If at least 2 CR or PR are observed in the first 20 patients in either of the 2 pretreated expansion arms (Arm B1 or B2), then an additional 25-32 patients may be enrolled.

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 chance that fewer than 12 patients with CR or PR (responding) will be observed, given the true fraction of patients responding is 35%, is 9%. The chance that at least 15 patients responding is observed, given the true fraction of patients responding is 25%, is 20%. 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.

In anti-PD-(L)1 pretreated patients, approximately 10 to 52 patients will be treated in each of the 2 combination therapy arms (B1, B2). In anti-PD-(L)1 naïve patients, approximately 12 to 35 patients will be treated in each of the 2 combination therapy arms (B3 or B4). If in Arm B4, the arm is stopped due to lack of efficacy at the IA (following N=20) a higher dose may be tested under the original sample size requirements (N=35) so the total number of patients in Arm B4 would then be N=55 (N=20 from the original IA and N=35 under the original design for Arm B4). In anti-PD-(L)1 naïve patients, 12 patients will be treated in each of the 2 monotherapy arms (B5, B6). 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. As a result, the total number of patients in Part B will be between 207 and approximately 255.

8.3 Definitions of 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 (e.g., those assigned to receive dose A, who actually received dose B, those who failed to meet the selection criteria) will be accounted for in the actual dose group received.

Table 15 Analysis sets

Analysis Set	Definition
Safety	All patients who received at least 1 dose of AZD9150, AZD5069, or MEDI4736
Pharmacokinetics	All dosed patients with reportable AZD9150, AZD5069, or MEDI4736 plasma concentrations and no important AEs or protocol deviations that may impact PK
Pharmacodynamics	All patients who provided biological samples for pharmacodynamic research
Efficacy	All patients with unidimensional measurable disease at baseline as per the RECIST 1.1 criteria who received at least 1 dose of study treatment

8.3.1 Efficacy analysis set

All patients with unidimensional measurable disease at baseline as per the RECIST 1.1 criteria who received at least 1 dose of study treatment.

8.3.2 Safety analysis set

All patients who received at least 1 dose of AZD9150, AZD5069, or MEDI4736 tremelimumab (for patients in Arm A4).

8.3.3 PK analysis set

All patients who provided biological samples for pharmacodynamic research.

8.3.4 PD analysis sets

All patients who provided biological samples for pharmacodynamic research.

8.4 Calculation or derivation of safety variables

Safety and tolerability will be assessed in terms of AEs, SAEs, laboratory data, vital signs, ECG changes, and physical examinations. These will be collected for all patients. Appropriate summaries of these data will be presented.

ECG changes

Immediate clinical management of patients will be according to local assessment of the QT interval. For the CSR, QTc will be calculated using Fridericia's formula:

$QTcF=QT/(\sqrt[3]{RR})$.

Creatinine clearance

Creatinine clearance may be measured by 24-hour urine collection or calculated by using the Cockcroft and Gault equation (Cockcroft and Gault 1976).

For creatinine values in µmol/L:

Men: [(140-age) × weight (kg)×1.23)]/serum creatinine (µmol/L)]

Females: [(140-age) × weight (kg)×1.04)]/serum creatinine (µmol/L)]

For creatinine values in mg/dL:

Men: [(140-age) × weight (kg)/[72×serum creatinine (mg/dL)]

Females: 0.85 × [(140-age)×weight (kg)/[72×serum creatinine (mg/dL)]

Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs. Based on the expert's judgement, 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. A similar review of laboratory values, vital signs, ECGs, and other safety assessments will be performed for identification of OAEs.

8.5 Calculation or derivation of pharmacokinetic variables

Pharmacokinetic analysis of plasma (for all compounds) and urine (for AZD9150 only) concentration data for AZD9150, AZD5069, and MEDI4736 will be performed by a central laboratory on behalf of AstraZeneca. The actual sampling times will be used in the parameter calculations and PK parameters will be derived using standard non-compartmental methods.

Where possible, the following PK parameters will be determined for AZD9150, AZD5069, and MEDI4736.

Pharmacokinetic parameters for AZD9150:

- Single dose: C_{max}, T_{max}, $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-48)}$, CL, V_z/F, MRT, $t_{1/2}$, as data permit
- Multiple dose: $C_{ss\ max}$, $C_{ss\ min}$, $T_{ss\ max}$, C_{trough}, $AUC_{(0-24)}$, V_{ss}, extent of accumulation on multiple dosing (R_{ac}), Ae, and %Fe

Pharmacokinetic parameters for AZD5069:

- Single dose: C_{max}, T_{max}, $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, apparent plasma clearance (CL/F), apparent volume of distribution (Vd/F), MRT, and $t_{1/2}$, as data permit

- Multiple dose: $C_{ss\ max}$, $T_{ss\ max}$, C_{trough}, $AUC_{(0-24)}$, V_{ss}/F, apparent plasma clearance at steady state (CL_{ss}/F), R_{ac}

Pharmacokinetic parameters for MEDI4736:

- C_{max}, T_{max}, C_{trough}

The C_{max}, the $C_{ss\ max}$, T_{max}, and the $T_{ss\ max}$ will be determined by inspection of the concentration-time profiles. 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 ($t_{1/2\lambda z}$) will be calculated as ln 2/λz. The $AUC_{(0-t)}$ and the $AUC_{(0-24/48)}$ 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, $AUC_{(ss)}$ will be calculated using the linear up, log down trapezoidal rule. The CL/F following the single dose and CL_{ss}/F following multiple dosing) will be determined from the ratio of dose/AUC or dose/$AUC_{(ss)}$. The volume of distribution (V_{ss}, V_{ss}/F, or V_z/F) will be determined from the MRT×CL/F and/or the accumulation ratio (R_{AC}) will be calculated as the ratio of the $AUC_{(0-24)}$ on Cycle 2 Day 1. The time dependency of the PK on multiple dosing will be assessed by the calculation of the ratio of $AUC_{(ss)}$/AUC(single dose).

8.6 Calculation or derivation of pharmacodynamic variables

Change from baseline and percent change from baseline for pharmacodynamic variables will be calculated for all patients.

8.7 Pharmacokinetics/Pharmacodynamic analysis

The plasma concentration data for AZD9150, MEDI4736, tremelimumab, and AZD5069 may be analysed using a population PK approach, which may include exploring the influence of covariates on PK, if the data allows. A population pharmacodynamic approach will be used to investigate the relationship between PK and selected primary, secondary, and/or exploratory endpoints, where deemed appropriate. Results may be reported separately from the CSR for the main study. The PK, pharmacodynamic, demographic, safety, and tumor response data collected in this study may also be combined with similar data from other studies and explored using population PK and/or PK-pharmacodynamic methods. The results of any such analyses will be reported separately from the CSR.

8.8 Calculation or derivation of exploratory research variables

Results from the exploratory biomarker research and/or pharmacogenetic research will be reported separately from the CSR for the main study.

8.9 Calculation or derivation of tumor response variables

At each visit, patients will be programmatically assigned a RECIST version 1.1 overall visit response of CR, PR, SD, or PD, not evaluable (NE) depending on the status of their disease compared with baseline and previous visit assessments.

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

If a patient has had a tumor assessment that cannot be evaluated (either because the scan was unreadable or taken before Day 15 of Cycle 2), the patient will be assigned an overall visit response of NE unless there is evidence of progression, in which case the response will be assigned as PD.

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

- If ≤ one-third of all lesions recorded at baseline are missing, the results will be scaled up (based on the nadir sizes, including baseline) to give an estimated sum of diameters and this will be used in calculations. (This is equivalent to comparing the visit sum of diameters of the non-missing lesions to the nadir sum of diameters excluding the lesions that are missing and determining at what rate the lesions are changing.)
- If > one-third of all lesions recorded at baseline are missing, the TL response will be NE. However, if the sum of non-missing TL diameters would result in PD (i.e., if using a value of 0 for missing lesions the sum of diameters has still increased by >20% or more compared with the smallest sum of diameters on study); PD takes precedence over NE.
- Only responses of PR, SD, PD, or NE will be permitted if any of the TL data are missing.

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

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

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

Best overall response

A best overall response (CR, PR, SD, PD, or NE ordered from best to worst here) will be determined for each patient based on the best overall visit response recorded from start of study treatment to the EOT, including any assessments for confirmation after the EOT. Confirmation (values of CR or PR in the case of PR and CR for CR is required for best overall response values of CR or PR).

Objective response

A patient is said to have an objective response if he/she has had at least 1 response of confirmed CR or PR before any evidence of progression (as defined by RECIST version 1.1) that is confirmed at least 4 weeks later.

Disease control

A patient is said to have achieved disease control at a given visit if they have a tumor response of SD, PR, or CR at that visit. Disease control will be assessed at 12 weeks after the start of study drug and is defined as the proportion of all patients dosed 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.

Duration of response

Duration of response will be defined as the time from the date of first documented confirmed response until date of documented progression or death in the absence of disease progression. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first overall visit response of PR or CR.

If a patient does not progress following a response, then his/her DOR will use the PFS censoring time.

Durable response

A patient is said to have a durable response of 3 months if they have either a confirmed CR or PR that lasts 3 months following the initial confirmation of the response.

Progression-free survival

Progression-free survival is defined as the time from start of treatment (Cycle 1, Day 1) until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy before progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST version 1.1 assessment. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable RECIST version 1.1 assessment. If the patient has no evaluable visits or does not have baseline data, he/she will be censored at 0 days unless he or she dies within 2 visits of baseline.

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

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

- Date of progression will be determined based on the earliest of the dates of the component that triggered the progression
- When censoring a patient for PFS the patient will be censored at the latest of the dates contributing to a particular overall visit assessment

Overall survival

Overall survival is defined as the time from the date of Cycle 1, Day 1 until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

Survival at 12 months

Patients who are alive 1 year following the beginning of treatment are said to have survived 12 months. Patients whose vital status is unknown at 12 months will be censored at the last date that the patient was known to be alive.

8.10 Methods of statistical analysis

The statistical analyses will be performed [redacted], under the direction of the Early Clinical Biometrics Group, AstraZeneca.

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

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

Data will be presented separately for each combination group (cohort) within Part A and by anti-PD-(L)1 status and treatment arm in Part B. Further, within arms A6 and A7, data will be presented by primary indication (metastatic breast [ER+ve for Arm A6, 50% ER+ve and 50% HER2+ve metastatic breast cancer patients for Arm A7] or castrate-resistant prostate cancer).

Data for the combination cohorts in Part A will be presented in order of increasing order of expected probability of DLT as illustrated in Table 16 and Table 17.

Table 16 Expected probability of DLT in treatment arm A1 of Part A (AZD9150/MEDI4736)

Ranked in Increasing Order of Expected Probability of DLT	Dose of AZD9150 (mg/kg)	Dose of MEDI4736 (mg/kg)	Note
1	2	10	
2	2	20	Planned starting combination
3	3	10	
4	3	20	

Abbreviation: DLT=dose-limiting toxicity.

Table 17 Expected probability of DLT in treatment arm A2 of Part A (AZD5069/MEDI4736)

Ranked in Increasing Order of Expected Probability of DLT	Dose of AZD5069 (mg) BID	Dose of MEDI4736 (mg/kg)	Note
1	20	3	
2	20	10	
3	40	10	Planned starting combination
4	80	10	
5	80	3	
6	120	10	

Abbreviations: BID=twice daily; DLT=dose-limiting toxicity.

Data for the 8 randomised treatment arms in dose-expansion Part B will be presented in the following order:

1. Anti-PD-(L)1 naïve patients – AZD9150 monotherapy
2. Anti-PD-(L)1 naïve patients – AZD5069 monotherapy
3. Anti-PD-(L)1 naïve patients – AZD9150 + MEDI4736
4. Anti-PD-(L)1 naïve patients – AZD5069 + MEDI4736
5. Anti-PD-(L)1 pretreated patients – AZD9150 + MEDI4736
6. Anti-PD-(L)1 pretreated patients – AZD5069 + MEDI4736
7. Anti-PD-(L)1 naïve patients – AZD9150+MEDI4736-1L
8. Anti-PD-(L)1 naïve patients – AZD9150 (flat dose) + MEDI4736 (flat dose)-1L

Demographic data

Characteristics of the patients, including medical history and disease characteristics at baseline, will be listed for each patient and summarised by cohort.

Reasons for discontinuation of IP will be listed, including the study day of treatment discontinuation, and will be summarised by cohort.

Exposure

Exposure to IP (i.e., total amount of study drug received) will be listed for all patients by cohort.

Total exposure (date of last dose minus date of first dose + 1) and total time on study (date of discontinuation minus date of first dose + 1) will be summarised by the following: Mean, standard deviation, minimum, maximum, median, and number of observations. In addition, the number and percentage of patients with at least 1 dose interruption/dose delay and at least 1 dose-reduction will be presented separately for the initial period of evaluability defined as 28 days and for any time following this initial period of the study.

Relative dose intensity and percentage intended dose for AZD9150, AZD5069, and MEDI4736 will be derived and summarised by the following: Median, minimum, maximum, 75th percentile, 25th percentile, and number of observations. Relative dose intensity is the percentage of actual dose intensity delivered relative to the intended dose intensity through treatment discontinuation. The entire intended treatment period will be used in the derivation of relative dose intensity.

Safety

No inferential testing will be performed on safety data. Safety data will be summarised using descriptive statistics. At the end of the study, appropriate summaries of all safety data will be produced, as defined below.

AEs will be listed individually by patient and treatment group. For patients who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the associated initial dose combination/treatment dose.

AESIs will also be summarised and listed separately for each compound.

The number of patients experiencing each AE will be summarised by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term and CTCAE grade. The number and percentage of patients with AEs in different categories (e.g., causally related, CTCAE ≥3) will be summarised by dose group, and events in each category will be further summarised by MedDRA system organ class and preferred term, by cohort (as appropriate). SAEs and other significant AEs will be summarised separately if a sufficient number occur.

Any AE occurring before the first dose of IP will be included in the data listings but will not be included in the summary tables of AEs. Summary tables will include only AEs observed following the beginning of combination dosing up to and including 28 days after last dose. One table summarising the incidence of AE occurring from the beginning of monotherapy up to the beginning of combination therapy will be generated.

Any AE occurring within the defined 28-day follow-up period after discontinuation of IP will be included in the AE summaries. AEs occurring after the 28-day follow-up period after discontinuation of IP will be listed separately but not included in the summaries.

Haematology, clinical chemistry, vital signs, and ECG data will be listed individually by patient and suitably summarised. For all laboratory variables, which are included in the current version of CTCAE, the CTCAE grade will be calculated. Summary statistics of mean, median, standard deviation, minimum, maximum, and number of observations will be used.

Details of any deaths will be listed for all patients.

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

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

Pharmacokinetics

Plasma concentrations for each of the drug substances AZD9150, AZD5069, tremelimumab, and MEDI4736 measured within each of the combination groups with any associated metabolites will be summarised by nominal sample time.

The following summary statistics will be presented for plasma concentrations at each time point and for the following PK parameters including, AUC, $AUC_{(0-24)}$, $AUC_{(0-48)}$, $AUC_{(0-t)}$, $AUC_{(ss)}$, C_{max}, $C_{ss\ max}$, C_{trough}, and $C_{ss\ min}$:

- The geometric mean (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], where s is the standard deviation of the data on a log-scale)
- Gmean ± standard deviation (calculated as exp[μ±s])
- Arithmetic mean calculated using untransformed data
- Standard deviation calculated using untransformed data
- Minimum
- Maximum
- Number of observations

The following summary statistics will be presented for CL, CL/F, CL_{ss}/F, volume of distribution, $t_{1/2\lambda z}$, R_{ac}, A_e, and % dose excreted:

- Arithmetic mean
- Standard deviation
- Minimum
- Maximum
- Number of observation

The following summary statistics will be presented for T_{max} and $T_{max\ ss}$:

- Median
- Minimum
- Maximum
- Number of observations

The PK data for AZD9150, MEDI4736, tremelimumab, and AZD5069 will also be displayed graphically as appropriate. Displays will include plasma concentration patient profiles (on the linear and log-scale) versus time and gmean concentration (± standard deviation) versus time, stratified by cohort and others as necessary.

Pharmacodynamics

Pharmacodynamic variables will be summarised using descriptive statistics (n, mean, standard deviation, median, minimum, maximum) by visit and cohort.

Summaries of change from baseline and percent change from baseline will also be presented for pharmacodynamic variables by visit and cohort.

Immunohistochemistry scores will be plotted as a function of dose combination.

Histograms for each of the pharmacodynamic variables will also be presented by visit and dose.

Pharmacokinetics/pharmacodynamics

Scatterplots of each pharmacodynamic variable as a function of plasma concentrations of MEDI4736, AZD5069, tremelimumab, or AZD9150 may be presented.

Population analysis of pharmacokinetic/pharmacodynamic variables

The plasma concentration data for AZD9150, MEDI4736, tremelimumab, and AZD5069 may be analysed using a population PK approach, which may include exploring the influence of covariates on PK, if the data allow. A population pharmacodynamic approach will be used to investigate the relationship between PK and selected primary, secondary, and/or exploratory endpoints, where deemed appropriate. Results may be reported separately from the CSR for the main study. The PK, pharmacodynamic, demographic, safety, and tumor response data collected in this study may also be combined with similar data from other studies and explored using population PK and/or PK-pharmacodynamic methods. The results of any such analyses will be reported separately from the CSR.

Exploratory biomarker research and pharmacogenetics

Results will be reported separately and will not be part of the CSR.

Tumor response

Tumor response data will be summarised for dosed patients with measurable disease at baseline and separately for dosed patients who only had non-measurable disease at baseline.

Tumor response data will be listed and summarised by cohort using the following response categories: CR, PR, SD, PD, and NE.

The number (%) of patients with a response of CR, PR, or SD at the beginning of each even-numbered cycle and at the EOT visit will be summarised.

Waterfall plots (bar charts) indicating the percentage change from baseline at Week 12, and best percentage change from baseline in sum of the diameters of TLs will be produced by cohort.

The number (%) of patients who have a confirmed response (complete or partial) who have a durable response will be summarised.

For Part B, duration of overall response will be analysed using Kaplan-Meier (KM) methods, where patients who do not progress before dying will be censored at time of death or at the administrative end of the trial.

Best overall response

For patients with baseline measurable disease, best overall response will be summarised for the number (%) of patients in each category of response (CR, PR, SD, PD, or NE, ordered from best to worst here). Confirmation of CR and PR responses is required.

For Part B, an exact 2-sided 80% CI will be computed using the method of Clopper and Pearson (Clopper and Pearson 1934). Summaries only will be provided as appropriate for Part A.

Objective response rate

Objective response rate is defined as the proportion of patients who have an objective response (confirmed CR or PR) at a given visit. The ORR will be summarised by treatment group. For the primary endpoint in Part B, an exact 2 sided 80% CI for the ORR will be computed using the method of Clopper and Pearson (Clopper and Pearson 1934).

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

Disease control rate

Disease control rate is defined as the proportion of patients who have achieved disease control at a given visit. Disease control rate will be summarised by treatment and visit. For Part B, an exact 2-sided 80% CI will be computed using the method of Clopper and Pearson (Clopper and Pearson 1934) at 12 weeks. Summaries only will be provided as appropriate for Part A.

Duration of response

Duration of response will be summarised using KM based methods and will include minimum, 25th percentile, median, 75th percentile, and maximum. Kaplan-Meier plots will also be presented. Only patients who achieve an overall response will be included in this analysis.

Durable response rate

Durable response rate is defined as the percentage of patients who have a durable response. The denominator for the durable response rate will be the efficacy analysis set (see Section 8.3).

Progression-free survival

Progression-free survival will be analysed using KM methods in an exploratory manner. Summaries of PFS (number of events, medians, quartiles, and proportion progression free at 1, 2, 3, and 4 months after the first dose of IP) will be presented.

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

Overall survival

Summaries of OS (n, deaths, medians, quartiles), and KM plots will be provided as appropriate.

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

Proportion of patients surviving at 12 months

The proportion of patients surviving at 12 months will be presented. An exact 2-sided 80% CI will be computed using the method of Clopper and Pearson (Clopper and Pearson 1934). In addition, OS at 12 months will be estimated using the survival probability at 12 months from the KM analyses.

9 STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site staff

Before the first subject is entered into the study, an AstraZeneca representative will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study-specific procedures and web-based system(s) utilised.

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

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

9.2 Monitoring of the study

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

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the CSP, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

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

9.2.1 Source data

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site. Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

9.2.2 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this CSP and the Clinical Study Agreement, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or subjects are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement.

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last subject undergoing the study'.

The study may be terminated at individual centres if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD5069, AZD9150, MEDI4736, and tremelimumab.

9.4 Data management by AstraZeneca

Data management will be performed [redacted], according to the Data Management Plan.

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

AEs and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the WHO Drug Dictionary. All coding will be performed by the Medical Coding Team [redacted].

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

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

responsibilities of the various functions and personnel involved in the data management process.

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

Serious Adverse Event (SAE) Reconciliation

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

Data Management of genotype data

Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyse the samples.

AstraZeneca and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organizations, or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results, but they will not be able to see individual patient data or any personal identifiers.

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

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratories internal or external to AstraZeneca. Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse samples. The results from this genetic research will be reported separately from the clinical study report for the main study. Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Management of external data

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

Data from external providers (e.g., central laboratories) will be validated as appropriate to ensure it is consistent with the clinical data and included in the final database. In the case of biomarker (tumor tissue or blood for exploratory analyses) data, the results of any analyses

will not be recorded in the database, but information relating to the processing of the sample, including the original date of biopsy (historical tumor tissue sample and the actual date the sample[s] were collected) will be recorded in the eCRF and database.

10 ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH)/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Subject data protection

The Informed Consent Form (ICF) will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and regulatory review

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

The opinion of the Ethics Committee should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any subject into the study.

The Ethics Committee should approve all advertising used to recruit subjects for the study.

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

If required by local regulations, the CSP should be re-approved by the Ethics Committee annually.

Before enrolment of any subject into the study, the final CSP, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

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

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

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

10.4 Informed consent

The Principal Investigator(s) at each centre will:

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

10.5 Changes to the Clinical Study Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of, National Co-ordinating Investigator, and the Principal Investigator and AstraZeneca.

If there are any substantial changes to the CSP, then these changes will be documented in a new version of the study protocol.

The new version of the CSP is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for new versions of CSPs.

AstraZeneca will distribute any new versions of the CSP to each Principal Investigator(s). For distribution to Ethics Committee see Section 10.3.

If a change to a CSP requires a change to a centre's ICF, AstraZeneca and the centre's Ethics Committee are to approve the revised ICF before the revised form is used.

10.6 Audits and inspections

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

11 LIST OF REFERENCES

Alvarez et al 2005
Alvarez JV, Febbo PG, Ramaswamy S, Loda M, Richardson A, Frank DA. Identification of a genetic signature of activated signal transducer and activator of transcription 3 in human tumors. Cancer Res 2005;65:5054-62.

American Cancer Society 2014
American Cancer Society. Cancer Facts and Figures 2014. Atlanta, GA: American Cancer Society.

Antonia et al 2014
Antonia SJ, Ou SI, Khleif S, Brahmer JR, Blake-Haskins A, Robbins PB, et al. Clinical activity and safety of MEDI4736, an anti-programmed cell death ligand 1 (PD L1) antibody, in patients with non-small cell lung cancer. (Poster presented at the European Society for Medical Oncology [ESMO] Meeting, Madrid, Spain, 26–30 September 2014.) Ann Oncol 2014;25(Suppl 4):iv426-70.

AstraZeneca
AstraZeneca. Investigator's Brochure for AZD5069: CXCR2 inhibition in oncology indications.

AstraZeneca 2016 (a)
Summary of safety and pharmacokinetics AZD9150 in combination with MEDI4736

AstraZeneca 2016 (b)
Summary of safety and pharmacokinetics AZD5069 in combination with MEDI4736

Bauml et al 2017
Bauml Joshua, Seiwert TY, Pfister DG et al. Pembrolizumab for platinum-and cetuximab-refractory head and neck cancer: Results from a single-Arm, Phase II study.

Bloomer et al 2013
Bloomer J, Derimanov G, Dumont E, Ellens H, Matheny C. Optimizing the in vitro and clinical assessment of drug interaction risk by understanding co-medications in patient populations. Expert Opin Drug Metab Toxicol 2013;9(6):737-51.

Brahmer et al 2012
Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD L1 antibody in patients with advanced cancer. N Engl J Med 2012;366:2455-65.

Cheung 2011
Cheung YK. Dose finding by the continual reassessment method. Boca Raton (FL): Chapman and Hall/CRC; 2011.

Chikamatsu et al 2012
Chikamatsu K, Sakakura K, Toyoda M, Takahashi K, Yamamoto T, Masuyama K. Immunosuppressive activity of CD14+ HLA-DR- cells in squamous cell carcinoma of the head and neck. Cancer Sci 2012;103: 976-83.

Clopper and Pearson 1934
Clopper C, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404-13.

Cockcroft and Gault 1976
Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16: 31-41.

Di Mitri et al 2014
Di Mitri D, Toso A, Chen JJ, Sarti M, Pinton S, Jost TR, et al. Tumor-infiltrating Gr-1+ myeloid cells antagonize senescence in cancer. Nature 2014;515:134-7.

Dorr et al 1999
Dorr A, Bruce J, Monia B, Johnston J, Geary R, Kwoh T, et al. Phase I and pharmacokinetic trial of ISIS 2503, a 20 mer antisense oligonucleotide against H-ras, by 14-day continuous infusion (CIV) in patients with advanced cancer. Proc Am Soc Clin Oncol 1999;18:A603.

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.

Fayette et al 2010
Fayette J, Montella A, Chabaud S, Bachelot T, Pommier P, Girodet D, et al. Paclitaxel is effective in relapsed head and neck squamous cell carcinoma: a retrospective study of 66 patients at a single institution. Anticancer Drugs 2010;21:553-8.

Fife and Bluestone 2008
Fife BT, Bluestone JA. Control of peripheral T cell tolerance and autoimmunity via the CTLA-4 and PD 1 pathways. Immunol Rev 2008;224:166-82.

Filipazzi et al 2007
Filipazzi P, Valenti R, Huber V, Pilla L, Canese P, Iero M, et al. Identification of a new subset of myeloid suppressor cells in peripheral blood of melanoma patients with modulation by a granulocyte-macrophage colony-stimulation factor-based antitumor vaccine. J Clin Oncol 2007;25:2546-53.

Forastiere et al 1992
Forastiere AA, Metch B, Schuller DE, Ensley JF, Hutchins LF, Triozzi P, et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: a Southwest Oncology Group study. J Clin Oncol 1992;10:1245-51.

Gabrilovich and Nagaraj 2009
Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol 2009;9:162-74.

Gibson et al 2005
Gibson MK, Li Y, Murphy B, Hussain MH, DeConti RC, Ensley J, et al; Eastern Cooperative Oncology Group. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2005;23:3562-7.

Guardiola et al 2004
Guardiola E, Peyrade F, Chaigneau L, Cupissol D, Tchiknavorian X, Bompas E, et al. Results of a randomised phase II study comparing docetaxel with methotrexate in patients with recurrent head and neck cancer. Eur J Cancer 2004;40:2071-6.

Highfill et al 2014
Highfill SL, Cui Y, Giles AJ, Smith JP, Zhang H, Morse E, et al. Disruption of CXCR2-mediated MDSC tumor trafficking enhances anti-PD1 efficacy. Sci Transl Med 2014;6:237ra67.

Hitt et al 2012
Hitt R, Irigoyen A, Cortes-Funes H, Grau JJ, Garcia-Saenz JA, Cruz-Hernandez JJ, et al. Phase II study of the combination of cetuximab and weekly paclitaxel in the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of head and neck. Ann Oncol 2012;23:1016-22.

Hodi et al 2010
Hodi F S, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711-23.

Hoechst et al 2009
Hoechst B, Voigtlaender T, Ormandy L, Gamrekelashvili J, Zhao F, Wedemeyer H, et al. Myeloid-derived suppressor cells inhibit natural killer cells in patients with hepatocellular carcinoma via the NKp30 receptor. Hepatology 2009;50:799-807.

Huang et al 2007
Huang X, Biswas S, Oki Y, Issa JP, Berry DA. A parallel phase I/II clinical trial design for combination therapies. Biometrics. 2007 Jun;63(2):429-36.

Hussain et al 1999
Hussain M, Gadgeel S, Kucuk O, Du W, Salwen W, Ensley J. Paclitaxel, cisplatin, and 5-fluorouracil for patients with advanced or recurrent squamous cell carcinoma of the head and neck. Cancer 1999;86:2364-9.

Iop et al 1998
Iop A, Cartei G, Isaia A. Vinorelbine, bleomycin and methotrexate as a salvage therapy for patients with head and neck squamous carcinoma in relapse after cisplatin/fluorouracil. Ann Oncol 1998;9:225-7.

Isis Pharmaceuticals, Inc. 2014
Abbreviated Clinical Study Report, Isis Study Number 481464-CS1. A Phase 1/2 Study of AZD9150 (ISIS 481464), an Antisense Oligonucleotide Inhibitor of STAT3, Administered to Patients with Advanced Cancer. October 20, 2014. (On file)

Isis Pharmaceuticals, Inc.
Investigator's Brochure for AZD9150 (ISIS 481464) STAT3 Antisense Oligonucleotide.

Jemal et al 2010
Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277-300.

Jennison and Turnbull 2000
Jennison C, Turnbull BW. Group sequential methods: applications to clinical trials. Boca Raton (FL): Chapman and Hall/CRC; 2000.

Kortylewski et al 2009
Kortylewski M, Xin H, Kujawski M, Lee H, Liu Y, Harris T, et al. Regulation of the IL 23 and IL-12 balance by Stat3 signaling in the tumor microenvironment. Cancer Cell 2009;15:114-23.

Larkin et al 2015
Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 2015;373:23-34.

León et al 2005
León X, Hitt R, Constenla M, Rocca A, Stupp R, Kovács AF, et al. A retrospective analysis of the outcome of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck refractory to a platinum-based chemotherapy. Clin Oncol (R Coll Radiol) 2005;17:418-24.

Luke et al 2015
Luke JJ, Ott PA. PD-1 pathway inhibitors: the next generation of immunotherapy for melanoma. Oncotarget vol6, no.6 pg 3479-3492

Martinez-Trufero et al 2010
Martinez-Trufero J, Isla D, Adansa JC, Irigoyen A, Hitt R, Gil-Arnaiz I, et al. Phase II study of capecitabine as palliative treatment for patients with recurrent and metastatic squamous head and neck cancer after previous platinum-based treatment. Br J Cancer 2010;102:1687-91.

MedImmune, LLC
Investigator's Brochure for MEDI4736.

MedImmune, LLC
Investigator's Brochure for Tremelimumab.

Mellman et al 2011
Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature 2011;480:480-9.

Molin and Fayette 2011
Molin Y, Fayette J. Current chemotherapies for recurrent/metastatic head and neck cancer. Anticancer Drugs 2011;22:621-5.

Moroni et al 2003
Moroni M, Giannetta L, Gelosa G, Secondino S, Chillura G, Colombo E, et al. Second-line chemotherapy with bleomycin, methotrexate, and vinorelbine (BMV) for patients with squamous cell carcinoma of the head, neck and esophagus (SCC-HN&E) pretreated with a cisplatin-containing regimen: a phase II study. J Chemother 2003;15:394-9.

Numico and Merlano 2002
Numico G, Merlano M. Second-line treatment with docetaxel after failure of a platinum-based chemotherapy in squamous-cell head and neck cancer. Ann Oncol 2002;13:331 3.

Pai and Paloucek 2000
Pai MP, Paloucek FP. The origin of the "ideal" body weight equations. Ann Pharmacother 2000;34:1066-9.

Pak et al 1995
Pak AS, Wright MA, Matthews JP, Collins SL, Petruzzelli GJ, Young MR. Mechanisms of immune suppression in patients with head and neck cancer: presence of CD34(+) cells which suppress immune functions within cancers that secrete granulocyte-macrophage colony-stimulating factor. Clin Cancer Res 1995;1:95-103.

Péron et al 2012a
Péron J, Ceruse P, Lavergne E, Buiret G, Pham BN, Chabaud S, et al. Paclitaxel and cetuximab combination efficiency after the failure of a platinum-based chemotherapy in recurrent/metastatic head and neck squamous cell carcinoma. Anticancer Drugs 2012;23:996-1001.

Péron et al 2012b
Péron J, Poupart M, Ceruse P, Ramade A, Girodet D, Zrounba P, et al. Efficacy and safety of capecitabine in heavily pretreated recurrent/metastatic head and neck squamous cell carcinoma. Anticancer Drugs 2012;23:1107-11.

Sampson et al 2006
Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391-7.

Segal et al 2016
Segal NH, Ou SI, Balmanoukian AS, Massarelli E et al. updated safety and efficacy of Durvalumab (MEDI4736), an anti-PDL1 antibody, in patients from Squamous cell carcinoma of head and neck.

Seiwert et al 2015
Seiwert TY, Haddad RI, Gupta S, Mehra R, Tahara M, Berger R, et al. Antitumor activity and safety of pembrolizumab in patients (pts) with advanced squamous cell carcinoma of the head and neck (SCCHN): Preliminary results from KEYNOTE-012 expansion cohort. J Clin Oncol 2015;33(18 suppl): abstract LBA6008.

Seth et al 2009
Seth PP, Siwkowski A, Allerson CR, Vasquez G, Lee S, Prakash TP, et al. Short antisense oligonucleotides with novel 2′ -4′ conformationaly restricted nucleoside analogues show improved potency without increased toxicity in animals. J Med Chem 2009;52:10-3.

Swanson et al 2015
Swanson MS, Sinha UK. Rationale for combined blockade of PD-1 and CTLA-4 in advanced head and neck Squamous cell cancer-review of current data. J. oral oncology 2015; 51;12-15

Vasquez-Dunddel et al 2013
Vasquez-Dunddel D, Pan F, Zeng Q, Gorbounov M, Albesiano E, Fu J, et al. STAT3 regulates arginase-I in myeloid-derived suppressor cells from cancer patients. J Clin Invest 2013;123:1580-9.

Vermorken et al 2008
Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116-27.

Weber et al 2012
Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol 2012;30:2691-7.

Wolchok et al 2009
Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15:7412-20.

Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life-threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation

Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

When making an assessment of causality, consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

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

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

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

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgement. With limited or insufficient information in the case, it is probably that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix B Further Guidance On The Definition Of A Serious Adverse Event (SAE)

Life-threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation

Development of drug dependency or drug abuse

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

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

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

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

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgement. With limited or insufficient information in the case, it is probable that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

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

Labelling and shipment of biohazard samples

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

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

Appendix D Ethical and Regulatory Requirements

1. ETHICAL AND REGULATORY REQUIREMENTS

1.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the ICH/ GCP guidelines, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

1.2 Ethics and regulatory review

An Ethics Committee should approve the final CSP, including the final version of the ICF and any other written information and/or materials to be provided to the patients. This will include approval of the exploratory biomarker and pharmacogenetic research and associated consent(s) forms. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study. If applicable this approval should clearly state that the exploratory biomarker and pharmacogenetic research is approved.

The Ethics Committee should approve all advertising used to recruit patients for the study.

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

If required by local regulations, the CSP should be re-approved by the Ethics Committee annually.

Before enrolment of any patient into the study, the final CSP, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

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

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

Each Principal Investigator is responsible for providing the Ethics Committees/Institutional Review Board (IRB) with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

1.3 Informed consent

Any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation should be described in the ICF that is approved by an Ethics Committee.

The Principal Investigator at each centre will:

- Ensure that each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study and the optional exploratory biomarker and genetic research component(s)
- Ensure that each patient is notified that they are free to withdraw from the study or the research components at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure each original, signed ICF is stored in the Investigator's Study File
- Ensure a copy of each signed ICF is given to the patient

The exploratory biomarker and genetic research component(s) of this study are voluntary and the patient may participate in the main study without participating in the exploratory biomarker and/or genetic research part(s) of the study. To participate in the exploratory biomarker and/or genetic component of the study the patient should sign and date the consent form for the main study and as applicable separate consent forms for the exploratory biomarker and/or the genetic components of the study.

1.4 Changes to the Clinical Study Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca.

If there are any substantial changes to the CSP, then these changes will be documented in a CSP Amendment and where required in a new version of the CSP (Revised Protocol).

The amendment should be approved by each Ethics Committee and if applicable, also the national regulatory authority, before implementation. Local requirements should be followed for Revised Protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator. For distribution to Ethics Committee see Section 1.2.

If a protocol amendment requires a change to a centre's ICF, AstraZeneca and the centre's Ethics Committee should approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

1.5 Audits and inspections

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

Appendix E Data and Study Management

1. DATA AND STUDY MANAGEMENT

1.1 Patient data protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

Due to the exploratory nature of the biomarker and genetic research, there will be no routine communication of these results to patients. AstraZeneca will not provide individual results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

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

1.2 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the Investigator(s) (and other personnel involved with the study) their responsibilities with regard to CSP adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the Investigator

1.3 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will visit the study site to review and discuss the requirements of the CSP and related documents with the investigational staff and also to train them in any study-specific procedures including collection of samples and the WBDC system utilised. The additional requirements for the collection of the patients' samples for the exploratory biomarker and genetic research will also be clarified.

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

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

1.4 Source data

Refer to the Clinical Study Agreement for location of source data.

1.5 Monitoring of the study

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

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the CSP including the specific requirements of the biomarker and genetic research, that data are being accurately and timely recorded in the CRFs, and that IP accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of the ICF(s)of participating patients. This will require direct access to all original records for each patient (e.g., clinic charts)
- If applicable, ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient

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

1.6 Data management

Data management will be performed [redacted] on behalf of AstraZeneca.

Data entered in the WBDC system or data captured electronically will be immediately saved to the applicable database and changes tracked to provide an audit trail.

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

AEs and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be

classified according to the AstraZeneca Drug Dictionary. All coding will be performed [redacted] on behalf of AstraZeneca.

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

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

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

Genotype data generated in this study will be stored in the AstraZeneca genotyping Laboratory Information Management System (LIMS) database, or other appropriate secure system, separate from the database used for the main study.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database. The results from this genetic research will be reported separately from the Clinical Study Report for the main study.

1.7 Study agreements

The Principal Investigator at each centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this CSP and the Clinical Study Agreement, the CSP shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, the terms of the Clinical study Agreement shall prevail.

Specific reference to requirements relating to this optional biomarker and genetic research will be included in the study agreement(s).

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

1.7.1 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement.

1.8 End of study

The end of the study is defined as the last visit of the last patient undergoing the study.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD9150.

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

1. INTRODUCTION

This appendix details the implementation of RECIST 1.1 Guidelines (Eisenhauer et al 2009) for the study with regards to Investigator assessment of tumor burden including CSP-specific requirements for this study.

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

Only patients with measurable disease at baseline should be included in the study. Measurable disease is defined by the presence of at least one measurable lesion which has not been previously irradiated.

Measurable:

A lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with CT or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15mm short axis at baseline).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Previously irradiated lesions
- Skin lesions assessed by clinical examination
- Brain metastasis

Special Cases:

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

Target lesions:

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

Non-Target lesions:

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

3. METHODS OF ASSESSMENT

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

A summary of the methods to be used for RECIST assessment is provided below and those excluded from tumor assessments for this study are highlighted, with the rationale provided.

Table 1: Summary of Methods of Assessment

Target Lesions	Non-Target Lesions	New Lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Clinical examination	Clinical examination
	Plain X-ray (includes Chest X-ray)	Plain X-ray (includes Chest X-ray)
		Ultrasound
		Bone Scan
		FDG-PET

3.1 CT and MRI

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

In this study it is recommended that CT examinations will be used to assess tumor burden at baseline and follow-up visits. CT examination with intravenous (i.v.) contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contraindicated. For brain lesion assessment, MRI is the preferred method.

3.2 Clinical examination

In this study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as target lesions if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTLs in patients who also have other lesions assessable by CT, MRI or plain X-ray and to identify the presence of new lesions.

3.3 X-ray

3.3.1 Chest X-ray

Chest X-ray assessment will not be used for assessment of TL as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

3.3.2 Plain X-ray

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

3.4 Ultrasound

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

3.5 Endoscopy and laparoscopy

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

3.6 Tumor markers

Tumor markers will not be used for tumor response assessments as per RECIST 1.1.

In this study CA-125 will be collected for patients with ovarian cancer for separate analysis However, the results will not contribute to tumor response based on RECIST 1.1 assessment.

3.7 Cytology and histology

Histology will not be used as part of the tumor response assessment as per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumor has met criteria for response or SD.

In such circumstances, the cytology is necessary to differentiate between response/SD (an effusion may be a side effect of the treatment) and PD (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or appearance of clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTL, or disease progression due to new lesions.

3.8 Isotopic bone scan

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

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

3.9 FDG-PET scan

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

4. TUMOR RESPONSE EVALUATION

4.1 Schedule of evaluation

Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 30 days before the start of study treatment. Follow-up assessments will be performed every 6 weeks (± 1 week) until objective disease progression as defined by RECIST 1.1 or withdrawal of consent. In addition to the above, for Japanese sites only, an additional assessment is performed at Day 1 of Cycle 2 (± 3 days). Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

4.2 Target lesions (TL)

4.2.1 Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.

- If the CT/MRI slice thickness used is > 5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into 2 or more parts, then record the sum of the diameters of those parts.
- If 2 or more TL merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention, e.g., radiotherapy, embolisation, surgery etc., during the study, the size of the TL should still be provided where possible.

4.2.2 Evaluation of target lesions

This Section provides the definitions of the criteria used to determine objective tumor visit response for TL.

Table 2: Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm.
Not Evaluable (NE)	Only relevant if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the PD criteria, PD overrides not evaluable as a target lesion response

4.3 Non-Target lesions (NTL)

4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This Section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

Table 3: Evaluation of Non-Target Lesions

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

To achieve 'unequivocal progression' on the basis of non-target lesions, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

4.4 New Lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor.

If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

4.5 Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

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

4.6 Evaluation of Overall Visit Response

The overall visit response will be derived using the algorithm shown in Table 4.

Table 4: Overall Visit Response

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

CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease, NE=not evaluable, NA=not applicable (relevant when no TL/NTLs at baseline).

5. SPECIFICATIONS FOR RADIOLOGICAL IMAGING

These notes are recommendations for use in clinical studies. The use of standardized protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

5.1 CT Scan

CT scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomic region of interest.

The most critical CT image acquisition parameters for optimal tumor evaluation using RECIST 1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

a. Anatomic coverage: Optimal anatomic coverage for most solid tumors is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumor measurements but also identification of new disease.

b. IV contrast administration: Optimal visualisation and measurement of metastases in solid tumors requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow- up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumor type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study then the recommended methods are: CT thoracic examination without contrast and abdominal and pelvis MRI with contrast. If MRI cannot be performed then CT without i.v. contrast is an option for the thorax, abdomen and pelvis examination. For brain lesions assessment, MRI is the preferred method.

c. Slice thickness and reconstruction interval: It is recommended that CT scans be performed at 5mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not "selected" images of the apparent lesion.

5.2 MRI Scan

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium-enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the specific body part being imaged as well as the scanner utilised. It is beyond the scope appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the imaging modality of choice.

5.3 FDG-PET scans

FDG-PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. If FDG-PET scans are included in a protocol, an FDG uptake period of 60 minutes prior to imaging has been decided as the most appropriate for imaging of patients with malignancy. Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 minutes post-injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical trial.

5.3.1 PET/CT scans

At present, low dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for tumor measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. However, this is not recommended because the PET portion of the CT introduces additional data that may bias an Investigator if it is not routinely or serially performed.

6. REFERENCES

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer 45 (2009) 228-247

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

1. INTRODUCTION

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on the managing liver abnormalities can be found in Section 6.9.1 of the CSP.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory and/or elevated TBL from a local laboratory.

The Investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates with AstraZeneca clinical project representatives in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the IP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

Potential Hy's Law (PHL)

AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law (HL)

AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, where no other reason, other than the IP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

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

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

Central laboratories being used:

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

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

- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

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

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

Local laboratories being used:

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

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

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

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

- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (see Section 6 of this Appendix)
- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of PHL; serious criteria 'important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting
- For subjects that met PHL criteria prior to starting IP, the Investigator is not required to submit a PHL SAE unless there is a significant change[#] in the patient'condition
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data.
    - Subsequent to this contact the Investigator will:
        - Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Complete the follow-up SAE Form as required
        - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the HL lab kit should be used
        - Complete the 3 Liver CRF Modules as information becomes available

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

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

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review with other subject matter experts as appropriate.

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

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE: update the previously submitted PHL AE/SAE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZenca standard processes

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

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'medically important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to IP and seriousness criteria is medically important, according to CSP process for SAE reporting

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined

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

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

At the first on-study treatment occurrence of PHL criteria being met the Investigator will determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met[#]

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

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

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

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

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

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

Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study, e.g., chronic or progressing malignant disease, severe infection or liver disease, or did the patient meet PHL criteria prior to starting study

treatment and at their first on study treatment visit (as described in Section 6 of this Appendix)?

If No: Follow the process described in Section 4.2 of this Appendix for reporting PHL as an SAE.

If Yes: Determine if there has been a significant change in the subject's condition[#] compared with when PHL criteria were previously met.

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section 4.2 of this Appendix for reporting PHL as an SAE

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

8. LABORATORY TESTS

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory. For studies using a local laboratory, the list may be modified based on clinical judgement. If required, additional assistance on which tests could be used to evaluate other potential causes of liver dysfunction consult with the Hepatic Safety Knowledge Group. Any test results need to be recorded**.**

Law lab kit for central laboratories (18 December 2018)

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA IgG anti-HCV HCV RNA* IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	CD-transferrin**

Autoimmune hepatitis	ANA Anti-LKM Ab ASMA
Metabolic diseases	Alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

* HCV RNA is only tested when IgG anti-HCV is positive or inconclusive
** CD-transferrin is not available in China. Study teams should amend this list accordingly
Abbreviations: Ab=antibody; ANA=antinuclear antibody; ASMA=anti-smooth muscle Ab; CD=carbohydrate deficient; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; EBV=Epstein-Barr virus; GGT=gamma-glutamyl transferase; HAV=Hepatitis A virus; HBc=Hepatitis B core; HBsAg=Hepatitis B surface antigen; HBV=Hepatitis B virus; HCV=Hepatitis C virus; HEV= Hepatitis E virus; HSV=Herpse simplex virus; IgG=Immunoglobulin G; IgM=Immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; LKM=liver/kidney microsomal; RNA=ribonucleic acid.

REFERENCES

Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther 2011;89(6):806-15.

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

Revision History

Version	Description of Change
1.0	The previous version of the Hy's Law Appendix E was not numbered. Version numbering introduced with version 2.0 of the SOP Detection and Handling of Potential Hy's Law Cases And Hy's Law Cases In Clinical Studies AZDoc0007120 Document revised with updated SOP.
2.0	Section 8 Laboratory Tests revised to clarify tests are recommended. Table of tests updated to include footnotes.

Appendix H MEDI4736 Adverse Events of Special Interest

1. MEDI4736 ADVERSE EVENTS OF SPECIAL INTEREST

1.1 Immune-related adverse events (general)

An immune-related AE (irAE) is defined as a clinically significant AE of unknown etiology of any organ that is associated with drug exposure and is consistent with an immune-mediated mechanism. Serologic, immunologic, and histologic (biopsy) data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

If the Investigator has any questions in regards to an AE being an irAE, the Investigator should immediately contact the Study Physician.

1.2 Pneumonitis

If new or worsening pulmonary symptoms (e.g., dyspnoea or cough) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further diagnostic work-up should be performed to exclude pneumonitis. The differential diagnosis should include the possibility of both immune-related and non-immune related processes. AEs of pneumonitis are of interest for AstraZeneca as pneumonitis has been observed with use of anti-PD-1 monoclonal antibodies (mAbs), (although not with anti-PD-L1 mAbs), and instances of pneumonitis have been reported in patients undergoing olaparib treatment.

Initial work-up should consider the inclusion of a clinical evaluation, high-resolution CT scan, ruling out infection, pulse oximetry, and other appropriate laboratory work-up. Pulmonary consultation is highly recommended. Guidelines for the management of patients with irAEs including pneumonitis are provided in MEDI4736 Annex 1.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the Investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Study Physician.

1.3 Infusion reactions

AEs of infusion reactions (also termed infusion-related reactions) are of special interest to AstraZeneca and are defined, for the purpose of this CSP, as all AEs occurring from the start of study drug infusion up to 48 hours after the infusion start time. For all infusion reactions, the eCRF should be completed as instructed in Section 7.1.4, and all SAEs should be reported to AstraZeneca Patient safety as described in Section 7.1.5.

1.4 Hypersensitivity reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy. As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of mAbs can be caused by various mechanisms, including acute anaphylactic (immunoglobulin E-mediated) and anaphylactoid reactions against the mAbs and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnoea, cyanosis, respiratory failure, urticaria, pruritis, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting, and unresponsiveness. Guidelines for the management of patients with hypersensitivity (including anaphylactic reaction) and infusion-related reactions are provided in MEDI4736 Annex 1.

1.5 Hepatic function abnormalities (hepatotoxicity)

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in TBL to be greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the study medication. Guidelines for management of patients with hepatic function abnormality are provided in MEDI4736 Annex 1.

1.6 Endocrine disorders

Immune-mediated endocrinopathies include hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism. Guidelines for the management of patients with immune-mediated endocrine events are provided in MEDI4736 Annex 1.

1.7 Neurotoxicity

Immune-mediated nervous system events include encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in MEDI4736 Appendix J.

Annex 1 Toxicity Management Guidelines for Durvalumab (MEDI4736)

The most current version of these guidelines is maintained within the Site Master File. In addition, a version of the current Dosing Modifications and Toxicity Management Guidelines is available through the following link: https://tmg.azirae.com. Please contact the clinical research associate for information on how to gain access to this website.