AstraZeneca

Clinical Study Protocol

Drug Substance	MEDI4736 and tremelimumab
Study Code	D4193C00003
Version Number	05
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A Phase II, Randomized, Open-Label, Multi-Center, Global Study of MEDI4736 Monotherapy, Tremelimumab Monotherapy, and MEDI4736 in Combination with Tremelimumab in Patients with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

EudraCT Number: 2014-003717-29

VERSION HISTORY

Version 5.0, 20 September 2017 (Revised Edition 4.0 but 5th version of the protocol)
Changes made to the protocol are summarized below:

The protocol was revised to reflect the addition of an overall survival (OS) extension period to the study design, in order to collect longer-term OS data.

Synopsis (Study site[s] and number of patients planned): The estimated date of last patient completed was updated to Q3 2018.

Synopsis (Study design): A new sub-section was added (Overall survival extension period) to define and describe the OS Extension period study procedures. A new sub-section (End of analysis portion of the study) was added describing study procedures once all planned analyses have been performed, including patient retreatment if applicable, and the procedures to be taken in the event that a future roll over or safety extension study becomes available.

Synopsis (Statistical methods): Text was added to detail the objective of the OS Extension period and to detail that the final analysis of OS will be conducted after the OS Extension period.

Section 1.2.6 (Rationale for the overall survival extension period): A new section was added to describe the rationale for the extension of OS data collection.

Section 1.4. (Study design): A new sub-section (Overall survival extension) was added to define and describe the OS Extension period study procedures. A new sub-section (End of analysis portion of the study) was also added to detail that once the planned statistical analyses have been performed, the analysis portion of the clinical study will have been completed. Assessments, retreatment procedures, safety reporting, and general procedures in the event of a future roll over or safety extension study are described. Figure 2 (Study flow chart) was also updated to include the OS Extension period.

Section 3.1 (Inclusion criteria): A statement was added to detail that patients who are progression-free following randomized treatment and potentially eligible for retreatment after the OS Extension DCO will be eligible for retreatment with their previously assigned treatment if they meet the eligibility criteria.

Section 3.3 (Patient enrollment): A statement was added to detail that the Interactive Voice Response-Interactive Web Response System may be closed after the 12-month analysis. In this case a manual process will be followed.

Section 4 (Study plan and timing of procedures): Two new tables were added. Table 8 shows the schedule of assessments for patients continuing on or entering into retreatment during the OS Extension period, and Table 9 shows the schedule of assessments for all patients in

follow-up during the OS Extension period.

Section 4.1 (Enrollment/screening period): Text was added to detail that patients who are progression-free following randomized treatment and potentially eligible for retreatment are to undergo sampling for local laboratory assessments (Table 9), and in such a way that continued per-protocol retreatment eligibility can be properly determined.

Section 4.4 (Overall survival extension period): A new section was added describing the schedules of assessments for the OS Extension period in Table 8 and Table 9.

Section 5 (Study Assessments): Text was added detailing that starting during the OS Extension period, all patients will be followed for survival. Overall survival, safety-related data and IP administration details will be collected in the clinical database.

Section 5.1 (Efficacy assessments): Text was added to detail that during and after the OS Extension period, all patients should receive scans/RECIST assessments as per the local standard of care.

Section 5.2.1 (Laboratory safety assessments): Text was added to describe laboratory assessments during and after the OS Extension period.

Section 5.2.3 (Electrocardiograms): Text was added to detail that starting during the OS Extension period, electrocardiograms will be collected locally and as clinically indicated.

Section 5.3 (Other assessments): Text was added to detail that 'Other' assessments will not be performed during the OS Extension period.

Section 5.4.1 (Collection of samples and determination of drug concentration): Text was added to detail that pharmacokinetic assessments will not be conducted during or after the OS Extension period.

Section 5.4.2 (Collection of samples to measure for the presence of ADAs): Text was added to detail that ADA assessments will not be conducted during or after the OS Extension period.

Section 5.5 (Pharmacogenetics): Text was added to detail that pharmacogenetic assessments will not be conducted during or after the OS Extension period.

Section 5.6 (Biomarker analysis): Text was added to detail that biomarker assessments will not be conducted during or after the OS Extension period.

Section 6 (Safety reporting and medical management): Text was added to detail that protocol defined safety guidelines around SAE reporting will remain in effect after the OS Extension period.

Section 6.3.1 (Time period for collection of adverse events): Text was added to describe AE reporting during and after the OS Extension period.

Section 6.7.1 (Adverse events of special interest): The tremelimumab Investigator Brochure was added as a source of further information.

Section 6.7.2 (Immune-related adverse events): Table 13 (Dosing modification and toxicity management guidelines for immune mediated, infusion-related, and nonimmune mediated reactions [MEDI4736 monotherapy or combination therapy with tremelimumab or tremelimumab monotherapy]) was updated to the 19 August 2016 version.

Section 7.8 (Post study access to study treatment): Text was added detailing the procedures in the event that a roll-over or safety extension study becomes available, and the procedures for retreating and monitoring patients following the OS Extension DCO.

Section 8.4.1.3 (Secondary endpoints): Text was added to the sub-section Overall survival, to detail that no OS data will be recorded in the study database after the OS Extension DCO, but such information may continue to be collected for operational purposes.

Section 8.5 (Methods for Statistical Analysis): Text was revised to detail the timings of the DCO for primary analysis and the final analysis of OS.

Section 9.3 (Study timetable and end of study): The text was revised to describe the revised estimated end of-study date, the procedures if a roll-over or extension study becomes available, the circumstances under which the study would be terminated, and procedures after the OS Extension period.

Section 10.4 (Informed consent): A new bullet point was added detailing that patients who are eligible for retreatment must sign the retreatment informed consent form prior to restarting their originally-assigned study treatment.

Minor editorial corrections were also made throughout the protocol, additions were made to the list of abbreviations, and the version details were updated.

Version 4.0, 09 March 2016 (Revised Edition 3.0 but 4th version of the protocol)
Changes made to the protocol are summarized below:

Synopsis: The words ‘approximately’ and ‘at least’ were added to the sentences describing the number of patients who will be enrolled and randomized and the number of evaluable patients, respectively. Text describing the study design and the target patient population was updated to include patients who have received only 1 systemic palliative regimen for recurrent or metastatic disease that must have contained a platinum agent. Text was also added to indicate that patients will have scans submitted for Blinded Independent Central Review (BICR) instead of Independent Central Review (ICR), and details pertaining to the required MEDI4736 discontinuation in the event of confirmed progressive disease (PD) in target lesions that showed

a previous response to MEDI4736 were added. The method of analysis for study endpoints was changed from immune-related response criteria (irRC) to immune-related Response Evaluation Criteria in Solid Tumors version 1.1 (irRECIST 1.1). Text was added to clarify the timing and method of confirmation of PD for patients with clinical evidence of progression who do not meet PD criteria by RECIST 1.1. The name of the Ventana assay was updated to 'Ventana SP263'. Additionally, overall survival (OS) was added as a secondary objective related to the assessment of efficacy for MEDI4736 + tremelimumab combination therapy, time to recurrence (TTR) was added as a secondary objective, and the health-related quality-of-life (QoL) secondary objectives were updated (including proposed statistical analyses). Details were provided in the statistics section related to assessment of efficacy in terms of progression free survival (PFS) and OS and to clarify that no formal statistical comparison is planned for the primary objective. Details were added to the statistics section to indicate that duration of response (DoR) and disease control rate (DCR) will be assessed using Investigator tumor data according to RECIST 1.1. Details were also added to the secondary objective outcome measures section and to indicate that sensitivity analyses of the objective response rate (ORR) and PFS will use site Investigator data. Additional information related to data cut-off, formal analysis of PFS and OS, and patient-reported outcomes (PRO) was included.

Section 1.2 (Rationale for study design, doses, and control groups): Text was updated to clarify that patients who have received only 1 systemic **palliative** regimen for recurrent or metastatic disease that must have contained a platinum agent will be evaluated.

Section 1.2.4 (Study population rationale): Text was updated to clarify that eligible patients must have progressed during or after treatment with only 1 systemic **palliative** regimen for recurrent or metastatic disease that must have contained a platinum agent.

Section 1.2.5 (Rationale for endpoints): Throughout this section, references to ICR and irRC were replaced with BICR and irRECIST 1.1, respectively.

Section 1.3.2.1 (Potential risks, MEDI4736): Text describing specific immune-mediated reactions that are considered health risks based on the mechanism of action for MEDI4736 was removed to reflect the latest safety information for MEDI4736 and replaced with a reference to Section 6.7.1.

Section 1.3.3 (Overall benefit/risk and ethical assessment): Text was updated to clarify that eligible patients must have progressed during or after treatment with only 1 systemic **palliative** regimen for recurrent or metastatic disease that must have contained a platinum agent.

Section 1.4 (Study design): The words 'approximately' and 'at least' were added to the sentences describing the number of patients who will be enrolled and randomized and the number of evaluable patients, respectively. Text in this section and Figure 1 were updated to clarify that this study will include patients with recurrent or metastatic programmed cell death ligand 1 (PD-L1)-negative squamous cell carcinoma of the head and neck who have progressed during or after treatment with **only** 1 systemic **palliative** regimen that contained a platinum agent. Figure 1 was updated to indicate that **at least** 208 patients will be evaluable for the primary endpoint. Language in footnote d in Figure 2 was added to clarify that patients who show confirmed PD following a previous response **in target lesions** to MEDI4736 should be discontinued. Text was added to footnote b of Figure 2 to clarify the timing of confirmation of PD for patients with clinical evidence of progression who do not meet PD criteria by RECIST 1.1. The name of the Ventana assay was updated to 'Ventana SP263'. Additionally, instances of ICR and irRC were updated to BICR and irRECIST 1.1, respectively. Text was added to indicate that DoR and DCR will be assessed by sensitivity analyses using Investigator tumor data in addition to BICR tumor data. Text referring to an additional 12-month period of retreatment was removed for clarity. Additionally, text from the charter was added to confirm the timing of Independent Data Monitoring Committee (IDMC) meetings.

Section 2.1 (Primary objective): Instances of ICR were updated to BICR.

Section 2.2 (Secondary objectives): Instances of ICR and irRC were updated to BICR and irRECIST 1.1, respectively. DoR, DCR, and BoR were removed as outcome measures for the secondary objective to further assess efficacy of MEDI4736 + tremelimumab, and OS was added as a secondary objective to assess the efficacy of MEDI4736 + tremelimumab compared to MEDI4736 or tremelimumab monotherapy. Selected domains the European Organisation for Research and Treatment of Cancer (EORTC) 30-item core quality of life questionnaire (QLQ-C30) and the 35-item head and neck quality of life questionnaire (QLQ-H&N35) were prioritized as secondary objectives. Details pertaining to sensitivity analyses were updated.

Section 3.1 (Inclusion criteria): Text in Inclusion criterion no. 4 was updated to include patients with tumor progression or recurrence during or after treatment with only 1 systemic **palliative** regimen for recurrent or metastatic disease that must have contained a platinum agent. Language was also rephrased to state that patients who have only received chemo-radiation **with curative intent for** of their treatment of **locally advanced disease or** recurrent disease are **not** eligible. Text from the same criterion that excluded patients who had only received chemo-radiation therapy with curative intent for locally advanced disease was removed. The name of the Ventana assay mentioned in inclusion criterion no. 6 was updated to 'Ventana SP263'.

Section 3.2 (Exclusion criteria): Exclusion criterion no. 2 was updated to clarify that patients who received more than 1 systemic **palliative** regimen for recurrent or metastatic disease cannot participate in the study. Text in Exclusion criterion no. 4 was revised to the following text: prior randomization or treatment in a previous MEDI4736 and/or tremelimumab clinical study regardless of treatment arm assignment or receipt of any investigational anticancer therapy within 28 days or 5 half-lives, whichever is longer, prior to the first dose of study treatment. This was added to avoid confounding other MEDI4736 or tremelimumab outcome studies in which a patient may be participating. Text in Exclusion criterion no. 10 was revised to 'other chronic skin conditions' instead of psoriasis.

Section 3.3 (Patient enrollment): Text was added to clarify that patients do not need to re-consent for PD-L1 testing using the Ventana SP263 assay if it was performed for a previous AstraZeneca/MedImmune study. Re-consent is not required because it was already provided previously under a different study.

Section 3.10.2 (Withdrawal of the informed consent): Text was added to clarify which study assessments and visits that patients who withdraw consent from study treatment administration will continue after consent is withdrawn. This language was added to clarify that patients can withdraw consent for the entire study, including further contact, withdraw consent for study treatment administration only, or withdraw consent for study treatment administration and further assessments except for consent for survival follow-up contact.

Section 4 (Study plan and timing of procedures): Tables 5, 6, and 7 were modified to include reflex free triiodothyronine or free thyroxine assessments only if the thyroid-stimulating hormone (TSH) assessment is abnormal. The associated footnote c in Table 5 was also revised for consistency, and the reference to the requirement of TSH results prior to infusion was removed as it is not required prior to infusion. Additional text pertaining to discontinuation of MEDI4736 following confirmed PD was added to footnote g in Table 5 for consistency with the rest of the document. Abbreviations for Tables 5, 6, and 7 were updated for consistency with the table footnotes. Reference to restarting 'treatment with the combination' in footnote f in Table 5 was rephrased to restarting 'treatment with the IP' for clarity.

Section 4.1 (Enrollment/screening period): Language about screening procedures was revised for clarity. A statement that patients do not need to re-consent to PD-L1 testing if the status was determined during the screening process for another AstraZeneca/MedImmune study was included. In the same paragraph, the name of the Ventana assay was updated to 'Ventana SP263'.

Section 5.1 (Efficacy assessments): In the sentence stating that efficacy will be measured in patients until confirmed objective disease progression**,** irrespective of reason for stopping treatment, the reference to subsequent therapy was removed. Additionally, text describing discontinuation of treatment due to progression was updated to include **radiographic documentation** as the method of confirmed objective disease progression. The method of confirmation of objective disease progression for patients who discontinue IP was updated. Language was also added to describe confirmation of PD for patients who do not meet PD criteria by Response Evaluation Criteria in Solid Tumors version 1.1. Language describing receipt of a subsequent cancer therapy was removed from a paragraph describing patient discontinuation.

Section 5.1.1 (Central reading of scans): Instances of ICR and irRC were updated to BICR and irRECIST 1.1, respectively.

Section 5.2.3 (Electrocardiograms): The timing of electrocardiograms was clarified.

Section 5.2.4 (Vital signs): Language was added to clarify that blood pressure and pulse should be collected no more than 30 minutes prior to MEDI4736 infusion. This window was added to accommodate collection of vital signs prior to infusion of study treatment. The requirement for a 1-hour post-infusion observation period at 30 (±5) and 60 (±5) minutes after the infusion ends was also added.

Section 5.3.1 (Patient-reported outcomes): Text indicating that a subject's PD-L1 status must be known before patient-reported outcomes questionnaires are administered during the screening window was removed. This change was made because timing of the patient-reported outcomes questionnaires administered during the screening window is no longer relevant.

Section 5.3.2 (Administration of the patient-reported outcome questionnaires): The timing of the PRO questionnaires during the screening window was updated such that the questionnaires no longer need to be administered after the patient's PD-L1 status is known.

Section 5.3.1.2 (EORTC QLQ-H&N35): QLQ was added to the section title and text within the section for consistency with the rest of the document.

Section 5.5 (Pharmacogenetics): The pharmacogenetics section was moved from Section 5.6 (and is now between the Pharmacokinetics and Biomarker analysis sections) to align with the

most recent version of the clinical study protocol template.

Section 5.6.1 (Collection of patient samples for PD-L1 status identification): Text indicating that a RECIST 1.1 target lesion for biopsy must be ≥2 cm in the longest diameter was removed, as it is not relevant. Additionally, the name of the Ventana assay was updated to 'Ventana SP263'.

Section 6.3.7 (Adverse events based on examinations and tests): Text referring to 'laboratory values' was changed to 'test values'.

Section 6.5 (Overdose): A reference to Section 7.1 was added to this section to provide additional guidance for determination of excess MEDI4736 doses.

Section 6.7 (Management of IP-related toxicities): Text related to the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for MEDI4736, discontinuation of study treatment, and dose modifications or reductions was added for clarification. Text was updated to include reference information for tremelimumab monotherapy and MEDI4736 + tremelimumab combination therapy.

Section 6.7.1 (MEDI4736 adverse events of special interest): Text pertaining to MEDI4736 and/or tremelimumab adverse events of special interest was updated to align with the most recent version of this information.

Section 6.7.2 (Immune-related adverse events): Specific terms of enterocolitis, dermatitis, hepatitis, and endocrinopathy were removed and replaced with 'the adverse event' in order to capture all possible immune-related events that may occur. The most recent version of the dosing modification and toxicity management guidelines for immune-mediated, infusion related, and nonimmune-mediated reactions was included.

Section 6.8 (Study governance and oversight): The timing of IDMC meetings was clarified.

Section 7.1 (Identity of investigational product): Language was updated from '...**must** be removed' to '...**should** be removed' in reference to the volume of saline to be added to the IV bag. This text was updated to clarify that saline does not need to be removed if the correct dose can be given during the appropriate time frame and if the IV bag can accommodate the extra volume.

Section 7.2 (Dose and treatment regimens): Text was added to clarify the timing and method of confirmation of PD for patients with clinical evidence of progression who do not meet PD criteria by RECIST 1.1.

Section 8.2 (Sample size estimate): The words 'approximately' and 'at least' were added to the sentences describing the number of patients who will be enrolled and randomized and the number of evaluable patients, respectively. Details pertaining to the primary objective and analysis that were included in the synopsis were reproduced in this section.

Section 8.3 (Definitions of analysis sets): Definitions of the analysis sets for the outcome variables and populations in Table 14 were updated.

Section 8.3.1 (Full Analysis Set): Text describing the Full Analysis Set (FAS) was updated.

Section 8.3.2 (Evaluable Analysis Set): The Evaluable Analysis Set was updated such that it is no longer a subset of the FAS, and the instance of ICR was updated to BICR.

Section 8.3.3 (Safety Analysis Set): The Safety Analysis Set was updated to include all patients who received at least 1 dose of study treatment, and other details were provided.

Section 8.4 (Outcome measures for analyses): Instances of ICR and irRC were updated to BICR and irRECIST 1.1, respectively, in the entire section.

Section 8.4.1.1 (RECIST 1.1-based endpoints): BICR Charter was updated to Imaging Charter as suggested by the Food and Drug Administration guidance. RECIST 1.1 modified for confirmation of progression and irRECIST 1.1 were also added as assessments for the BICR.

Section 8.4.1.2 (Primary endpoint [objective response rate]): Text was added to clarify that the ORR (per RECIST 1.1 as assessed by the BICR) will also be analyzed using the FAS population. Text related to methods of assessing ORR was updated.

Section 8.4.1.3 (Secondary endpoints): Text was added to clarify the analysis of DCR as a secondary endpoint. Text was added to indicate that DoR and DCR will be assessed using RECIST 1.1 data obtained from the site Investigator, and text describing DoR assessments using irRECIST 1.1 data obtained from BICR was removed. Details pertaining to sensitivity analyses were added for PFS.

Section 8.4.2.2 (Other significant adverse events): This section was deleted from the protocol because these events are essentially covered in the adverse event of special interest section (Section 6.7.1).

Section 8.5 (Methods for statistical analyses): In the entire section, all instances of ICR and irRC were updated to BICR and irRECIST 1.1, respectively. Text pertaining to the timing of the initial data cut-off and analysis of study endpoints was updated. The endpoint of time to treatment response was added to Table 17. Text pertaining to sensitivity analyses for all endpoints analyzed was updated in Table 17.

Section 8.5.1.1 (Primary objective [assess the efficacy of MEDI4736 + tremelimumab combination therapy, in terms of ORR]): Text was added that the ORR will also be analyzed using the FAS population. Text describing additional sensitivity analyses for ORR was removed.

Section 8.5.1.2 (Secondary objective [assess the efficacy of MEDI4736 + tremelimumab combination therapy compared with a) MEDI4736 monotherapy and b) tremelimumab, in terms of ORR and PFS]): Text was added to indicate that the sensitivity analyses will be performed for ORR using site Investigator tumor data according to RECIST 1.1. Details pertaining to analysis of OS were transferred from Section 8.5.2 (Analysis of the secondary variable[s]).

Section 8.5.2 (Analysis of the secondary variable[s]): Details pertaining to the QLQ-C30 and QLQ-H&N35 were updated. Text was added to indicate that DoR will use RECIST 1.1 data from the site Investigator. Text was added to indicate that DCR will be summarized using BICR data and site Investigator data.

Section 8.5.3 (Subgroup analysis [if applicable]): Subgroup analysis was limited to smoking status (>10 years versus ≤10 years) and Human papilloma virus status (positive versus negative).

Section 8.5.4 (Interim analysis): Text describing the MEDI4736 + tremelimumab combination therapy treatment group was removed in the sentence describing the interim safety assessment. The timing of IDMC meetings was updated to align with the IDMC charter and clarified for consistency throughout the document.

Section 12 (Appendices): The appendices were incorporated into the document, but no content changes were made to the appendices for this version of the protocol except for Appendix A (Signature page). Appendix A (Signature

page) was removed, and the remaining Appendices B through G were renamed Appendices A through F throughout.

Version 3.0, 06 August 2015 (Revised Edition 2.0 but 3rd version of the protocol) Changes made to the protocol are summarized below:
For a summary of changes, please refer to Study D4193C00003: Clinical Study Protocol Amendment 02, dated 06 August 2015 Administrative change, dated 06 March 2015 Administrative change, dated 09 July 2015

Version 2.0, 25 February 2015 (Revised Edition 1.0 but 2nd version of the protocol) Changes made to the protocol are summarized below:
For a summary of changes, please refer to Study D4193C00003: Clinical Study Protocol Amendment 01, dated 25 February 2015 Administrative change, dated 09 October 2014 Administrative change, dated 11 December 2014

Version 1.0, 14 August 2014
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.

PROTOCOL SYNOPSIS

A Phase II, Randomized, Open-Label, Multi-Center, Global Study of MEDI4736 Monotherapy, Tremelimumab Monotherapy, and MEDI4736 in Combination with Tremelimumab in Patients with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

International Coordinating Investigator

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Study site(s) and number of patients planned

The study will screen approximately 384 patients to identify approximately 240 patients with programmed cell death ligand 1 (PD-L1)-negative disease suitable for enrollment (ie, who fulfill the eligibility criteria) and randomization. Of these, at least 208 patients are likely to be evaluable for the primary endpoint. The patients will be randomized in a 1:1:2 fashion (60:60:120 patients) to MEDI4736 monotherapy, tremelimumab monotherapy, or MEDI4736 + tremelimumab combination therapy.

Study period		Phase of development
Estimated date of first patient enrolled	Q2 2015	II
Estimated date of last patient completed	Q3 2018	II

Study design

This is a randomized, open-label, multi-center, global, Phase II study to determine the efficacy and safety of MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, and tremelimumab monotherapy in the treatment of patients with recurrent or metastatic PD-L1-negative squamous cell carcinoma of the head and neck (SCCHN) who have progressed during or after treatment with only 1 systemic palliative regimen for recurrent or metastatic disease that must have contained a platinum agent.

The primary objective of the study is to assess the efficacy of MEDI4736 + tremelimumab combination therapy in patients with PD-L1-negative SCCHN in terms of objective response rate (ORR).

A secondary objective is to assess the efficacy of MEDI4736 + tremelimumab combination therapy compared with a) MEDI4736 monotherapy and b) tremelimumab monotherapy, in terms of ORR, progression-free survival (PFS), and overall survival (OS).

Patients will undergo an assessment on their tumor tissue sample to determine PD-L1 status prior to treatment (Day 0). Patients with tumoral PD-L1 expression below a pre-specified cut-off level, less than 25% of tumor cells with membrane staining, as determined by an immunohistochemistry assay (referred to hereafter as patients with PD-L1-negative tumors), will be enrolled in the study. If the patient's PD-L1 status has already been assessed using the analytically validated Ventana SP263 assay as a part of the screening process for D4193C00001 or another AstraZeneca/MedImmune study, this test result can be used for the determination of eligibility.

Patients will be randomized in a stratified manner according to prognostic factors, including human papillomavirus (HPV) status and smoking status to achieve a balance between treatments for each of the factors. Patients will be randomized in a 1:1:2 fashion (60:60:120 patients) to receive MEDI4736 monotherapy, tremelimumab monotherapy, or MEDI4736 + tremelimumab combination therapy for a total of at least 208 evaluable patients (52 in MEDI4736 monotherapy, 52 in tremelimumab monotherapy, and 104 in MEDI4736 + tremelimumab combination arm).

Patients in the MEDI4736 monotherapy treatment group will receive 10 mg/kg MEDI4736 via intravenous (IV) infusion every 2 weeks (q2w) for up to 12 months (up to 26 doses). Patients in the tremelimumab monotherapy treatment group will receive 10 mg/kg tremelimumab via IV infusion every 4 weeks (q4w) for 7 doses then every 12 weeks for 2 additional doses for up to 12 months (up to 9 doses in total). Patients in the MEDI4736 + tremelimumab group will receive 20 mg/kg MEDI4736 via IV infusion q4w for 4 months (up to 4 doses) and 1 mg/kg tremelimumab via IV infusion q4w for 4 months (up to 4 doses in total). After completion of the initial 4 doses of combination therapy, single agent MEDI4736 will continue at 10 mg/kg q2w to complete a total of 12 months of therapy (up to 18 additional doses with the final dose at Week 50). The first MEDI4736 dose at 10 mg/kg q2w will be 4 weeks after the final dose of the combination of tremelimumab and MEDI4736 at 20 mg/kg.

All treatments will be administered beginning on Day 0 for 12 months or until confirmed progression of disease (PD; unless, in the Investigator's opinion, the patient continues to receive benefit from the treatment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Patients with confirmed PD who, in the Investigator's opinion, continue to receive benefit from their assigned investigational product (IP) and who meet the criteria for treatment in the setting of PD may continue to receive their assigned IP treatment for a maximum of 12 months after consultation with the Sponsor and at the Investigator's discretion. The monotherapy arms (tremelimumab and MEDI4736) should be discontinued if there is confirmed PD following a previous response in target lesions (CR or PR).

Patients who the Sponsor and Investigator determine may not continue treatment after confirmed PD during the 12-month initial treatment period or in the 12-month retreatment

period will enter follow-up. Patients who have discontinued treatment due to toxicity or symptomatic deterioration, or who have commenced subsequent anticancer therapy, will be followed up until confirmed disease progression and death.

Tumor assessments will be performed using computed tomography or magnetic resonance imaging. Efficacy for all patients will be assessed by objective tumor assessments every 8 weeks (q8w) for the first 48 weeks (relative to the date of the first infusion) then q12w in patients who have disease control after 12 months until confirmed objective disease progression as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1; irrespective of the reason for stopping treatment). If an unscheduled scan is performed in the absence of suspicion of progression within 2 weeks of a scheduled scan, the scan does not need to be repeated. However, every attempt should be made to follow the original scan schedule.

Categorization of objective tumor response assessment will be based on RECIST 1.1: complete response (CR), partial response (PR), stable disease (SD), and PD. RECIST 1.1 measurements based on Blinded Independent Central Review (BICR) assessment will be used to programmatically derive the primary variable of ORR and the secondary variables of duration of response (DoR), disease control rate (DCR), best objective response (BoR), and progression-free survival (PFS). Results of these independent reviews will not be communicated to the Investigators, and the management of patients will be based solely upon the results of the RECIST 1.1 assessment conducted by the Investigator. ORR, DoR, DCR, BoR, and PFS will also be assessed as secondary variables using BICR assessment according to immune-related Response Evaluation Criteria in Solid Tumors, version 1.1 (irRECIST 1.1). DoR and DCR will also be assessed using site Investigator data according to RECIST 1.1. Sensitivity analyses from RECIST 1.1 measurements per the site Investigator and from the BICR according to RECIST 1.1 modified for confirmation of progression will also be performed. While BICR assessment will be used to define study endpoints, determination of CR,PR, SD, and PD during the trial and subsequent appropriate management will be based on individual Investigator review of tumor response assessments as per RECIST 1.1. Additional secondary objectives will include safety and tolerability and health-related quality of life. Exploratory objectives will also be assessed.

Objective tumor response (CR or PR) should be confirmed preferably at the next scheduled visit and not less than 4 weeks after the visit when the response was first observed. All scans showing PD should be confirmed preferably at the next scheduled visit and no earlier than 4 weeks after the prior assessment of PD in the absence of clinically significant deterioration. Treatment with IP will continue between the assessment of progression and its confirmation. Patients with clinical evidence of progression who do not meet PD criteria by RECIST 1.1 should have radiographic documentation of PD. If progression is not confirmed, then the patient should continue receiving study treatment and participating in study assessments.

Patients who achieve and maintain disease control (ie, CR, PR, or SD) through the end of the 12-month treatment period will enter follow-up. When these patients experience evidence of PD, with or without confirmation, during follow-up and meet the criteria for treatment in the

setting of PD, they will be given the option to restart their assigned IP treatment for up to an additional 12 months with the same treatment guidelines followed during the initial 12-month treatment period. Patients should have a baseline tumor assessment within 28 days of restarting treatment with their assigned IP; all further scans should occur q8w (relative to the date of restarting treatment) until study treatment is stopped (maximum of 12 months of further treatment).

Only patients who the Investigator determines do not have any significant, unacceptable, or irreversible toxicities and would continue to receive benefit from therapy can restart a second 12 months of retreatment upon PD. Patients with confirmed progression in the MEDI4736 monotherapy arm, tremelimumab monotherapy arm, or in the combination portion of therapy in the MEDI4736 + tremelimumab arm cannot continue therapy or obtain retreatment if the progression occurred during dosing and after confirmed response in the target lesions (ie, the response and progression events both occurred while receiving active IP during the same treatment period in the target lesions). Retreatment in the combination arm can only occur if PD occurs during the monotherapy portion or after completion of 12 months of therapy. During the retreatment period, the patient would resume MEDI4736 dosing at 20 mg/kg q4w as during the initial induction period, along with 1 mg/kg of tremelimumab q4w for 4 doses. Monotherapy with MEDI4736 would then resume at 10 mg/kg q2w 4 weeks after the last combination dose is administered for a total of up to 18 additional doses with the final dose at Week 50.

Patients with confirmed PD who continue to receive their assigned IP at the discretion of the Investigator (after consultation with the Sponsor) may do so for a maximum of 12 months.

Patients with confirmed PD who discontinue their assigned IP should have scans conducted according to local practice and submitted for BICR until the patient commences a new treatment (these scans are optional). Patients who discontinue treatment in 1 treatment group may not switch to treatment in a different group.

Following completion or discontinuation of treatment, patients will enter a follow-up period.

Overall survival extension period

The OS Extension period will start following the 12-month analysis DCO, and will extend the OS data collection period until approximately 30 months after Last Patient Dosed (LPD), or until 85% OS event maturity is reached, whichever occurs first.

During the OS Extension period, all patients will be followed for survival. Overall survival, safety-related data, and IP administration details will be collected in the clinical database. Once the final OS analysis has been completed, the clinical database will be closed.

Patients will receive scans/RECIST assessments as per local standard of care. All other study efficacy assessments and centralized assessments will cease. Patients will continue with scheduled site visits, safety laboratory assessments, and other safety assessments.

Patients who are progression-free following randomized treatment and potentially eligible for retreatment are to undergo sampling for local laboratory assessments, and in such a way that continued per-protocol retreatment eligibility can be properly determined.

End of analysis portion of study

The DCO for the final analysis of OS will take place approximately 30 months after LPD, or when 85% OS event maturity is reached, whichever occurs first. At this point, the clinical study database will be closed to new data. Once all planned statistical analyses have been performed, the analysis portion of the clinical study will have been completed. Progressed patients in OS follow-up will be withdrawn from the study. Patients who are progression-free following randomized treatment and potentially eligible for retreatment may decide to continue in the study; these patients would remain eligible for possible future retreatment upon progression if they meet retreatment criteria and the Investigator believes that the patient will gain clinical benefit. Patients already receiving retreatment at the time of the OS Extension DCO may continue receiving study treatment, if the Investigator believes that they are gaining clinical benefit.

Scans will be collected in accordance with local clinical practice. Patients who are progression-free following randomized treatment and potentially eligible for retreatment after the OS Extension DCO are to undergo sampling for local laboratory assessments in such a way that continued per-protocol retreatment eligibility can be properly determined.

For patients receiving retreatment after the OS Extension DCO, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patient's safety laboratory assessments prior to and periodically during study treatment in order to manage AEs in accordance with the toxicity management guidelines.

For patients who either continue to receive treatment or begin retreatment after the time of the OS Extension DCO, Investigators will report all SAEs to the AstraZeneca representative until 90 days after the investigational product (IP) is discontinued. Following the OS Extension DCO, SAE reporting will apply only to patients who are active on study treatment and within 90 days post the last dose; in all other cases only a statement of death notification is to be sent to the AstraZeneca representative.

In the event that a roll-over or safety extension study will become available, patients currently receiving treatment with study drug or patients who are progression-free following randomized treatment and potentially eligible for retreatment may be transitioned to such a study, and the current study would reach its end. The roll-over or safety extension study would ensure treatment continuation with visits assessment per its protocol. Any patient that would be proposed to move to such a study would be given a new informed consent form (ICF).

Objectives

Primary Objective:	Outcome Measure:
To assess the efficacy of MEDI4736 + tremelimumab combination therapy in terms of ORR	ORR using BICR assessments according to RECIST 1.1[a]

[a] Sensitivity analysis of ORR will be performed based on tumor information recorded in the clinical database by the Investigator according to RECIST 1.1 and will also be performed based on BICR assessment according to RECIST 1.1 modified for confirmation of progression.

BICR Blinded Independent Central Review; ORR Objective response rate; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1.

Secondary Objective:	Outcome Measures:
To further assess the efficacy of MEDI4736 + tremelimumab combination therapy in terms of ORR, TTR, DoR, DCR, BoR, PFS, and OS	DoR, DCR, BoR, and PFS [a] using BICR assessments according to RECIST 1.1 ORR and PFS using BICR assessments according to irRECIST 1.1 OS
To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared with a) MEDI4736 monotherapy and b) tremelimumab monotherapy, in terms of ORR, PFS, and OS	ORR and PFS using BICR assessments according to RECIST 1.1[b] OS
To assess disease-related symptoms and health-related quality of life (QoL) in patients treated with MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, and tremelimumab monotherapy using the EORTC QLQ-C30 v3 and the QLQ-H&N35 module	EORTC QLQ-C30: global health QoL, functioning (physical), and symptoms (fatigue) EORTC QLQ-H&N35: symptoms (pain and swallowing) Changes in WHO/ECOG performance status will also be assessed.

[a] Sensitivity analysis of PFS will be performed based on tumor information recorded in the clinical database by the Investigator according to RECIST 1.1.

[b] Sensitivity analyses of ORR will be performed based on tumor information recorded in the clinical database by the Investigator according to RECIST 1.1 and PFS will also be performed based on BICR assessment according to RECIST 1.1 modified for confirmation of progression.

BICR Blinded Independent Central Review; BoR Best objective response; DCR Disease control rate; DoR Duration of response; ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; irRECIST 1.1 Immune-related Response Evaluation Criteria in Solid Tumors version 1.1; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; QLQ-C30 v3 30-item core quality of life questionnaire, version 3; QLQ-H&N35 35-item head and neck quality of life questionnaire; QoL Quality of life; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1; TTR Time to recurrence; WHO World Health Organization.

Safety Objective:	Outcome Measures:
To assess the safety and tolerability profile of MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, and tremelimumab monotherapy	AEs, physical examinations, laboratory findings (including clinical chemistry, hematology, and urinalysis), vital signs (including blood pressure, pulse, and oxygen saturation), and ECGs

AE Adverse event; ECG Electrocardiogram.

Target patient population

Males and females aged 18 and over with histologically confirmed, PD-L1-negative, recurrent or metastatic SCCHN (oral cavity, oropharynx, hypopharynx, or larynx) with measurable disease (as per RECIST 1.1) who have progressed during or after treatment with only 1 systemic palliative regimen for recurrent or metastatic disease that must have contained a platinum agent.

Duration of treatment

Treatment with MEDI4736 monotherapy, tremelimumab monotherapy, or MEDI4736 + tremelimumab combination therapy will commence on Day 0 following confirmation of eligibility and randomization. Patients will be treated with their assigned IP for a maximum of 12 months or until confirmed disease progression (unless, in the Investigator's opinion, the patient continues to receive benefit from the treatment and after discussion with the Sponsor), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other treatment discontinuation criterion is met, whichever occurs first.

Patients who have a dose interruption due to toxicity at any point in the first 12 months of treatment may resume treatment with their assigned IP and complete the 12-month treatment period. Additional doses are not permitted to compensate for missed doses.

Disease progression requires confirmation. Treatment with IP will continue between the initial assessment of progression and confirmation of progression. Patients with clinical evidence of progression who do not meet PD criteria by RECIST 1.1 should have radiographic documentation of PD. If progression is not confirmed, then the patient should continue receiving study treatment and participating in study assessments.

A further description of treatment duration and retreatment options is provided in the Study Design section of this synopsis.

Investigational product, dosage, and mode of administration

<u>MEDI4736 monotherapy</u>

Patients in the MEDI4736 monotherapy group will receive the following treatment:

- MEDI4736 (10 mg/kg) will be administered via IV infusion q2w for up to 12 months (up to 26 doses).

<u>Tremelimumab monotherapy</u>

Patients in the tremelimumab monotherapy group will receive the following treatment:

- Tremelimumab (10 mg/kg) will be administered via IV infusion q4w for 7 doses then q12w for 2 additional doses for up to 12 months (up to 9 doses in total).

MEDI4736 + tremelimumab combination therapy

Patients in the MEDI4736 + tremelimumab combination therapy group will receive both of the following treatments:

- MEDI4736 (20 mg/kg) will be administered via IV infusion q4w for up to 4 months (up to 4 doses). After completion of the initial 4 doses of combination therapy, single agent MEDI4736 will continue at 10 mg/kg q2w to complete 12 months of therapy (up to 18 additional doses with the final dose at Week 50). The first MEDI4736 dose at 10 mg/kg q2w will be 4 weeks after the final dose of the combination of tremelimumab and MEDI4736 at 20 mg/kg. Tremelimumab (1 mg/kg) will be administered via IV infusion q4w for 4 months (up to 4 doses in total).

Statistical methods

The primary objective of this study is to assess the efficacy of MEDI4736 + tremelimumab in patients with PD-L1-negative SCCHN, in terms of ORR. A secondary objective is to assess the efficacy of MEDI4736 + tremelimumab combination therapy compared with a) MEDI4736 monotherapy and b) tremelimumab monotherapy, in terms of ORR, PFS, and OS in patients with PD-L1-negative SCCHN. ORR (per RECIST 1.1 as assessed by BICR) is defined as the number (%) of patients with a confirmed CR or confirmed PR and will be based on all treated patients who are PD-L1-negative with measurable disease at baseline per BICR (Evaluable Set).

A total of approximately 240 patients who have PD-L1-negative tumors will be enrolled and randomized (in a 1:1:2 fashion) to obtain at least 208 evaluable patients (ie, evaluable for the primary and secondary endpoints). Patients will be randomized to MEDI4736 monotherapy (60 randomized, 52 evaluable patients), tremelimumab monotherapy (60 randomized, 52 evaluable patients), and MEDI4736 + tremelimumab combination therapy (120 randomized, 104 evaluable patients). Patients will be stratified according to prognostic factors, including HPV status and smoking status.

A total of 120 patients who are PD-L1-negative will be enrolled to obtain 104 evaluable patients (ie, evaluable for the primary endpoint). The primary objective of the trial is to assess the efficacy of MEDI4736 + tremelimumab in terms of ORR. If the true ORR is 27%, a sample size of 104 evaluable patients in the MEDI4736 + tremelimumab combination therapy arm will provide a precision of ± 8.5% around this estimate, using a 95% confidence interval. Although no formal statistical comparisons are planned, a sample size of 104 evaluable patients will provide adequate power to test the hypothesis H_0: ORR ≤13% versus H_1: ORR >13%. If the true ORR is 27%, the study will have 92% power to reject the null hypothesis

(H_0) at the 1-sided 0.025 alpha level (or, equivalently, 2-sided 0.05 alpha level) using an exact binomial test.

To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared with a) MEDI4746 monotherapy and b) tremelimumab monotherapy, in terms of ORR, a sample size of 156 evaluable patients (52 versus 104 for MEDI4736 monotherapy or tremelimumab monotherapy versus MEDI4736 + tremelimumab combination therapy) will be required. This sample size will provide 90% power to demonstrate a statistically significant difference in ORR at a 2-sided 0.05 significance level assuming a true ORR difference of 22% (5% on monotherapy and 27% on combination therapy). Based on the assumptions above, the minimum difference in ORR that would be statistically significant at the 0.05 level is 10.4%.

To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared with a) MEDI4746 monotherapy and b) tremelimumab monotherapy, in terms of PFS, 116 PFS events (74% maturity) need to be observed in the 156 evaluable patients (52 versus 104 for MEDI4736 or tremelimumab versus MEDI4736 + tremelimumab). If the true hazard ratio (HR) is 0.60 (15 versus 37% PFS rates at 6 months), 116 PFS events will provide 80% power to demonstrate a statistically significant difference in PFS at a 0.05 two-sided significance level, with the smallest treatment difference that could be statistically significant being an average HR of 0.70. With an assumed 10-month recruitment period and an assumed minimum follow-up period of 6 months, it is anticipated that this analysis will be performed 16 months after the first patient has been recruited.

To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared with a) MEDI4746 monotherapy and b) tremelimumab monotherapy in terms of OS, 125 death events (80% maturity) need to be observed in 156 evaluable patients (52 or 104 for MEDI4736 or tremelimumab, respectively, versus MEDI4736 + tremelimumab). If the true HR is 0.60 (10% versus 31% survival rates at 18 months), 125 death events will provide 80% power to demonstrate a statistically significant difference in OS at a 0.05 two-sided significance level, with the smallest treatment difference that could be statistically significant being an average HR of 0.70. With an assumed 10-month recruitment period and an assumed minimum follow-up period of approximately 18 months, it is anticipated that this analysis will be performed 28 months after the first patient has been recruited.

Secondary efficacy variables include: DoR, time to recurrence (TTR), DCR, BoR, PFS, and OS. The initial DCO will take place approximately 6 months after the last patient is first dosed. All study endpoints will be analyzed at this time. However, if the required number of PFS events are not observed, only descriptive analyses of PFS and OS will be presented at this time. A further analysis of efficacy will take place approximately 12 months after the last patient is dosed or after the occurrence of approximately 116 PFS events between the MEDI4736 + tremelimumab therapy group and the MEDI4736 monotherapy group, whichever occurs first.

A formal analysis of OS will be conducted approximately 18 months after the last patient is dosed or after the occurrence of 125 death events between the MEDI4736 + tremelimumab therapy group and the MEDI4736 monotherapy group, whichever occurs first. Kaplan-Meier

plots and median DoR, PFS, BoR, and OS will be presented. Also, summaries (ie, number of patients [%]) of PFS, death events, and DCR will be provided. Formal analysis of PFS and OS will only be done when approximately 116 PFS events and 125 death events are observed or 18 months after the last patient is dosed, whichever comes first, for MEDI4736 + tremelimumab combination therapy versus MEDI4736 monotherapy.

The final analysis of OS will be conducted after the OS Extension period. The OS Extension period is defined as the period after the DCO for the 12-month analysis until approximately 30 months after LPD or once OS events reach 85% maturity, whichever occurs first. The objective of the OS Extension period is to determine the longer-term OS of patients treated with MEDI4736 and tremelimumab up to 30 months after LPD.

The primary analysis of ORR, TTR, DoR, DCR, BOR, and PFS will be based on BICR assessments according to RECIST 1.1 using all scans regardless of whether they were scheduled or not. Secondary analysis of ORR and PFS will be performed using BICR assessment according to irRECIST 1.1.

Sensitivity analyses of TTR, ORR, DoR, BoR, and PFS will be performed based on tumor information recorded in the clinical database by the Investigator according to RECIST 1.1 and will also be performed on PFS based on BICR assessment according to RECIST 1.1 modified for confirmation of progression.

Patient-reported outcomes will be assessed by the European Organisation for Research and Treatment of Cancer (EORTC) 30-item core quality of life questionnaire (QLQ-C30) and 35-item head and neck-specific module (H&N35). All items/ questionnaires will be scored according to published scoring guidelines. All PRO analyses will be based on the Full Analysis Set (FAS; ITT population). Time to deterioration in health-related QoL and head and neck cancer-specific symptoms will be formally analyzed. Change from baseline and absolute values for individual items by treatment group at each time point will also be explored and summarized descriptively. Summaries of MEDI4736 and tremelimumab pharmacokinetic data and exposure parameters will be provided for all evaluable patients. Summaries of immunogenicity data will be provided for the number and percentage of patients who develop detectable anti-MEDI4736 and anti-tremelimumab antibodies. Safety data will be summarized descriptively and will not be formally analyzed. This will be based on the safety analysis set. Exploratory biomarker and pharmacogenetics research will be reported outside of the clinical study report.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AChE	Acetylcholine esterase
ADA	Antidrug antibody
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma drug concentration-time curve
$AUC_{0\text{-}28day}$	Area under the plasma drug concentration-time curve from time zero to Day 28 post-dose
BICR	Blinded Independent Central Review
BoR	Best objective response
BUN	Blood urea nitrogen
CD	Cluster of differentiation
CI	Confidence interval
C_{max}	Maximum plasma concentration
CR	Complete response
CRF	Case report form
CSA	Clinical Study Agreement
CSR	Clinical study report
CT	Computed tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4
DCO	Data cutoff
DCR	Disease control rate
DLT	Dose-limiting toxicity
DoR	Duration of response

Abbreviation or special term	Explanation
EC	Ethics Committee, synonymous with Institutional Review Board (IRB)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
H&N35	35-item head and neck quality of life questionnaire
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin
ILD	Interstitial lung disease
IM	Intramuscular
IMT	Immunomodulatory therapy
IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional Review Board, synonymous with Ethics Committee (EC)
irRC	Immune-related response criteria
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent-to-Treat

Abbreviation or special term	Explanation
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LFT	Liver function test
LLN	Lower limit of normal
LPD	Last patient dosed
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	Micro ribonucleic acid
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non-small-cell lung cancer
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PCP	Pneumocystis pneumonia
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PFS	Progression-free survival
PGx	Pharmacogenetic research
PK	Pharmacokinetic
PO	By mouth
PR	Partial response
PRO	Patient-reported outcome
q2w	Every 2 weeks
q4w	Every 4 weeks
q12w	Every 12 weeks
QLQ-C30 v3	30-item core quality of life questionnaire, version 3

Abbreviation or special term	Explanation
QoL	Quality of life
QTcF	QT interval corrected for Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RR	Response rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable disease
sPD-L1	Soluble programmed cell death ligand 1
T_3	Triiodothyronine
T_4	Thyroxine
TB	Total bilirubin
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor
TSH	Thyroid-stimulating hormone
TTR	Time to recurrence
ULN	Upper limit of normal
WBDC	Web Based Data Capture
WHO	World Health Organization

1. INTRODUCTION

1.1 Background and rationale for conducting this study

1.1.1 Squamous cell carcinoma of the head and neck

Head and neck cancer is a collective term that encompasses the malignant tumors arising out of the oral cavity, pharynx, and larynx. Worldwide, over half a million new head and neck cancer cases are diagnosed each year, accounting for approximately 5% of all incident cancers. Over 90% of these head and neck cancers are squamous cell carcinoma subtype (SCCHN). SCCHN diagnosed at a localized stage (Stage I/II) can be effectively treated with single-modality treatment (either surgery or radiation), and the 5-year survival rate in these cases is over 80%. However, about 70% of SCCHN patients are diagnosed with a locally advanced or metastatic disease, where the survival rates are poor (Siegel et al 2014). Patients with locally advanced disease typically receive a multi-modality treatment with curative intent, usually involving varied combinations of surgical resection, radiation therapy, and chemotherapy. Most of these patients, however, eventually relapse with either locoregional recurrence, metastatic disease (20% to 30% of patients), or both (Vermorken and Specenier 2010).

First-line palliative treatment options for patients with locally recurrent (without salvage surgical or radiation option) and/or metastatic SCCHN include supportive care in conjunction with systemic therapy. Most regimens involve platinum compounds (cisplatin and carboplatin), either as single agents or in combination with other agents. Other most widely used agents include taxanes (docetaxel and paclitaxel), methotrexate, 5-fluorouracil, and cetuximab. After failure of first-line chemotherapy, objective responses to second-line cytotoxic chemotherapy are uncommon. Additionally, these regimens are associated with greater toxicity, and there is no evidence that second line treatment prolongs survival. The only approved targeted therapy for these second-line patients is Erbitux® (cetuximab), which has shown an objective response rate (ORR) of approximately 13% in patients who have failed first-line palliative therapy (Vermorken et al 2007).

Patients with recurrent or metastatic disease have a poor prognosis, with ORRs of approximately 20% to 35% and overall survival (OS) of 7 to 10 months observed with platinum-based chemotherapy and cetuximab regimens (Vermorken et al 2008). The management of patients with later stage disease is even more challenging, with currently available therapies providing ORRs of approximately 4% with methotrexate to 13% with cetuximab and OS of approximately 6 months (Shin and Khuri 2013, Vermorken et al 2008). In addition to poor response and survival outcomes, many palliative treatments may cause substantial toxicity. In summary, SCCHN represents a population with a large unmet need for new treatment options in the palliative setting (American Cancer Society 2012).

1.1.2 Immunotherapies

It is increasingly understood that cancers are recognized by the immune system, and under some circumstances, the immune system may control or even eliminate tumors (Dunn et al 2004). Studies in mouse models of transplantable tumors have demonstrated that manipulation of co-stimulatory or co-inhibitory signals can amplify T-cell responses against tumors (Peggs et al 2009). This amplification may be accomplished by blocking co-inhibitory molecules, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) or programmed cell death 1 (PD-1), from binding with their ligands, B7 or B7-H1 (programmed cell death ligand 1 [PD-L1]). Biologically, SCCHN has attributes that suggest susceptibility to immune checkpoint blockade. Multiple lines of evidence suggest that SCCHN tumors create a highly immunosuppressive environment and that the PD-1/PD-L1 axis and inhibition of the activation of T cells play an important role in many cancers, including SCCHN, and may be amenable to therapeutic intervention with immune-modulating agents (Badoual et al 2010, Badoual et al 2013, Lyford-Pike et al 2013). Virally driven tumors, including human papillomavirus (HPV)-associated SCCHN, express viral antigens that may be recognized by the immune system. In HPV-associated cancers, the E6 and E7 tumor-specific antigens are known to be immunogenic, and studies have shown that HPV-specific T-cell responses form upon vaccination with these proteins (Kaufmann et al 2002). Administering an immunotherapeutic agent to patients with HPV-positive SCCHN may result in an anti-tumor immune response versus HPV tumor-specific antigens. In patients with HPV-negative SCCHN, the driving etiology is thought to be tobacco use. Data suggest that cancers associated with smoking such as non-small-cell lung cancer (NSCLC), small-cell lung cancer, and SCCHN may carry a high mutational burden (Alexandrov et al 2013, Vogelstein et al 2013). Tumors with high mutational burden produce neoantigens, which may generate T-cell immunity. This hypothesis may explain the observation that patients with NSCLC with a history of heavy smoking may be more prone to respond to anti-PD-1 or anti-PD-L1 therapy as compared to light or never smokers. Specifically, higher ORRs following treatment with an anti-PD-L1 monoclonal antibody (mAb) were observed in patients with NSCLC with a history of smoking as compared to those without a history of smoking (Champiat et al 2014). These data suggest that application of immune-modulating therapies in SCCHN may have a positive impact on clinical outcomes.

1.1.3 MEDI4736 (durvalumab)

MEDI4736 is a human mAb of the immunoglobulin G1 kappa subclass that inhibits binding of PD-L1 and is being developed by AstraZeneca/MedImmune for use in the treatment of cancer. (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) The proposed mechanism of action for MEDI4736 is interference of the interaction of PD-L1, expressed on cancer cells and a subset of leukocytes, with the PD-1 (cluster of differentiation [CD] 279) and B7-1 (CD80) molecules on antigen-presenting cells and T-cells. By binding to PD-L1 on tumor cells, the mechanism of action of MEDI4736 includes stimulation of the patient's antitumor immune response.

MEDI4736 has been given to humans as part of ongoing studies as a single drug or in combination with other drugs. As of June 2014, patients are being enrolled in 10 ongoing clinical studies of MEDI4736 (5 employing MEDI4736 as monotherapy and 5 as combination therapy). No studies have yet been completed. Refer to the MEDI4736 Investigator's Brochure (IB) for a complete summary of non-clinical and clinical information; see Section 6.7 for guidance on management of MEDI4736-related toxicities.

The majority of the safety data currently available for MEDI4736 are based on the first-time-in-human, single-agent study (Study CD-ON-MEDI4736-1108; referred to hereafter as Study 1108) in patients with advanced solid tumors. As of 18 February 2014, 177 of 198 patients enrolled in Study 1108 have received MEDI4736 at 10 mg/kg every 2 weeks (q2w; either in the dose-escalation or dose-expansion phase of the study). Of these 177 patients, 121 patients (71.8%) had at least 1 treatment-emergent adverse event (TEAE). The most frequently reported (≥10% of patients) TEAEs (all National Cancer Institute [NCI] Common Terminology Criteria for Adverse Event [CTCAE] grades) were fatigue, dyspnea, nausea, constipation, and decreased appetite. The important potential risks, based on the mechanism of action of MEDI4736, as well as data from studies of relevant or similar therapies, include immune-mediated reactions, such as enterocolitis, dermatitis, hepatitis/hepatotoxicity, endocrinopathy, pneumonitis, neuropathy, and other events such as serious infections, infusion-related reactions, anaphylaxis or serious allergic reactions, and immune complex disease. The development of a serious infection is a theoretical risk based on findings from non-clinical safety studies. As of June 2014, no patients have experienced immune complex disease following exposure to MEDI4736. Antidrug antibodies (ADAs) have been identified in 3 of the 31 patients tested.

1.1.4 Tremelimumab

Tremelimumab, a CTLA-4 mAb of the IgG2 kappa isotype, is an immunomodulatory therapy (IMT) that is being developed by AstraZeneca for use in the treatment of cancer. Tremelimumab is a human immunoglobulin G2 mAb directed against CTLA-4. CTLA-4 is a critical regulatory signal for T-cell expansion and activation following an immune response, and it serves as a natural braking mechanism that maintains T-cell homeostasis. During T-cell activation, T cells upregulate CTLA-4, which binds to B7 ligands on antigen-presenting cells, sending an inhibitory signal that limits T-cell activation. Tremelimumab blocks the inhibitory signal resulting from CTLA-4 binding to B7, leading to prolongation and enhancement of T-cell activation and expansion. Thus, the mechanism of action of tremelimumab is indirect and is applied through enhancing T-cell-mediated immune response.

An extensive program of non-clinical and clinical studies has been conducted for tremelimumab both as monotherapy and combination therapy with conventional anticancer agents to support various cancer indications using different dose schedules. Tremelimumab has been administered as a single-agent treatment to patients participating in 10 sponsored clinical studies, 2 of which continue to follow patients. In total, more than 973 patients with a variety of tumor types have been treated in these studies (not including ongoing Phase II Study D4880C00003). In addition, 116 patients with a variety of tumor types have received tremelimumab in combination with other anticancer agents in 5 sponsored clinical studies.

Refer to the tremelimumab IB for a complete summary of non-clinical and clinical information; see Section 6.7 for guidance on management of tremelimumab-related toxicities.

Diarrhea, rash, and pruritus are considered to be identified risks with tremelimumab. The important potential risks for tremelimumab that require further evaluation in clinical studies are colitis, intestinal perforation, pancreatitis, hepatitis, hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, immune-mediated cytopenia (including thrombocytopenia and anemia), and hypersensitivity (including infusion reactions). The mechanism for many of these is thought to be immune mediated and reflective of the pharmacology of tremelimumab. Overall, a low incidence of ADAs (<6%) was observed for treatment with tremelimumab. For additional details on the safety profile of tremelimumab, please refer to the current tremelimumab IB.

1.1.5 MEDI4736 in combination with tremelimumab

Study D4190C00006 is a Phase Ib dose-escalation study to establish safety, pharmacokinetics (PK)/pharmacodynamics, and preliminary antitumor activity of MEDI4736 + tremelimumab combination therapy in patients with advanced NSCLC. The dosing schedule utilized is MEDI4736 every 2 or 4 weeks (q2w;q4w) up to Week 50 and 48 (12 months), combined with tremelimumab q4w up to Week 24 for 7 doses then every 12 weeks (q12w) for 2 additional doses for up to 12 months. The study is ongoing and continues to accrue.

As of 27 January 2015, a total of 74 subjects with advanced non-small cell lung cancer have been treated in Study D4190C00006 (see Table 1). The 74 subjects have received between 1 and 9 doses of tremelimumab and between 1 and 13 doses of MEDI4736.

Table 1 Treatments Received, Study 4190C00006

Cohort	MEDI4736 Dose (mg/kg)	Tremelimumab Dose (mg/kg)	Subjects Treated
Q4W Dosing Schedule			
1a	3	1	3
2a	10	1	3
3a	15	1	12
3b	10	3	3
4	20	1	11
4a	15	3	11
5	15	10	9
5a	20	3	6
Q4W Total			58
Q2W Dosing Schedule			
8	10	1	6
9	10	3	10
Q2W Total			16
Overall Total			74

Q2W Every 2 weeks; Q4W Every 4 weeks

Overall, 62 (83.8%) of the 74 subjects reported an adverse event (AE) regardless of causality (Table 2 and Table 3). The most frequently reported AEs (10 or more subjects) were fatigue (37.8%; 28 subjects); diarrhea (32.4%; 24 subjects); amylase increased and pruritus (16.2%; 12 subjects); decreased appetite, dyspnea, nausea, and rash (14.9%; 11 subjects each); and headache and pyrexia (13.5%; 10 subjects).

Twenty of the 62 subjects who experienced AEs regardless of causality had events that were Grade 1 or 2 in severity. Forty two of the 62 subjects reported ≥ Grade 3 events. The most frequently reported ≥ Grade 3 events (in 3 or more subjects) were diarrhea (7 subjects); colitis (6 subjects); increased lipase (4 subjects); and anemia, increased alanine aminotransferase, increased aspartate aminotransferase, dehydration, and pneumonitis (3 subjects each).

Fifty of the 74 subjects reported a treatment-related AE. The most frequently reported treatment-related AEs were fatigue (24.3%; 18 subjects); diarrhea (21.6%; 16 subjects); increased alanine aminotransferase (13.5%, 10 subjects); pruritus (12.2%; 9 subjects); and rash (10.8%; 8 subjects). Twenty-four of the 50 subjects who experienced treatment-related AEs reported Grade 1 or 2 events only. Twenty-six of the 50 subjects reported ≥ Grade 3 events. The most frequently reported treatment-related ≥ Grade 3 events (in 3 or more subjects) were colitis and diarrhea (6 subjects each); increased lipase (4 subjects); and

increased alanine aminotransferase, increased aspartate aminotransferase, and pneumonitis (3 subjects each).

Two subjects treated in the Q4W M20/T3 cohort (Cohort 5a) experienced a DLT (dose-limiting toxicity). These 2 DLTs were the following:

Grade 3 increased aspartate aminotransaminase (8 × upper limit of normal) considered also as a serious adverse event (SAE) that occurred in a 50 year-old female on Cycle 1 Day 29 of treatment. The AE improved to Grade 1 with steroids and resolved.

Grade 3 increased amylase levels (considered also as an SAE) and asymptomatic Grade 4 increased lipase that occurred in a 74 year-old female on Cycle 1 Day 9. There were no clinical sequelae per Investigator.

Of the 74 treated subjects, 40 subjects (54.1%) have experienced 88 SAEs regardless of causality. The most frequently reported SAEs (2 or more subjects) in the Q4W cohorts were colitis (6 subjects); diarrhea (5 subjects); pneumonitis (4 subjects); and aspartate aminotransferase increased and pyrexia (3 subjects each).

Twenty-six subjects (35.1%) experienced 47 SAEs that were considered related to study drugs, including 22 subjects in the Q4W cohorts and 4 subjects in the Q2W cohorts. The most frequently reported (2 or more subjects) treatment-related SAEs in the Q4W cohorts were colitis (6 subjects), diarrhea (5 subjects), pneumonitis (4 subjects), increased aspartate aminotransferase (3 subjects), and increased alanine aminotransferase (2 subjects). The incidence of diarrhea was highest in the 20M/3T cohort (50.0%, 3 subjects). Pneumonitis was only observed in the M15/T3 and M15/T10 cohorts (18.2% [2/11] and 22.2% [2/9], respectively).

The only SAE reported by more than 1 subject in the Q2W cohorts was colitis (2 subjects). The percentage of subjects reporting SAEs was higher in the M10/T3 cohort than the M10/T1 cohort (50.0% [5/10] versus 16.7% [1/6], respectively). The treatment-related SAEs reported in the Q2W cohorts were colitis (2 subjects), and diarrhea, fatigue, and pneumonitis (1 subject each). These only occurred in the M10/T3 cohort.

Within the total study population, 21 subjects (28.4%) discontinued treatment due to AEs. The most frequent AEs (more than 1 subject) leading to treatment discontinuation were colitis (5 subjects); pneumonitis (4 subjects); diarrhea (3 subjects); and increased aspartate aminotransferase and dyspnea (2 subjects each). The episodes of colitis, diarrhea, increased aspartate aminotransferase, and pneumonitis were all considered to be treatment related. The percentage of subjects with AEs leading to discontinuation was highest in the M20/T3 cohort (83.3%, 5/6).

Eleven subjects (14.9%) have died, of which 9 were due to disease and 2 to treatment-related toxicities (Grade 5 polymyositis and Grade 5 neuromuscular disorder [verbatim term]). Ten of the 11 subjects died within 90 days after the last dose.

Table 2 Rate Summary of all Adverse Events in the Q4W Cohorts, As-treated Population, Study D4190C00006

Adverse Event Outcome (MedDRA V 17.1)	M3/T1 (N=12) n (%)	M10/T1 (N=3) n (%)	M15/T1 (n+12) (n %)	M10/T3 (N=3) n (%)	M20/T1 (N=11) n (%)	M15/T3 (N=11) n (%)	M15/ T10 (N=9) n (%)	M20/ T3 (N=6) n (%)	Total (N=58) n (%)
1 or more event	3 (100)	3 (100)	12 (100)	3 (100)	7 (63.6)	11 (100)	9 (100)	6 (100)	54 (93.1)
1 or more Grade 3 event	0	2 (66.7)	9 (75.0)	3 (100)	3 (27.3)	5 (45.5)	7 (77.8)	6 (100)	35 (60.3)
1 or more Grade 4 event	0	1 (33.3)	1 (8.3)	1 (33.3)	1 (9.1)	0	0	1 (16.7)	5 (8.6)
1 or more serious event	1 (33.3)	2 (66.7)	7 (58.3)	2 (66.7)	2 (18.2)	7 (63.60)	7 (77.8)	6 (100)	34 (58.6)
1 or more event leading to discontinuation of study drug	1 (33.3)	1 (33.3)	2 (16.7)	2 (66.7)	0	5 (45.5)	3 (33.3)	5 (83.3)	19 (32.8)
Death	0	1 (33.3)	1 (8.3)	0	0	2 (18.2)	0	2 (33.3)	6 (10.3)
1 or more related event	1 (33.3)	3 (100)	7 (58.3)	3 (100)	7 (63.6)	9 (81.8)	8 (88.9)	5 (83.3)	43 (74.1)
1 or more ≥ Grade 3 related event	0	2 (66.7)	5 (41.7)	2 (66.7)	2 (18.2)	4 (36.4)	4 (44.4)	5 (83.3)	24 (41.4)
1 or more related serious event	0	1 (33.3)	3 (25.0)	2 (66.7)	2 (18.2)	5 (45.5)	4 (44.4)	5 (83.3)	22 (37.9)
1 or more related event leading to discontinuation of study drug	0	1 (33.3)	1 (8.3)	2 (66.7)	0	4 (36.4)	3 (33.3)	4 (66.7)	15 (25.9)
Death related to study drug	0	1 (33.3)	0	0	0	0	0	1 (16.7)	2 (3.4)

MedDRA Medical Dictionary for Regulatory Activities; M(x)/T(y) MEDI4736 (x) mg/kg and tremelimumab (y) mg/kg; Q4W every 4 weeks.

Table 3 Rate Summary of all Adverse Events in the Q2W Cohorts, As-treated Population, Study D4190C00006

Adverse Event Outcome (MedDRA V 17.1)	M10/T1 (N=6) n (%)	M10/T3 (N=10) n (%)	Total (N=16) n (%)
1 or more event	2 (33.3)	6 (60.0)	8 (50.0)
1 or more Grade 3 event	2 (33.3)	4 (40.0)	6 (37.5)
1 or more Grade 4 event	0	0	0
1 or more serious event	1 (16.7)	5 (50.0)	6 (37.5)
1 or more event leading to discontinuation of study drug	1 (16.7)	1 (10.0)	2 (12.5)
Death	1 (16.7)	1 (10.0)	2 (12.5)
1 or more related event	1 (16.7)	6 (60.0)	7 (43.8)
1 or more ≥ Grade 3 related event	0	2 (20.0)	2 (12.5)
1 or more related serious event	0	4 (40.0)	4 (25.0)
1 or more related event leading to discontinuation of study drug	0	1 (10.0)	1 (6.30)
Death related to study drug	0	0	0

MedDRA Medical Dictionary for Regulatory Activities; M(x)/T(y) MEDI4736 (x) mg/kg and tremelimumab (y) mg/kg; Q2W every 2 weeks.

In terms of efficacy, early signs of clinical activity have been noted with the combination.

Limited efficacy data are available for Study D4190C00006. A total of 53 of 74 subjects were evaluable for efficacy with at least 8-weeks of follow-up. Of these, there were 12 subjects (23%) with PR, 14 subjects (26%) with SD, and 19 subjects (36%) with progressive disease (PD).

In Study D4190C00006, PK (n=55), ADA (n=60), and soluble PD-L1 (sPD-L1; n=69) data were collected from 10 cohorts following Q4W or Q2W regimens. An approximately dose-proportional increase in PK exposure (maximum plasma concentration [Cmax] and area under the plasma drug concentration-time curve from time zero to Day 28 post-dose [AUC0-28day]) of both MEDI4736 and tremelimumab was observed over the dose range of 3 to 20 mg/kg MEDI4736 Q4W or Q2W and 1 to 10 mg/kg tremelimumab Q4W. The observed PK exposures of MEDI4736 and tremelimumab following combination were in line with respective monotherapy data, indicating no PK interaction between these 2 agents.

Four of 60 patients (2 at 15 mg/kg MEDI4736 Q4W + 10 mg/kg tremelimumab Q4W, one each at 15 mg/kg MEDI4736 Q4W + 1 mg/kg tremelimumab Q4W and 10 mg/kg MEDI4736 Q4W + 3 mg/kg tremelimumab Q4W) were ADA positive for either anti-MEDI4736 or anti-tremelimumab antibodies post treatment. MEDI4736 PK was impacted in only 2 of 4 patients following 15 mg/kg MEDI4736 Q4W + 1 mg/kg tremelimumab Q4W and 15 mg/kg MEDI4736 Q4W + 10 mg/kg tremelimumab Q4W. 1 of 53 patients (15 mg/kg MEDI4736 Q4W + 1 mg/kg tremelimumab Q4W) was ADA positive with no impact on PK.

Following MEDI4736 in combination with tremelimumab, complete sPD-L1 suppression (surrogate for PD-L1 targeting) was observed in almost all patients over the dose range of 3 to 20 mg/kg MEDI4736 Q4W or Q2W. Two patients (1 patient each at 10 mg/kg MEDI4736 Q4W + 1 mg/kg tremelimumab Q4W and 15 mg/kg MEDI4736 Q4W + 1 mg/kg tremelimumab Q4W), showed partial sPD-L1 suppression at some visits followed by complete suppression after repeated dosing. One patient following 15 mg/kg MEDI4736 Q4W + 10 mg/kg tremelimumab Q4W showed partial suppression on Day 29 and was ADA positive with an impact on PK. No clear dose-dependent changes in sPD-L1 were identified over the dose range of 3 to 20 mg/kg MEDI4736 Q4W or Q2W.

Cohort 4 (20 mg/kg MEDI4736 and 1 mg/kg Tremelimumab)
In the 20 mg/kg MEDI4736 and 1 mg/kg tremelimumab (M20/T1) cohort, 11 subjects have received 1-5 doses of tremelimumab and MEDI4736. Seven subjects (63.6%) reported at least 1 AE. Adverse events reported by more than 1 subject were fatigue (4 subjects) and diarrhea, blood thyroid stimulating hormone increased, decreased appetite, and dizziness (2 subjects each). All 7 of these subjects reported at least 1 treatment-related AE, with each event reported by 1 subject each.

Three subjects (27.3%) experienced Grade 3 or higher AEs regardless of causality. These events were sepsis, alanine aminotransferase increased, aspartate aminotransferase increased, blood potassium decreased, hemoglobin decreased, lipase increased, platelet count decreased, and sciatica (1 subject each). Two of the 3 subjects experienced Grade 3 or higher AEs that were treatment-related. These AEs were sepsis, alanine aminotransferase increased, aspartate aminotransferase increased, lipase increased, and platelet count decreased (1 subject each).

Two subjects (18.2%) experienced a total of 6 SAEs (colitis, sepsis, increased alanine aminotransferase, increased aspartate aminotransferase, decreased platelet count, and depressed level of consciousness).

There were no AEs leading to treatment discontinuation. No subject in this cohort died due to an AE.

A total of 5 of 11 subjects were evaluable for efficacy with at least 8-weeks of follow-up. Of these, there were 2 subjects (40%) with PR, 1 subject (20%) with SD, and 1 subject (20%) with PD.

Overall, the safety profile of 20 mg/kg MEDI4736 in combination with 1 mg/kg tremelimumab continues to be manageable. The safety profile in addition to the efficacy seen

supports further development of the combination at a dose of 20mg/kg MEDI 4736 and tremelimumab 1 mg/kg q4w during the combination portion of treatment.

1.1.6 Rationale for conducting this study

Patients with recurrent or metastatic SCCHN who have progressed during or after treatment with a platinum-containing regimen for recurrent or metastatic disease have poor prognosis with limited standard-of-care therapeutic options, which only have transient and limited benefit (ORR: 4% to 13%, progression-free survival [PFS]: 2.5 months, and OS: 5.5 months) (Shin and Khuri 2013, Vermorken et al 2008). Thus, there is a significant unmet medical need for additional treatment options for use in this patient population.

MEDI4736, an antibody that blocks the interaction between PD-L1 and its receptors, may relieve PD-L1-dependent immunosuppressive effects and, therefore, enhance the cytotoxic activity of anti-tumor T-cells. This hypothesis is supported by emerging clinical data from other mAbs targeting the PD-L1/PD-1 pathway which provide early evidence of clinical activity and a manageable safety profile (Brahmer et al 2012, Topalian et al 2012). In addition, although clinical experience with MEDI4736 is limited, currently available data from Study 1108 indicates encouraging response rates (RRs) and duration of response (DoR) with a manageable safety profile in patients with a variety of solid malignancies, including patients with SCCHN treated with MEDI4736 as monotherapy.

Tremelimumab, an anti-CTLA-4 targeting agent that blocks the interaction with CD80 and CD86, may help prolong and enhance T-cell activation and expansion. This hypothesis is supported by emerging clinical data from both tremelimumab studies (Kirkwood et al 2010, Ribas et al 2013) and studies with a related anti-CTLA-4 antibody, ipilimumab. However, data for tremelimumab monotherapy in SCCHN are not available.

The rationale for evaluating the combination of MEDI4736 + tremelimumab is supported both by preclinical and clinical data, including safety and tolerability data. Mouse models of transplantable solid tumors using surrogate antimouse antibodies show superior antitumor activity of combination therapy as compared to monotherapy. Furthermore, the CTLA-4 and PD-1/PD-L1 pathways are non-redundant, suggesting that targeting both may have additive or synergistic activity. Last, the combination of CTLA-4 and PD-1 blockades in melanoma has been shown to result in higher ORRs and 1-year survival compared to either agent alone (Wolchok et al 2013).

Based on the preliminary clinical efficacy and safety data observed in patients with solid tumors, including advanced SCCHN, in Study 1108 with MEDI4736 monotherapy and in patients with NSCLC in Study D4190C00006 with MEDI4736 + tremelimumab, the Sponsor plans a comprehensive development program of MEDI4736 in the SCCHN indication. The objective of this program is to determine the activity of MEDI4736 as monotherapy in patients with SCCHN and also to establish the role of MEDI4736 in combination with tremelimumab and other investigational agents and therapies in patients with SCCHN. The preliminary efficacy, safety, and tolerability data of the MEDI4736 + tremelimumab combination in Study D4190C00006 support the development of this combination in SCCHN. This Phase II

study will determine the activities of MEDI4736 and tremelimumab as a combination therapy in PD-L1-negative SCCHN patients, as well as the efficacy of MEDI4736 + tremelimumab combination therapy versus MEDI4736 or tremelimumab monotherapy.

1.2 Rationale for study design, doses, and control groups

In this study, the safety and efficacy of MEDI4736, tremelimumab, and MEDI4736 + tremelimumab combination therapy are being evaluated in patients with recurrent or metastatic SCCHN who have progressed during or after treatment with only 1 systemic palliative regimen for recurrent or metastatic disease that must have contained a platinum agent.

1.2.1 Rationale for combining MEDI4736 and tremelimumab

Cancer evades immune recognition using several distinct mechanisms. Efficacious interventions to start and sustain an immune response will likely require a number of agents to simultaneously or sequentially trigger several immune mechanisms. Although master switches controlling various functions may exist, achievement of a curative immune response may ultimately demand the combined actions of several therapeutic components. Synergy occurs when drugs interact in ways that enhance the therapeutic effect. In cancer immunotherapy, agents that have limited therapeutic effects as single agents can be powerful when combined. Combining immunotherapy agents has been shown to result in improved response rates relative to those for monotherapy. For example, the concurrent administration of nivolumab and ipilimumab to patients with advanced melanoma induced higher ORRs than those obtained with single-agent therapy. Furthermore, responses appeared to be rapid, deep, and durable (Wolchok et al 2013).

Multiple lines of evidence suggest that SCCHN tumors create a highly immunosuppressive environment and may be amenable to therapeutic intervention with immune-modulating agents. The rationale for combining MEDI4736 and tremelimumab is that the mechanisms of CTLA-4 and PD-1 are non-redundant, suggesting that targeting both pathways may have additive or synergistic activity (Pardoll 2012), resulting in higher response rates in SCCHN. Support for this is seen in mouse syngeneic models of transplantable solid tumors demonstrating superior anticancer activity of the combination therapy compared with monotherapy. Additional support has been observed in the preliminary efficacy data available for Study D4190C00006 (see Section 1.3.1.3).

1.2.2 Dose rationale

1.2.2.1 MEDI4736 monotherapy dose rationale

A MEDI4736 dose of 10 mg/kg q2w up to a maximum of 12 months is recommended for further development.

The proposed dose of 10 mg/kg q2w is supported by multiple lines of evidence including: in-vitro data, non-clinical activity, clinical PK/pharmacodynamic, biomarkers, and activity data (ongoing Study 1108). Although clinical activity has been observed at lower doses, no DLTs were observed up to a dose of 10 mg/kg q2w or 15 mg/kg every 3 weeks. The proposed

dosing regimen of 10 mg/kg q2w is expected to (a) achieve a target median concentration of ~100 µg/mL (identified based on preclinical and clinical data); (b) account for anticipated variability in PK, pharmacodynamic, and clinical activity in diverse cancer population; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal anti-tumor activity in animal model.

Based on PK/pharmacodynamic data from ongoing Study 1108 with dose ranging from 0.1 to 10 mg/kg q2w or 15 mg/kg every 3 weeks, MEDI4736 exhibited non-linear (dose-dependent) PK consistent with target mediated drug disposition. PK approached linearity at ≥3 mg/kg q2w dose, suggesting near complete target saturation (membrane bound and soluble PD-L1). The expected mean trough concentration following 3 mg/kg q2w is ~50 µg/mL. The expected $t_{½}$ with doses ≥3 mg/kg q2w is approximately 21 days. A dose-dependent suppression in peripheral soluble PD-L1 was observed over the dose range studied, consistent with engagement of MEDI4736 with PD-L1. PK simulations indicate that following 10 mg/kg q2w dose of MEDI4736, >90% patients are expected to maintain PK exposure yielding full target saturation throughout the dosing interval.

Data generated during the dose-escalation phase of Study 1108 also suggest that higher doses (ie, 10 mg/kg q2w) may be associated with better clinical activity while still providing an acceptable safety profile. Dose-related changes in a variety of peripheral biomarkers have been observed over the dose range of 0.1 to 3 mg/kg q2w. Thus far, a low level of immunogenicity has been observed. Three of 31 patients were detected ADA positive with an evidence of impact on PK and target suppression in only 1 individual.

1.2.2.2 Tremelimumab monotherapy dose rationale

The tremelimumab dose employed in this study will be 10 mg/kg tremelimumab via IV infusion q4w for 7 doses then q12w for 2 additional doses (up to 9 doses in total) for up to 12 months. The proposed dosing regimen is currently being evaluated in Phase IIb study in patients with mesothelioma.

The selected dose and schedule is informed by safety and efficacy data on tremelimumab that showed a relationship between exposure and survival in the advanced melanoma studies. Tremelimumab has been administered to approximately 1000 patients at doses of 10 mg/kg q4w or 15 mg/kg q12w. A retrospective exposure and survival analysis of 293 patients treated with tremelimumab in a Phase III study in patients with melanoma showed better OS in patients with higher exposure. The median OS was 18.4 months for the high-AUC (≥123665 µg·hr/mL) group compared to 9.0 months for the low-AUC (<123665 µg·hr/mL) group (hazard ratio [HR] 0.5; p<0.001).

The target trough concentration of tremelimumab is estimated to be approximately 30 µg/mL based on enhanced interleukin (IL)-2 release (in vitro) and anti-tumor activity (in vivo) in pre-clinical studies. PK simulations indicate that following tremelimumab administration at a dose of 10 mg/kg q4w, approximately 90% of patients are expected to be above the target concentration of approximately 30 µg/mL compared to approximately 50% with 15 mg/kg q12w. Therefore, the current study in patients with SCCHN will use a dosing regimen of

10 mg/kg q4w followed by 10 mg/kg q12w to maximize exposure to tremelimumab while managing safety according to the established guidelines（Weber et al 2012）.

1.2.2.3 MEDI4736 + tremelimumab combination therapy dose rationale

Based on preliminary safety and efficacy data from MEDI4736 + tremelimumab combination therapy in Study D4190C00006, MEDI4736 20 mg/kg q4w for 4 doses and tremelimumab 1 mg/kg q4w for 4 doses will be administered. After completion of the initial 4 doses of combination therapy, single agent MEDI4736 will continue at 10 mg/kg q2w to complete 12 months of therapy (up to an additional 18 doses with the final dose at Week 50). The first MEDI4736 dose at 10 mg/kg q2w will be 4 weeks after the final dose of the combination of tremelimumab and MEDI4736 at 20 mg/kg.

Preliminary safety data from Study D4190C00006 as of 27 January 2015 show a manageable safety profile in an advanced/metastatic NSCLC patient population using defined guidelines. The most frequent treatment-emergent adverse events (TEAEs) considered treatment-related by the Investigator were fatigue, colitis, diarrhea, AST or ALT increases, amylase and lipase increases, rash and pruritus and other immune-mediated reactions, which were mostly reversible and manageable by the available protocol treatment guidelines.

In the 20 mg/kg MEDI4736 and 1 mg/kg tremelimumab (M20/T1) cohort, 11 subjects have received 1-5 doses of tremelimumab and MEDI4736. Seven subjects (63.6%) reported at least 1 AE. Adverse events reported by more than 1 subject were fatigue (4 subjects) and diarrhea, blood thyroid stimulating hormone increased, decreased appetite, and dizziness (2 subjects each). All 7 of these subjects reported at least 1 treatment-related AE, with each event reported by 1 subject each.

Three subjects (27.3%) experienced Grade 3 or higher AEs regardless of causality. These events were sepsis, alanine aminotransferase increased, aspartate aminotransferase increased, blood potassium decreased, hemoglobin decreased, lipase increased, platelet count decreased, and sciatica (1 subject each). Two of the 3 subjects experienced Grade 3 or higher AEs that were treatment-related. These AEs were sepsis, alanine aminotransferase increased, aspartate aminotransferase increased, lipase increased, and platelet count decreased (1 subject each).

Two subjects (18.2%) experienced a total of 6 SAEs (colitis, sepsis, increased alanine aminotransferase, increased aspartate aminotransferase, decreased platelet count, and depressed level of consciousness).

There were no AEs leading to treatment discontinuation. No subject in this cohort died due to an AE.

In Study D4190C00006, PK (n=55), ADA (n=60), and soluble PD-L1 (sPD-L1; n=69) data were collected from 10 cohorts following q4w or q2w regimens. An approximately dose-proportional increase in PK exposure (maximum plasma concentration [C_{max}] and area under the plasma drug concentration-time curve from time zero to Day 28 post-dose [$AUC_{0\text{-}28day}$]) of both MEDI4736 and tremelimumab was observed over the dose range of 3 to 20 mg/kg

MEDI4736 q4w or q2w and 1 to 10 mg/kg tremelimumab q4w. The observed PK exposures of MEDI4736 and tremelimumab following combination were in line with respective monotherapy data, indicating no PK interaction between these 2 agents.

Four of 60 patients (2 at 15 mg/kg MEDI4736 q4w + 10 mg/kg tremelimumab q4w, one each at 15 mg/kg MEDI4736 q4w + 1 mg/kg tremelimumab q4w and 10 mg/kg MEDI4736 q4w + 3 mg/kg tremelimumab q4w) were ADA positive for either anti-MEDI4736 or anti-tremelimumab antibodies post treatment. MEDI4736 PK was impacted in only 2 of 4 patients following 15 mg/kg MEDI4736 q4w + 1 mg/kg tremelimumab q4w and 15 mg/kg MEDI4736 q4w + 10 mg/kg tremelimumab q4w. 1 of 53 patients (15 mg/kg MEDI4736 q4w + 1 mg/kg tremelimumab q4w) was ADA positive with no impact on PK.

Following MEDI4736 in combination with tremelimumab, complete sPD-L1 suppression (surrogate for PD-L1 targeting) was observed in almost all patients over the dose range of 3 to 20 mg/kg MEDI4736 Q4W or q2w. In 2 patients (1 patient each at 10 mg/kg MEDI4736 q4w + 1 mg/kg tremelimumab q4w and 15 mg/kg MEDI4736 q4w + 1 mg/kg tremelimumab q4w), showed partial sPD-L1 suppression at some visits followed by complete suppression after repeated dosing. One patient following 15 mg/kg MEDI4736 q4w + 10 mg/kg tremelimumab q4w showed partial suppression on Day 29 and was ADA positive with an impact on PK. No clear dose-dependent changes in sPD-L1 were identified over the dose range of 3 to 20 mg/kg MEDI4736 q4w or q2w.

A total of 5 of 11 subjects in the 20/1 cohort were evaluable for efficacy with at least 8 weeks of follow-up. Of these, there were 2 subjects (40%) with PR, 1 subject (20%) with SD, and 1 subject (20%) with PD.

Overall, the safety profile of 20 mg/kg MEDI4736 in combination with 1 mg/kg tremelimumab continues to be manageable. Based upon the available safety, efficacy, and PK/pharmacodynamic data to date, MEDI4736 20 mg/kg q4w and tremelimumab 1 mg/kg q4w was selected as the dosing regimen for this clinical trial.

1.2.3 Rationale for retreatment option

Patients who achieve and maintain disease control (ie, complete response [CR], PR, or SD) through the end of the 12-month treatment period may restart treatment with IP upon evidence of PD during follow-up (maximum of 12 months of further treatment). Only patients who the Investigator determines do not have any significant, unacceptable, or irreversible toxicities and would continue to receive benefit from therapy can continue to receive therapy through progression or restart a second 12 months of retreatment upon PD. Patients with confirmed progression in the MEDI4736 or tremelimumab monotherapy arm or in the combination portion of therapy in the MEDI4736 + tremelimumab arm cannot continue therapy or obtain retreatment if progression occurred after confirmed response in the target lesions (ie, the response and progression events both occurred while receiving active IP during the same treatment period in the target lesions). Retreatment in the combination arm can only occur if PD occurs during the monotherapy portion or after completion of 12 months of therapy. During the retreatment period, the patient in the combination arm would resume MEDI4736

dosing at 20 mg/kg q4w as during the initial induction period along with 1 mg/kg of tremelimumab q4w for 4 doses. Monotherapy with MEDI4736 would then resume at 10 mg/kg q2w 4 weeks after the last combination dose is administered for a total of up to 18 additional doses with the final dose at Week 50. Patients in the MEDI4736 monotherapy arm would resume 10 mg/kg MEDI4736 q2w for an additional 12 months of therapy. Similarly patients in the tremelimumab monotherapy arm would resume 10 mg/kg q4w for 7 doses then q12w for 2 additional doses for an additional 12 months of therapy. Retreatment can only occur once through the course of the study.

Several potential mechanisms of resistance to IMT exist, including loss of T-cell "memory" or recurrence of immune escape, which are consistent with the option of retreatment for patients who initially respond and then progress. In contrast to patients treated with chemotherapy, who are unlikely to respond to rechallenge with the same agent upon progression, responses have been observed upon retreatment with IMTs. Preliminary data in patients previously treated with IMTs, suggest that responses are similar to those observed following initial treatment (Forde et al 2014, Hodi et al 2010).

This evidence suggests that a retreatment option may be beneficial in this population.

1.2.4 Study population rationale

This study will enroll patients with recurrent or metastatic SCCHN who have progressed during or after treatment with only 1 systemic palliative regimen for recurrent or metastatic disease that must have contained a platinum agent. Over two-thirds of SCCHN cases are diagnosed at an advanced stage (Stages III to IV), although the stage distribution of SCCHN varies significantly by anatomical site. About 15% of patients with SCCHN are diagnosed with a metastatic disease (Siegel et al 2014). Five-year survival for local disease (83% for oral cavity and pharynx and 75% for larynx) is better than for regional disease (60% and 43%, respectively) and 5-year survival for distant disease (37% and 35%, respectively; NCI SEER statistics). In the recurrent or metastatic setting, ORRs of approximately 20% to 35% and OS of 7 to 11 months have been achieved with platinum-based chemotherapy (Vermorken et al 2008, Vermorken and Specenier 2010). The management of patients who have failed prior treatment is even more challenging, with currently available therapies providing ORRs ranging from approximately 4% with methotrexate to 13% with cetuximab and a median PFS of approximately 2.5 to 3 months (Shin and Khuri 2013, Vermorken et al 2008). Median OS in advanced recurrent/metastatic disease is approximately 6 months (Shin and Khuri 2013, Vermorken et al 2008).

Patients with recurrent or metastatic disease who have progressed during or after treatment with a platinum-containing regimen for recurrent or metastatic disease are appropriate candidates for a clinical study, as an unmet medical need exists for these patient populations given that available treatment options provide limited clinical benefit while being associated with significant toxicity.

Current experience with single-agent IMT studies suggests that clinical responses may be restricted to a subset of any given patient population and that it might be beneficial to enrich

the patient population by selecting patients likely to respond to therapy. To date, no assay has been established or validated, and no single approach has proven accurate for patient enrichment for IMTs. However, independent data from multiple sources using different assays and scoring methods suggests that PD-L1 expression on tumor cells and/or tumor-infiltrating cells may be associated with greater clinical benefit.

Data from ongoing studies with MEDI4736 and other agents targeting the PD-1/PD-L1 pathway suggest, as shown in a number of tumor types (eg, NSCLC, renal cell carcinoma, and melanoma), that monotherapy may be more efficacious in patients who are PD-L1-positive.

For example, data presented by Roche at the Annual Meeting of the American Society of Clinical Oncology 2013 (Powderly et al 2013) suggested that PD-L1 expression in NSCLC, melanoma, and renal cell carcinoma patient cohorts is associated with greater clinical benefit from anti-PD-L1 treatment. Using a proprietary assay for PD-L1 immunohistochemistry (IHC), a 36% ORR was observed in patients who had PD-L1–positive tumors, with 50% of patients with PD-L1-positive tumors having SD and 33% having PRs. In contrast, in patients with PD-L1-negative tumors, only a 13% ORR was observed, with 28% of patients having SD and 13% having PRs. Similarly, in data presented at the Annual Meeting of the American Society of Clinical Oncology 2013 by Bristol-Myers Squibb (Grosso et al 2013), PD-L1 staining, when assessed using a different method and scoring algorithm, appeared to be associated with greater clinical benefit in patients treated with nivolumab (anti-PD-1). A 44% ORR was observed in patients with PD-L1 positive tumors versus a 17% ORR in patients with PD-L1 negative tumors. Additionally, patients with tumors that were PD-L1 positive had a higher PFS (9.1 versus 2.0 months) and OS than patients with PD-L1 negative tumors (21 versus 12 months). Also, in a data set presented by Merck & Co at the World Conference on Lung Cancer (Garon et al 2013), analysis of the relationship between PD-L1 expression status and RRs in a cohort of patients with NSCLC indicated that tumor samples displaying high levels of PD-L1 expression (according to their assay criteria) were associated with RRs of 67% (6/9; per immune-related response criteria [irRC]) and 57% (4/7; per Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST 1.1]). In contrast, tumor samples expressing zero/low levels of PD-L1 were associated with RRs of 4% (1/24; per irRC) and 9% (2/22; per RECIST 1.1).

Similar data have also been presented by Merck & Co at the 2014 American Society of Clinical Oncology Meeting (Seiwert et al 2014) in patients with recurrent or metastatic SCCHN treated with an inhibitor of the PD-1/PD-L1 pathway, where patients with PD-L1 expression above a cut point had a 45.5% RR as opposed to an 11.4% RR in patients with levels of PD-L1 expression below the cut point, further suggesting that higher levels of PD-L1 expression may correlate with a better likelihood of clinical benefit. Preliminary data presented by AstraZeneca at the American Society for Clinical Oncology Meeting in 2014 (Segal et al 2014) also indicate that patients with PD-L1-positive tumors, ie, $\geq$25% tumoral membrane staining for PD-L1, had an overall RR of 22% when treated with MEDI4736 monotherapy, as opposed to patients with PD-L1-negative tumors, with 0-24% tumoral membrane staining for PD-L1, who had a 4% RR. In particular, patients with PD-L1-positive NSCLC had an RR of 39% and 5% in patients with PD-L1-negative tumors; the RR in

patients with SCCHN was 50% and 6% in PD-L1-positive and PD-L1-negative tumors, respectively.

Given these findings, a number of ongoing studies are assessing the activity of agents in patients with PD-L1–positive tumors. There is also, however, a significant unmet medical need in patients with PD-L1–negative tumors that needs to be addressed, and this need is particularly acute because the many of the agents currently in development focus on patients with PD-L1–positive tumors. Based on the data from ongoing studies, the likelihood of response to MEDI4736 monotherapy appears to be higher in PD-L1-positive patients. However, these data are still preliminary, only a relatively small number of patients with SCCHN have been treated with PD-1/PD-L1 directed therapies, and evidence of activity has also been reported in PD-L1-negative patients. Therefore, this study will focus enrollment on PD-L1-negative patients for all treatment groups, with the goal to assess objective responses with MEDI4736 or tremelimumab monotherapy and with combination of MEDI4736+Tremelimumab.

While anti-PD-1/PD-L1 agents may not be as effective in patients with PD-L1-negative tumors when given as monotherapy, and given that anti-CTLA-4 antibodies given as monotherapy have consistently shown modest RRs (5% to 12%) across different tumor types (Hodi et al 2010, Ribas et al 2013), there are compelling non-clinical and clinical data (Wolchok et al 2013) to suggest that combining agents within this class may have powerful synergistic effects. Thus, patients with low or no expression of PD-L1 in their tumors may be more likely to respond to the combination of MEDI4736 + tremelimumab than MEDI4736 monotherapy. In order to test this hypothesis in a Phase II setting, this study will focus on enrollment of those patients with PD-L1-negative tumors to all 3 treatment arms.

1.2.5 Rationale for endpoints

The primary aim of this study is to determine the efficacy of MEDI4736 monotherapy, tremelimumab monotherapy, and MEDI4736 + tremelimumab combination therapy in terms of ORR. ORR can be a useful endpoint in single arm studies because it is a direct measure of the drug's anti-tumor activity (Pazdur 2008). The use of ORR in the setting of recurrent/metastatic SCCHN, especially when the responses are sustained and durable (a key feature of immunotherapy), is justified because it is anticipated that it will serve as an early measure of clinical benefit that may be confirmed by the survival endpoints employed in a randomized confirmatory study. The kinetics of anti-PD-L1 response also favor the use of ORR as a potential surrogate endpoint, because response may occur as early as the first 6 weeks of treatment (earlier than other immunotherapeutic agents such as anti-CTLA-4) (Brahmer et al 2012, Spigel et al 2013). In patients treated with immunotherapies, including MEDI4736, responses appear to be durable, reinforcing the importance of ORR as a likely surrogate for clinical benefit.

Anti-tumor activity will be assessed according to RECIST 1.1 guidelines. The analysis of ORR will be programmatically derived ORR based on a Blinded Independent Central Review (BICR) assessment according to RECIST 1.1. The study has been sized to characterize the ORR of MEDI4736 monotherapy, tremelimumab monotherapy, and MEDI4736 +

tremelimumab combination therapy in patients with recurrent or metastatic SCCHN with PD-L1-negative tumors.

The secondary efficacy endpoints of DoR, disease control rate (DCR), best objective response (BoR), PFS, and OS are being examined to further evaluate the anti-tumor effect of MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, and tremelimumab monotherapy. DoR, DCR, BoR, and PFS will be assessed following the same analyses as ORR. In addition, ORR, DoR, DCR, BoR, and PFS will be evaluated in a secondary analysis using BICR assessments according to irRECIST 1.1.

Anti-tumor activity will be evaluated by irRECIST 1.1 as a secondary endpoint in order to assess the utility of modified RECIST 1.1 criteria in capturing the true clinical benefit of MEDI4736 and tremelimumab. Using irRECIST 1.1 will allow taking into account the unique kinetics of responses that have been observed and well characterized with this class of agents, including in the ongoing Study 1108. This includes patients who have RECIST 1.1 tumor shrinkage and the appearance of new lesions, as well as patients who present initially with an increase in tumor burden followed by a regression. Even patients who have PD, based on RECIST 1.1 criteria, either because of ≥20% increase in tumor lesions or appearance of new lesions, may still derive significant clinical benefit from treatment with IMT agents. Therefore, there is a need to develop new assessment tools that would allow to better capture the potential clinical benefit for patients treated with IMT, which may be different from the paradigm used for patients treated with chemotherapy and/or targeted therapy, for which the RECIST criteria were originally developed.

The secondary health-related quality of life (QoL) assessments (the European Organisation for Research and Treatment of Cancer [EORTC] 30-item core quality of life questionnaire, version 3 [QLQ-C30 v3] and 35-item head and neck quality of life questionnaire [QLQ-H&N35]) will show the overall influence of the benefits and toxicity of the treatment from a patient's perspective and will aid in understanding of the benefit/risk evaluation. These patient-reported outcome (PRO) questionnaires are well-established instruments that have been previously included in cancer clinical trials.

The PK of MEDI4736 and tremelimumab is being examined to assess the PK of both agents when administered in combination. Immunogenicity will be examined to determine the anti-MEDI4736 and anti-tremelimumab antibodies and their potential impact on PK, PD, safety, and efficacy parameters. Biological samples will be used to explore potential biomarkers in tumor, plasma, and/or serum, which may influence the progression of cancer (and associated clinical characteristics) and/or response. Blood samples will be taken to allow for future exploratory research into genes or genetic factors that may influence response of MEDI4736, tremelimumab, or MEDI4736 + tremelimumab and/or agents used in combination and/or as comparators (pharmacogenetic research optional [DNA element]).

1.2.6 Rationale for the overall survival extension period

Robust demonstration of long-term OS benefit of new drugs under investigation is critical to many payers of health care. Extending the OS data collection in this study will be used in

submissions to health care payers to provide supportive and more mature evidence of OS with use of these drugs.

1.3 Benefit/risk and ethical assessment

The following sections include summaries of the potential benefits and risks associated with MEDI4736 monotherapy, tremelimumab monotherapy, and MEDI4736 + tremelimumab combination therapy, respectively, prior to the overall benefit/risk assessment.

1.3.1 Potential benefits

1.3.1.1 MEDI4736

Patients are being enrolled in 10 ongoing clinical studies of MEDI4736 (5 employing MEDI4736 as monotherapy and 5 as combination therapy). No studies have yet been completed. Recent data are available for patients with SCCHN in the expansion cohort of Study 1108. Out of 54 SCCHN patients treated with MEDI4736 as monotherapy at 10 mg/kg q2w, disease assessments are currently available for 41 patients. Of those 41 patients, 12 have evidence of radiographic decreases in their target lesions. Four patients have achieved a PR (confirmed + unconfirmed) by RECIST 1.1, and 2 additional patients have >30% decrease in target lesions compared to baseline with simultaneous appearance of a new lesion. Radiographic responses have been observed as early as the first disease assessment at 6 weeks and in patients with both HPV-positive and HPV-negative tumors. Assessment of response according to PD-L1 expression is ongoing. Thus far, 12 of the 41 patients followed for at least 6 weeks have PD-L1-positive tumor as determined by an in-house IHC assay. Of those 12 patients, 6 have tumor reduction, including 3 with >30% decrease in target lesions.

Fifteen of the 54 SCCHN patients dosed with MEDI4736 have been assessed to be PD-L1 positive by a proprietary IHC assay to date. Of those 15 patients, disease assessment data are available for 8 patients, of which 4 have SD or PR. Further assessments of a correlation between clinical benefit and expression of PD-L1 within the tumor microenvironment are ongoing.

1.3.1.2 Tremelimumab

Across the clinical development program for tremelimumab, a limited pattern of efficacy as a single agent has been observed; this pattern has been also observed for the related anti-CTLA-4 antibody, ipilimumab, which appears to be consistent across tumor types for this mechanism of action. RRs to anti-CTLA-4 antibodies are generally low at approximately 10%. However, in patients who respond, the responses are generally durable, lasting several months even in those with aggressive tumors, in particular refractory metastatic melanoma. Moreover, survival benefit was reported even in patients without radiographic regression in tumor burden.

In a single-arm, Phase II study (Study A3671008) of tremelimumab administered at 15 mg/kg every 90 days to patients with refractory melanoma, an RR of 7% and a median OS of 10 months in the second-line setting (as compared to approximately 6 months with best supportive care reported from a retrospective analysis; [Korn et al 2008]) were observed

(Kirkwood et al 2010). In a randomized, open-label, first-line Phase III study of tremelimumab (administered at 15 mg/kg every 90 days) versus chemotherapy (dacarbazine or temozolomide) in advanced melanoma (Study A3671009), results of the final analysis showed an RR of 11% and a median OS of 12.58 months in this first-line setting as compared to 10.71 months with standard chemotherapy (Ribas et al 2013).

Additionally, in a Phase II maintenance study (Study A3671015) in patients with Stage IIIB or IV NSCLC that have responded or remained stable, PFS at 3 months was 22.7% in the tremelimumab arm (15 mg/kg) compared with 11.9% in the best supportive care arm (Study A3671015).

1.3.1.3 MEDI4736 + tremelimumab

Available data suggest that the combination of agents targeting PD-1/PD-L1 and CTLA-4 may have profound and durable benefit in patients with melanoma. Preliminary efficacy data are available for Study D4190C00006. A total of 53 of 74 subjects were evaluable for efficacy with at least 8-weeks of follow-up. Of these, there were 12 subjects (23%) with PR, 14 subjects (26%) with SD, and 19 subjects (36%) with PD, as assessed by RECIST 1.1 guidelines (Eisenhauer et al 2009). In a study reported by Wolchok et al., a total of 53 patients received concurrent therapy with nivolumab and ipilimumab (Wolchok et al 2013). The ORR (according to modified World Health Organization [WHO] criteria) for all patients in the concurrent regimen group (nivolumab, 0.3 to 10 mg/kg; ipilimumab, 1 to 10 mg/kg, both once every 3 weeks for 4 and 8 doses, respectively, followed by nivolumab or ipilimumab alone once q12w for 8 doses) was 40%. Evidence of clinical activity (conventional, unconfirmed, or immune-related response or SD for ≥24 weeks) was observed in 65% of patients.

1.3.2 Potential risks

1.3.2.1 MEDI4736

The potential risks, based on the mechanism of action of MEDI4736 as well as data from studies of relevant or similar therapies, include immune-mediated reactions (see Section 6.7.1). Of the patients treated with 10 mg/kg q2w in Study 1108, 121 patients (71.8%) had at least 1 TEAE. The most frequently reported (2 or more patients) treatment-related TEAEs (all NCI CTCAE grades) were fatigue, nausea, dyspnea, diarrhea, vomiting, pyrexia, myalgia, hypothyroidism, decreased appetite, dizziness, cough, pruritus, and rash. Grade ≥3 TEAEs were noted in 44 of 177 patients (24.9%). The events that occurred in more than 1 patient included dyspnea, dehydration, abdominal pain, fatigue, sepsis, increased AST, increased gamma-glutamyltransferase, hyperbilirubinemia, back pain, pulmonary embolism, respiratory failure, and hypotension. For further details on the safety profile of MEDI4736, please refer to the IB.

Other mAbs targeting the PD-1/PD-L1 pathway are currently in clinical development. Among the most frequent TEAEs noted with these antibodies are fatigue, rash, diarrhea, and pruritus. Immune-mediated AEs of Grade ≥3 reported include pneumonitis, diarrhea, increased ALT, and increased AST. Other relevant risks include those associated with biological and immunotherapeutic agents.

1.3.2.2 Tremelimumab

The profile of AEs and the spectrum of event severity have remained stable across the tremelimumab clinical program and are consistent with the pharmacology of the target. To date, no tumor type or stage appears to be associated with unique AEs (except for vitiligo that appears to be confined to patients with melanoma). As of the data cutoff (DCO) date of 30 August 2013, the events reported in the tremelimumab monotherapy studies at a frequency of >5% and assessed by the Investigator as treatment related were diarrhea (41.2%), rash (27.2%), pruritus (25.1%), fatigue (23.8%), nausea (21.9%), vomiting (13.5%), decreased appetite (11.3%), headache (7.2%), pyrexia (7.0%), abdominal pain (6.7%), and colitis (5.5%). The events of diarrhea, rash, and pruritus are considered as identified risks. Infusion-related side effects are rare. Acute renal failure was reported in patients who received the combination of tremelimumab and sunitinib in a Phase I study; however, acute renal failure has not been an expected AE for single-agent tremelimumab. The incidence and/or severity of many of the AEs observed following administration of tremelimumab can be reduced by following current guidelines for the management of immune-related toxicities.

1.3.2.3 MEDI4736 + tremelimumab

Evaluation of the safety of MEDI4736 + tremelimumab in the ongoing Study D4190C00006, in patients with NSCLC, has so far shown a manageable safety and tolerability profile of the combination therapy.

Overall, 62 (83.8%) of the 74 subjects reported an AE regardless of causality. The most frequently (10 or more subjects) reported AEs were fatigue (37.8%; 28 subjects); diarrhea (32.4%; 24 subjects); amylase increased and pruritus (16.2%; 12 subjects); decreased appetite, dyspnea, nausea, and rash (14.9%; 11 subjects each), and headache and pyrexia (13.5%; 10 subjects).

Twenty of the 62 subjects who experienced AEs regardless of causality had events that were Grade 1 or 2 in severity. Forty-two of the 62 subjects reported ≥ Grade 3 events. The most frequently reported ≥ Grade 3 events (in 3 or more subjects) were diarrhea (7 subjects); colitis (6 subjects); increased lipase (4 subjects); and anemia, increased alanine aminotransferase, increased aspartate aminotransferase, dehydration, and pneumonitis (3 subjects each).

Fifty of the 74 subjects reported a treatment-related AE. The most frequently reported treatment-related AEs were fatigue (24.3%; 18 subjects); diarrhea (21.6%; 16 subjects); increased alanine aminotransferase (13.5%, 10 subjects); pruritus (12.2%; 9 subjects); and rash (10.8%; 8 subjects). Twenty-four of the 50 subjects who experienced treatment-related AEs reported Grade 1 or 2 events only. Twenty-six of the 50 subjects reported ≥ Grade 3 events. The most frequently reported treatment-related ≥ Grade 3 events (in 3 or more subjects) were colitis and diarrhea (6 subjects each), increased lipase (4 subjects), and increased alanine aminotransferase, increased aspartate aminotransferase, and pneumonitis (3 subjects each).

Two subjects treated in the Q4W M20/T3 cohort (Cohort 5a) experienced a DLT. These 2 DLTs were the following:

1. Grade 3 increased aspartate aminotransaminase (8 × upper limit of normal) considered also as an SAE that occurred in a 50 year-old female on Cycle 1 Day 29 of treatment. The AE improved to Grade 1 with steroids and resolved.

2. Grade 3 increased amylase levels (considered also as an SAE) and asymptomatic Grade 4 increased lipase that occurred in a 74 year-old female on Cycle 1 Day 9. There was no clinical sequelae per Investigator.

In the 20 mg/kg MEDI4736 and 1 mg/kg tremelimumab (M20/T1) cohort, 11 subjects have received 1-5 doses of tremelimumab and MEDI4736. Seven subjects (63.6%) reported at least 1 AE. Adverse events reported by more than 1 subject were fatigue (4 subjects) and diarrhea, blood thyroid stimulating hormone increased, decreased appetite, and dizziness (2 subjects each). All 7 of these subjects reported at least 1 treatment-related AE, with each event reported by 1 subject each.

Three subjects (27.3%) experienced Grade 3 or higher AEs regardless of causality. These events were sepsis, alanine aminotransferase increased, aspartate aminotransferase increased, blood potassium decreased, hemoglobin decreased, lipase increased, platelet count decreased, and sciatica (1 subject each). Two of the 3 subjects experienced Grade 3 or higher AEs that were treatment-related. These AEs were sepsis, alanine aminotransferase increased, aspartate aminotransferase increased, lipase increased, and platelet count decreased (1 subject each).

Two subjects (18.2%) experienced a total of 6 SAEs (colitis, sepsis, increased alanine aminotransferase, increased aspartate aminotransferase, decreased platelet count, and depressed level of consciousness).

There were no AEs leading to treatment discontinuation. No subject in this cohort died due to an AE.

1.3.3 Overall benefit-risk and ethical assessment

There remains a significant unmet medical need for additional treatment options for patients with recurrent or metastatic SCCHN who have progressed during or after treatment with only 1 systemic palliative regimen for recurrent or metastatic disease that must have contained a platinum agent. Treatment with agents targeting PD-1/PD-L1 or CTLA-4 has shown activity in several tumor types, in a subset of patients deriving meaningful and durable benefit. MEDI4736 has shown clinical activity in patients with recurrent or metastatic SCCHN as a single agent. In addition, preliminary data generated with MEDI4736 + tremelimumab combination therapy in patients with NSCLC have shown promising activity with objective, durable responses. Thus, these agents may potentially offer benefit to this patient population. The study design aims to minimize potential risks, and intensive monitoring, including early safety assessment, is in place for those risks deemed to be most likely based on prior experience with the investigational products (IPs).

The toxicity profile of the combination MEDI4736 + tremelimumab includes fatigue, colitis, diarrhea, AST or ALT increases, amylase and lipase increases, rash and pruritus and other immune-mediated reactions, which were mostly reversible and manageable by the available protocol treatment guidelines.

In the literature (Wolchok et al 2013), using the combination of the same class of drugs (eg, anti-PD-1 and anti-CTLA4 antibodies), specifically nivolumab + ipilimumab in a study involving patients with malignant melanoma, the safety profile of this combination had shown occurrences of treatment-related AEs in 93% of treated patients, with the most frequent events being rash (55% of patients), pruritus (47% of patients), fatigue (38% of patients), and diarrhea (34% of patients). Grade 3 or 4 AEs, regardless of causality, were noted in 72% of patients, with grade 3 or 4 treatment-related events in 53%. The most frequent of these grade 3 or 4 treatment-related events include increased lipase (in 13% of patients), AST (in 13%), and ALT levels (in 11%). SAEs related to the treatment were noted in 49% of patients Frequent grade 3 or 4 selected AEs related to the combination therapy included hepatic events (in 15% of patients), gastrointestinal (GI) events (in 9%), and renal events (in 6%). Isolated cases of pneumonitis and uveitis were also observed.

No safety studies in animals have been performed combining tremelimumab with MEDI4736. As both CTLA 4 and PD-L1 have mechanisms of actions that enhance activation of immune cells, their potential to induce cytokine release was tested in a whole-blood assay system. MEDI4736 and tremelimumab, either alone or in combination did not induce cytokine release in blood from any donor.

Based upon the available non-clinical and clinical safety data, the limited survival benefit provided by the currently available treatment options to patients, the limited life expectancy due to malignant disease, and the strength of the scientific hypotheses under evaluation, the MEDI4736 + tremelimumab treatment proposed for evaluation in this study may have the potential to provide meaningful clinical benefit with a manageable safety and tolerability profile by generating durable clinical responses, thereby improving QoL and potentially extending survival. Patients with recurrent/metastatic SCCHN who have failed a prior line of therapy have a dismal prognosis with median survival of less than 6 months. Agents targeting the PD-1/PD-L1 pathway have shown promising activity in patients with recurrent/metastatic SCCHN. Although the patients who may be more likely to benefit from therapies with PD-1/PD-L1 targeting agents are those whose cancers express PD-L1 in the tumor microenvironment (see Section 1.2.4), an unmet need remains for patients with PD-L1 negative tumors despite the potential impact of immunotherapy. Preclinical and clinical evidence indicate that combination of PD-1/PD-L1 and CTLA4 targeting agents may provide synergistic antitumor activity, regardless of PD-L1 expression levels (Wolchok et al 2013). Therefore, the investigation of the potential therapeutic efficacy of MEDI4736 + tremelimumab combination in patients with recurrent/metastatic disease with PD-L1-negative tumors is acceptable, and the overall benefit/risk assessment is reasonable per the proposed study design.

1.4 Study design

This is a randomized, open-label, multi-center, global, Phase II study to determine the efficacy and safety of MEDI4736 in combination with tremelimumab, MEDI4736 monotherapy, and tremelimumab monotherapy in the treatment of patients with recurrent or metastatic PD-L1-negative SCCHN who have progressed during or after treatment with only 1 systemic palliative regimen for recurrent or metastatic disease that must have contained a platinum agent. A schematic diagram of the overall study design is shown in Figure 1 and a flow chart of the study design is presented in Figure 2.

Patients will undergo an assessment on their tumor tissue sample to determine PD-L1 status prior to treatment (Day 0). Patients with tumoral PD-L1 expression below a pre-specified cut-off level (25%), as determined by IHC assay (referred to hereafter as PD-L1-negative tumors), will be enrolled in the study. If the patient's PD-L1 status has already been assessed using the analytically validated Ventana SP263 assay as a part of the screening process for D4193C00001 or another AstraZeneca/MedImmune study, this test result can be used for the determination of eligibility.

Patients will be randomized in a stratified manner according to prognostic factors, including HPV status and smoking status. Randomization will be performed in a 1:1:2 ratio to MEDI4736 monotherapy, tremelimumab monotherapy, or MEDI4726 + tremelimumab combination therapy.

Patients in the MEDI4736 monotherapy treatment group will receive 10 mg/kg MEDI4736 via IV infusion q2w (up to 26 doses) for up to 12 months. Patients in the tremelimumab monotherapy treatment group will receive 10 mg/kg tremelimumab via IV infusion q4w for 7 doses then q12w for 2 additional doses (up to 9 doses in total) for up to 12 months.

Patients in the MEDI4736 + tremelimumab group will receive 20 mg/kg MEDI4736 via IV infusion q4w for 4 months (up to 4 doses) and 1 mg/kg tremelimumab via IV infusion q4w for 4 months (up to 4 doses in total). After completion of the initial 4 doses of combination therapy, single agent MEDI4736 will continue at 10 mg/kg q2w to complete 12 months of therapy (up to an additional 18 doses with the final dose at Week 50). The first MEDI4736 dose at 10 mg/kg q2w will be 4 weeks after the final dose of the combination of tremelimumab and MEDI4736 at 20 mg/kg.

All treatments will be administered beginning on Day 0 for 12 months or until confirmed PD (unless, in the Investigator's opinion, the patient continues to receive benefit from the treatment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met (see Section 3.9), whichever occurs first.

Patients with confirmed PD who, in the Investigator's opinion, continue to receive benefit from their assigned IP treatment and who meet the criteria for treatment in the setting of PD (see Section 3.1) may continue to receive their assigned IP treatment for a maximum of 12 months after consultation with the Sponsor and at the Investigator's discretion. The monotherapy arms (tremelimumab and MEDI4736) should be discontinued if there is

confirmed PD following a previous response in target lesions (CR or PR) (ie, the response and progression events both occurred while receiving active IP during the same treatment period in the target lesions).

Retreatment in the combination arm can only occur if PD occurs during the monotherapy portion or after completion of 12 months of therapy. In that event, an additional 12-month period of retreatment will be permitted. Patients in the combination arm who progress during dosing of the combination portion of therapy will not be eligible for retreatment. IP should be discontinued if there is confirmed PD following a previous response in target lesions (CR or PR) during the combination period of dosing (ie, the response and progression events both occurred while receiving combination therapy during the same treatment period in the target lesions).

Patients who the Sponsor and Investigator determine may not continue treatment after confirmed PD during the 12-month initial treatment period or in the 12-month retreatment period will enter follow-up (see Table 5). Patients who have discontinued treatment due to toxicity or symptomatic deterioration, or who have commenced subsequent anticancer therapy, will be followed up until confirmed disease progression and death. Patients who discontinue treatment in 1 treatment group may not switch to treatment in a different group.

Tumor assessments will be performed using computed tomography (CT) or magnetic resonance imaging (MRI) at the times specified in Table 5, Table 6, and Table 7. RECIST 1.1 measurements as given by the BICR will be used to derive the primary variable of ORR and the secondary variables of DoR, DCR, BoR, and PFS. ORR, DoR, DCR, BoR, and PFS will also be assessed as secondary variables using BICR assessment according to irRECIST 1.1. DoR and DCR will also be assessed by sensitivity analyses using site Investigator data according to RECIST 1.1. Sensitivity analyses from RECIST 1.1 measurements per the site Investigator and from the BICR according to RECIST 1.1 modified for confirmation of progression will also be performed. See Section 5.1 and Appendix E for further information regarding RECIST 1.1 tumor assessments in this study.

The study will screen approximately 384 patients to identify approximately 240 patients with PD-L1-negative disease suitable for enrollment (ie, who fulfill the eligibility criteria) and randomization. Of these, at least 208 patients likely to be evaluable for the primary endpoint.

Patients will be randomized in stratified manner according to prognostic factors, including HPV status and smoking status. Randomization will be done in a 1:1:2 fashion (60:60:120 patients) to MEDI4736 monotherapy, tremelimumab monotherapy, or MEDI4736 + tremelimumab combination therapy.

An interim safety analysis by an Independent Data Monitoring Committee (IDMC) will be conducted, for patients in the MEDI4736 + tremelimumab treatment group when the 20th patient has been randomized or 3 months after the 1st patient has been randomized, whichever occurs first, followed by 2 meetings for safety analysis 3 months apart, and subsequent meetings 6 months apart.

Overall survival extension period

The OS Extension period will start following the 12-month analysis DCO, and will extend the OS data collection period until approximately 30 months after Last Patient Dosed (LPD), or until 85% OS event maturity is reached, whichever occurs first.

During the OS Extension period, all patients will be followed for survival. Overall survival, safety-related data, and IP administration details will be collected in the clinical database. Once the final OS analysis has been completed, the clinical database will be closed.

Patients will receive scans/RECIST assessments as per local standard of care. All other study efficacy assessments and centralized assessments will cease. Patients will continue with scheduled site visits, safety laboratory assessments, and other safety assessments.

Patients who are progression-free following randomized treatment and potentially eligible for retreatment are to undergo sampling for local laboratory assessments (Table 9), and in such a way that continued per-protocol retreatment eligibility can be properly determined.

End of analysis portion of study

The DCO for the final analysis of OS will take place approximately 30 months after Last Patient Dosed (LPD), or when 85% OS event maturity is reached, whichever occurs first. At this point, the clinical study database will be closed to new data. Once all planned statistical analyses have been performed, the analysis portion of the clinical study will have been completed. Progressed patients in OS follow-up will be withdrawn from the study. Patients who are progression-free following randomized treatment and potentially eligible for retreatment may decide to continue in the study; these patients would remain eligible for possible future retreatment upon progression if they meet retreatment criteria (Section 3.1) and the Investigator believes that the patient will gain clinical benefit. Patients already receiving retreatment at the time of the OS Extension DCO may continue receiving study treatment, if the Investigator believes that they are gaining clinical benefit.

Scans will be collected in accordance with local clinical practice. Patients who are progression-free following randomized treatment and potentially eligible for retreatment after the OS Extension DCO are to undergo sampling for local laboratory assessments, and in such a way that continued per-protocol retreatment eligibility can be properly determined.

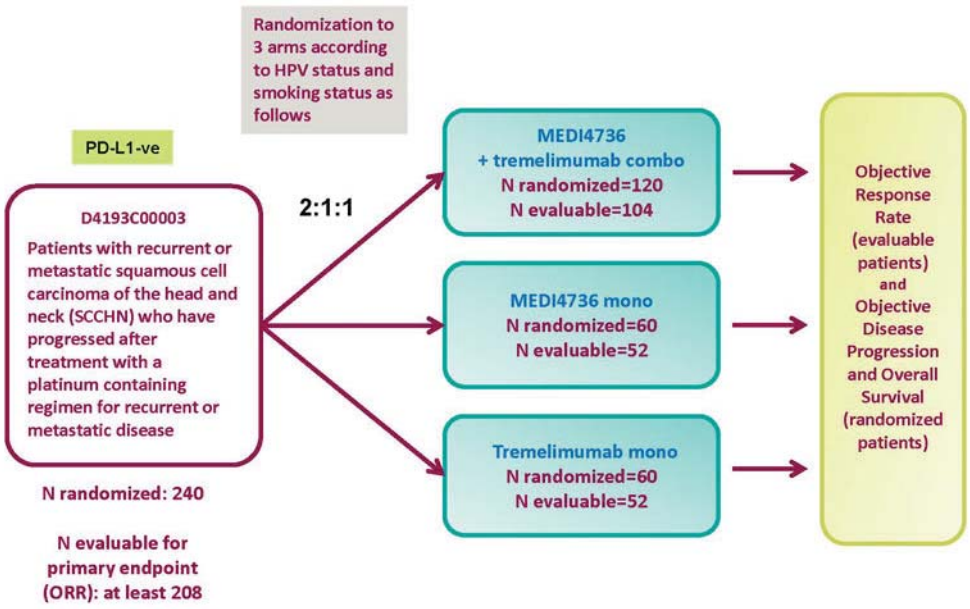
For patients receiving retreatment after the OS Extension DCO, it is recommended that the patients continue the scheduled site visits and investigators monitor the patient's safety laboratory assessments prior to and periodically during treatment with IP in order to manage AEs in accordance with the toxicity management guidelines (Table 13).

For patients who either continue to receive treatment or begin retreatment after the OS Extension DCO, investigators will report all SAEs to the AstraZeneca representative until 90 days after IP is discontinued. Following the OS Extension DCO, SAE reporting will apply only to patients who are active on study treatment and within 90 days post the last dose; in all

other cases only a statement of death notification is to be sent to the AstraZeneca representative.

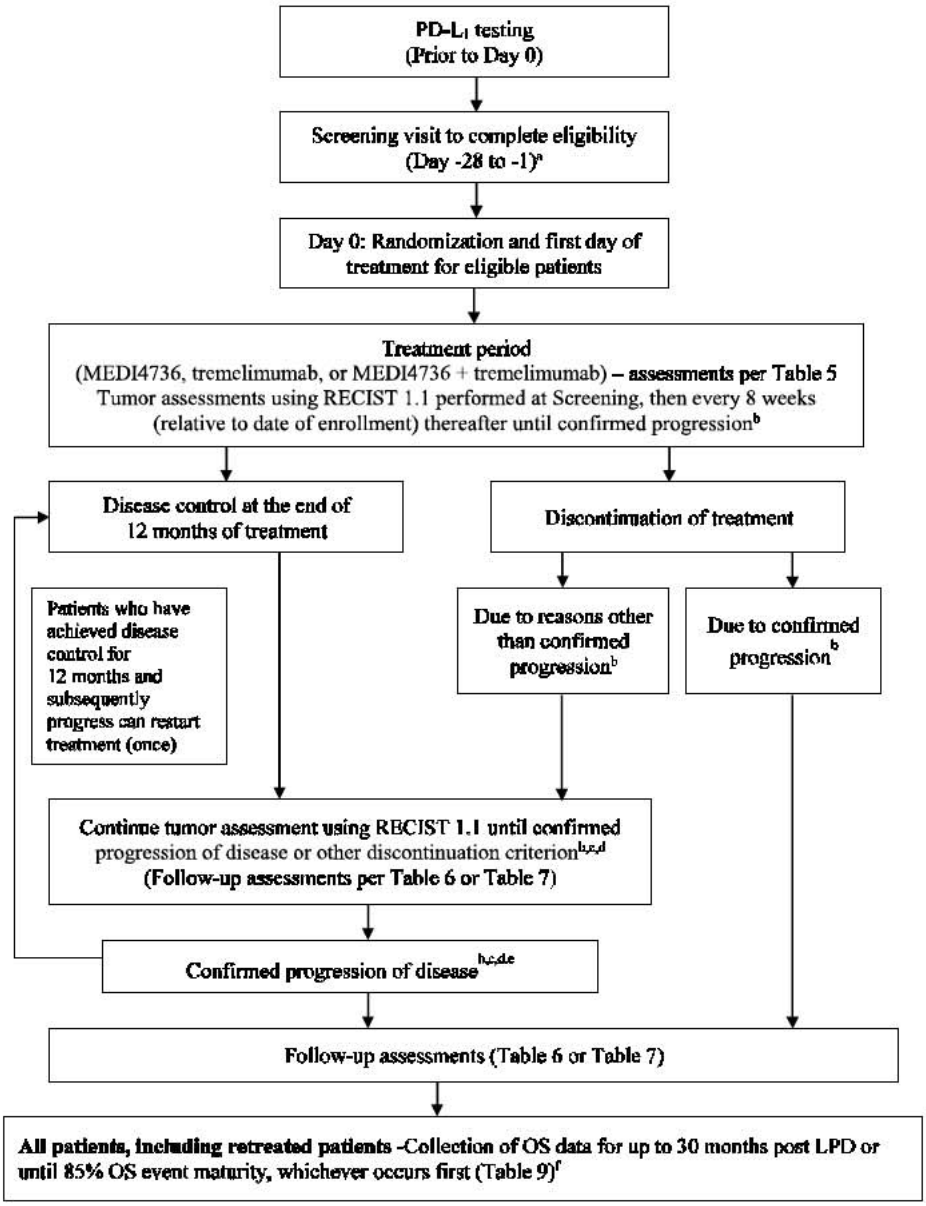
In the event that a roll-over or safety extension study will become available, patients currently receiving study treatment, or patients who are progression-free following randomized treatment and potentially eligible for retreatment may be transitioned to such a study, and the current study would reach its end. The roll-over or safety extension study would ensure treatment continuation with visits and assessments per its protocol. Any patient that would be proposed to move to such a study would be given a new informed consent form (ICF).

Figure 1 Overall study design



N Number of patients; HPV Human papilloma virus; ORR Objective response rate; PD-L1-ve Programmed cell death ligand-1 negative.

Figure 2 Study flow chart



[a] Screening assessments can be performed over multiple visits. Imaging and procedures performed before signing the ICF may be used for screening purposes if the patient consents. If the patient's PD-L1 status has already been assessed using the analytically validated Ventana SP263 assay as a part of the screening process for D4193C00001 or another AstraZeneca/MedImmune study, this test result can be used for the determination of eligibility.

[b] Disease progression needs to be confirmed. The confirmatory scan should occur preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of PD in the absence of clinical deterioration. Administration of study treatment will continue between the initial assessment of progression and confirmation for progression. Patients with clinical evidence of progression who do not meet PD criteria by RECIST 1.1 should have radiographic documentation of PD. For all patients who are treated through progression, the Investigator should ensure that patients do not have any significant, unacceptable, or irreversible toxicities that indicate that continuing treatment will not further benefit the patient, and that the patient still meets all of the inclusion criteria and none of the exclusion criteria for this study including re-consenting to continue treatment. Patients with rapid tumor progression or with symptomatic

progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) will not be eligible to continue to receive IP.

[c] Patients who achieve and maintain disease control (ie, CR, PR, or SD) through to the end of the 12-month treatment period may restart study treatment upon evidence of PD (with or without confirmation, according to RECIST 1.1) during follow-up. Before restarting study treatment, the Investigator should ensure that patients do not have any significant, unacceptable, or irreversible toxicities that indicate that continuing treatment will not further benefit the patient, and that the patient still meets all of the inclusion criteria and none of the exclusion criteria for this study including re consenting to restart treatment. To restart study treatment, the patient must not have received an intervening cancer therapy post study treatment discontinuation. Patients should have a baseline tumor assessment within 28 days of restarting study treatment; all further scans should occur q8w (relative to the date of restarting study treatment) (maximum of 12 months of further treatment). Patients with confirmed progression during dosing in the MEDI4736 or tremelimumab monotherapy arms or in the combination portion of therapy in the MEDI4736 + tremelimumab arm cannot continue therapy or obtain retreatment if progression occurred after confirmed response in the target lesions (ie, the response and progression events both occurred while receiving active IP during the same treatment period in the target lesions). Retreatment in the combination arm can only occur if PD occurs during the monotherapy portion or after completion of 12 months of therapy.

[d] Patients with confirmed PD who continue to receive study treatment at the discretion of the Investigator (following consultation with the Sponsor) can receive study treatment for a maximum of 12 months. This will not be considered retreatment but will be considered a part of the initial 12-month period of therapy. For all patients who are treated through progression, the Investigator should ensure that patients do not have any significant, unacceptable, or irreversible toxicities that indicate that continuing treatment will not further benefit the patient, and that the patient still meets all of the inclusion criteria and none of the exclusion criteria for this study including re-consenting to continue study treatment. The same exceptions as noted in footnote "b" apply. Patients will follow the assessments in Table 5 including tumor assessments q8w (relative to the date of enrollment) until study treatment is stopped. IP should be discontinued if there is confirmed PD following a previous response in target lesions (CR or PR) to IP.

[e] Patients with confirmed PD who discontinue IP should have scans conducted according to local practice and submitted for Blinded Independent Central Review until the patient commences a new treatment (these scans are optional).

[f] During and after the OS Extension period patients should receive scans/RECIST per local practice. During the OS Extension period, patients should follow Table 8 and Table 9 for safety laboratory assessments. After the OS Extension period, it is recommended that patients continue the scheduled site visits and Investigators monitor the patient's safety laboratory assessments during study treatment in order to manage adverse events in accordance with the toxicity management guidelines (Table 13).

CR Complete response; DCO Data cutoff; ICF Informed consent form; IP Investigational product; LPD Last patient dosed; OS Overall survival; PD Progressive disease; PD-L1 Programmed cell death ligand-1; PR Partial response; q8w Every 8 weeks; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1; SD Stable disease.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To assess the efficacy of MEDI4736 + tremelimumab combination therapy in terms of ORR	ORR using BICR assessments according to RECIST 1.1[a]

[a] Sensitivity analysis of ORR will be performed based on tumor information recorded in the clinical database by the Investigator according to RECIST 1.1 and will also be performed based on BICR assessment according to RECIST 1.1 modified for confirmation of progression.

BICR Blinded Independent Central Review; ORR Objective response rate; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1.

2.2 Secondary objectives

Secondary Objective:	Outcome Measures:
To further assess the efficacy of MEDI4736 + tremelimumab combination therapy in terms of ORR, TTR, DoR, DCR, BoR, PFS, and OS.	DoR, DCR, BoR, and PFS [a] using BICR assessments according to RECIST 1.1 ORR and PFS using BICR assessments according to irRECIST 1.1 OS
To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared with a) MEDI4736 monotherapy and b) tremelimumab monotherapy, in terms of ORR, PFS, and OS	ORR and PFS using BICR assessments according to RECIST 1.1[b] OS
To assess disease-related symptoms and health-related QoL in patients treated with MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, and tremelimumab monotherapy, using the EORTC QLQ-C30 v3 and the QLQ-H&N35 module	EORTC QLQ-C30: global health QoL, functioning (physical), and symptoms (fatigue) EORTC QLQ-H&N35: symptoms (pain and swallowing) Changes in WHO/ECOG performance status will also be assessed.

[a] Sensitivity analyses of PFS will be performed based on tumor information recorded in the clinical database by the Investigator according to RECIST 1.1

[b] Sensitivity analysis of ORR will be performed based on tumor information recorded in the clinical database by the Investigator according to RECIST 1.1 and PFS will also be performed based on BICR assessment according to RECIST 1.1 modified for confirmation of progression.

BICR Blinded Independent Central Review; BoR Best objective response; DCR Disease control rate; DoR Duration of response; ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; irRECIST 1.1 immune-related Response Evaluation Criteria in Solid Tumors version 1.1; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; QLQ-C30 v3 30-item core quality of life questionnaire, version 3; QLQ-H&N35 35-item head and neck quality of life questionnaire; QoL Quality of life; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1; TTR Time to recurrence; WHO World Health Organization.

2.3 Safety objective

Safety Objective:	Outcome Measures:
To assess the safety and tolerability profile of MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, and tremelimumab monotherapy	AEs, physical examinations, laboratory findings (including clinical chemistry, hematology, and urinalysis), vital signs (including blood pressure, pulse, and oxygen saturation), and ECGs

AE Adverse event; ECG Electrocardiogram.

2.4 Exploratory objectives

Exploratory Objective:	Outcome Measures:
To assess the PK of MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, and tremelimumab monotherapy	Concentration of MEDI4736/tremelimumab in blood and non-compartmental PK parameters (such as peak and trough concentrations, as data allow, with sparse sampling only)

Exploratory Objective:	**Outcome Measures:**
To investigate the immunogenicity of MEDI4736 and tremelimumab	Presence of ADA for MEDI4736 and tremelimumab (confirmatory results: positive or negative; titers)
To collect blood and tissue samples for analysis of biomarkers	Biomarker analysis of blood and tissue to assess exploratory markers that may include but are not limited to: immune cell gene expression profiles within the peripheral and tumoral compartments; the presence of IFN-γ TNF-α, IL-2, IL-6, IL-10, IL-8, and IL-12 as well as antibodies against tumor, self, or viral antigens; expression of PD-L1; and the number and phenotype of immune cells such as T-cells
To explore the relationship(s) between a patient's biomarker status before and after treatment with MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, and tremelimumab monotherapy and clinical outcomes, efficacy, AEs, and/or safety parameters	Biomarker status before and after treatment and relationship with clinical outcomes, efficacy, AEs, and/or safety parameters, as deemed appropriate
To explore potential biomarkers in residual biological samples (eg, tumor, plasma, and/or serum) that may influence the progression of cancer (and associated clinical characteristics) and/or prospectively identify patients likely to respond to MEDI4736 and tremelimumab. This includes HPV status.	Correlation of biomarkers with response to MEDI4736 and tremelimumab and/or the progression of cancer
To collect and store DNA according to each country's local and ethical procedures for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy) to study treatments and/or susceptibility to disease (optional)	Correlation of polymorphisms with variation in PK, pharmacodynamics, safety, or response parameters observed in patients treated with MEDI4736 and tremelimumab and/or susceptibility to disease

Note: Exploratory objective analyses may be reported separately from the main clinical study report.
ADA Antidrug antibody; AE Adverse event; ECOG Eastern Cooperative Oncology Group; IFN Interferon; IL Interleukin; PD-L1 Programmed cell death ligand 1; PK Pharmacokinetics; TNF Tumor necrosis factor; WHO World Health Organization.

3. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL

Each patient should meet all of the inclusion criteria (Section 3.1) and none of the exclusion criteria (Section 3.2) for this study. Under no circumstances will there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study, patients should fulfill the following criteria:

1. Age ≥18 years at the time of screening.

2. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the United States, European Union [EU] Data Privacy Directive in the EU) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.

3. Histologically confirmed recurrent or metastatic SCCHN (oral cavity, oropharynx, hypopharynx, or larynx) not amenable to therapy with curative intent (surgery or radiation therapy with or without chemotherapy). Patients who refuse radical resection are eligible.

4. Tumor progression or recurrence during or after treatment with only 1 systemic palliative regimen for recurrent or metastatic disease that must have contained a platinum agent. Patients who have only received chemo-radiation with curative intent for treatment of their locally advanced disease or recurrent disease are not eligible.

5. Able and willing to give valid written consent to provide newly acquired tumor tissue (preferred) or archival tissue (<3 years old) for the purpose of establishing PD-L1 status. Tumor lesions used for newly acquired biopsies should not be the same lesions used as RECIST 1.1 target lesions, unless there are no other lesions suitable for biopsy.

6. Confirmed PD-L1-negative SCCHN by the Ventana SP263 assay on newly acquired tumor tissue (preferred) or archival tissue (<3 years old)

   If the patient's PD-L1 status has already been assessed using the analytically validated Ventana assay as a part of the screening process for another AstraZeneca/MedImmune study, this test result can be used for the determination of eligibility.

   Note: A negative PD-L1 sample is measured using a defined cut-off based on less than 25% of tumor cells with membrane staining for PD-L1 of any intensity using the Ventana SP263 assay (ie, PD-L1-negative status is less than 25%).

7. WHO/ECOG performance status of 0 or 1 at enrollment

8. At least 1 lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with CT or MRI and that is suitable for accurate repeated measurements as per RECIST 1.1 guidelines. Lesions in a previously irradiated

field can be used as measurable disease provided that there has been demonstrated progression in the lesion.

9. Patients must have no prior exposure to immune-mediated therapy, including other anti-CTLA-4, anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies, excluding therapeutic anticancer vaccines. Exposure to other investigational agents may be permitted after discussion with the Sponsor.

10. Adequate organ and marrow function independent of transfusion for at least 7 days prior to screening and independent of growth factor support for at least 14 days prior to screening, defined as:

    - Hemoglobin ≥9 g/dL
    - Absolute neutrophil count ≥1500/mm^3
    - Platelet count ≥100000/mm^3
    - Serum bilirubin ≤1.5 × the upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia [predominantly unconjugated bilirubin] in the absence of evidence of hemolysis or hepatic pathology), who will be allowed in consultation with their physician.
    - ALT and AST ≤2.5 × ULN; for patients with hepatic metastases, ALT and AST≤5 × ULN
    - Calculated creatinine clearance ≥40 mL/min as determined by Cockcroft-Gault (using actual body weight)

11. Evidence of post-menopausal status, or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

    - Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.
    - Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced oophorectomy with last menses >1 year ago, had chemotherapy-induced menopause with >1 year interval since

last menses, or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).

Inclusion criteria for treatment in the setting of PD

For all patients who are treated through progression (including patients with confirmed PD who continue their assigned IP at the Investigator's discretion patients who achieve disease control [ie, CR, PR, or SD] and restart treatment upon evidence of PD during follow-up, and patients who undergo combination reinduction), the Investigator should ensure that patients still meet all of the inclusion criteria and none of the exclusion criteria for this study and that these patients meet the following specific criteria for treatment in the setting of PD:

1. Written informed consent to continue treatment or retreatment in the setting of PD. This consent document will specify that treatment beyond initial evidence of PD is not the standard-of-care and that alternative treatment options, either locally licensed treatments or other clinical trials, are available for this patient population.

2. Absence of clinical symptoms or signs indicating clinically significant disease progression

3. No decline in WHO/ECOG performance status to >1

4. Absence of rapid disease progression or threat to vital organs or critical anatomical sites (eg, central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) requiring urgent alternative medical intervention.

In order to restart their assigned IP treatment upon evidence of PD during follow-up, the patient also must not have received an intervening cancer therapy after IP treatment discontinuation. Patients who discontinue treatment in 1 treatment group may not switch to treatment in a different group.

Patients with confirmed progression during dosing in the MEDI4736 or tremelimumab monotherapy arms or in the combination portion of therapy in the MEDI4736 + tremelimumab arm cannot continue therapy or obtain retreatment if progression occurred after confirmed response in the target lesions (CR/PR) (ie, the response and progression events both occurred while receiving active IP during the same treatment period in the target lesions). Retreatment in the combination arm can only occur if PD occurs during the monotherapy portion or after completion of 12 months of therapy. Additional details pertaining to retreatment are presented in Section 7.2.

Patients who are progression-free following randomized treatment and potentially eligible for retreatment after the OS Extension DCO will be eligible for retreatment with their previously assigned treatment if they meet the eligibility criteria. Patients' eligibility should be recorded in their medical records.

Inclusion criteria for genetics research study (optional)

For inclusion in the optional (DNA) genetics research study, patients must fulfill the following criteria:

1. Provide informed consent for genetic sampling and analyses.

2. If a patient declines to participate in genetics research, there will be no penalty or loss of benefit to the patient. A patient who declines genetics research participation will not be excluded from any other aspect of the main study.

3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Histologically confirmed squamous cell carcinoma of any other primary anatomic location in the head and neck (eg, paranasal cavity), patients with squamous cell carcinoma of the head and neck of unknown primary, and non-squamous histologies (eg, nasopharynx or salivary gland).

2. Received more than 1 systemic palliative regimen for recurrent or metastatic disease.

3. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable. Note: Local treatment of isolated lesions for palliative intent is acceptable (eg, local surgery or radiotherapy).

4. Prior randomization or treatment in a previous MEDI4736 and/or tremelimumab clinical study regardless of treatment arm assignment or receipt of any investigational anticancer therapy within 28 days or 5 half-lives, whichever is longer, prior to the first dose of study treatment.

5. Receipt of last dose of an approved (marketed) anticancer therapy (chemotherapy, targeted therapy, biologic therapy, mAbs, etc) within 21 days prior to the first dose of study treatment. If sufficient washout time has not occurred due to the schedule or PK properties of an agent, a longer washout period will be required, as agreed upon by AstraZeneca and the Investigator.

6. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.

7. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criterion.

- Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis and may be included after consultation with the Study Physician.

- Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with their assigned IP (eg, hearing loss) may be included after consultation with the Study Physician.

8. Current or prior use of immunosuppressive medication within 14 days before the first dose of their assigned IP. The following are exceptions to this criterion:

   - Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection)

   - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent

   - Steroids as pre-medication for hypersensitivity reactions (eg, CT scan pre-medication)

9. History of allogeneic organ transplantation.

10. Active or prior documented autoimmune or inflammatory disorders (eg, inflammatory bowel disease [eg, colitis, Crohn's disease], diverticulitis with the exception of a prior episode that has resolved or diverticulosis, celiac disease, or other serious GI chronic conditions associated with diarrhea; systemic lupus erythematosus; Wegener syndrome [granulomatosis with polyangiitis]; myasthenia gravis; Graves' disease; rheumatoid arthritis, hypophysitis, uveitis, etc) within the past 3 years prior to the start of treatment. The following are exceptions to this criterion:

    - Patients with vitiligo or alopecia

    - Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement or other chronic skin conditions not requiring systemic treatment

11. Uncontrolled intercurrent illness, including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, or psychiatric illness or social situations that would limit compliance with study requirements, substantially increase the risk of incurring AEs from MEDI4736 or tremelimumab, or compromise the ability of the patient to give written informed consent

12. History of another primary malignancy except for

- Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of study drug and of low potential risk for recurrence

- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease

- Adequately treated carcinoma in situ without evidence of disease, eg, cervical cancer in situ

13. Patients with history of brain metastases, spinal cord compression, or leptomeningeal carcinomatosis, or involvement of any other anatomic area that, in the opinion of the Investigator, may cause significant symptoms if an inflammatory reaction occurs

14. History of active primary immunodeficiency

15. Known history of previous clinical diagnosis of tuberculosis

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

17. Receipt of live, attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine during the study and up to 30 days after the last dose of both IPs.

18. Female patients who are pregnant or breast-feeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days for those randomized to the MEDI4736 monotherapy arm or the tremelimumab monotherapy arm; or from screening to 180 days for those randomized to the MEDI4736 + tremelimumab combination therapy arm

19. Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fridericia's Correction

20. Known allergy or hypersensitivity to IP or any IP excipient

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

Procedures for withdrawal of incorrectly enrolled patients are presented in Section 3.4.

Exclusion criteria for genetics research study (optional)

Exclusion criteria for participation in the optional (DNA) genetics research component of the study include previous allogeneic bone marrow transplantation and non-leukocyte depleted

whole blood transfusion 120 days prior to genetic sample collection. Procedures for withdrawal of incorrectly enrolled patients will be provided in the protocol.

3.3 Patient enrollment

Investigators should keep a record (ie, the patient screening log) of patients whose tumor tissue has been submitted for PD-L1 testing and those patients who have participated in screening.

Prior to treatment (Day 0), the Investigators or suitably trained delegate will:

1. Obtain signed informed consent for PD-L1 testing. If the patient's PD-L1 status has already been assessed using the validated Ventana SP263 assay as part of the screening process for another AstraZeneca/MedImmune study, a separate D4193C00003 PD-L1 testing ICF is not mandatory. Investigator may obtain consent for the study.

2. Assign the potential patient a unique 7-digit enrollment number, beginning with 'E#'. This is obtained through the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) (ECCNNXXX: CC being the country code, NN being the center number, and XXX being the patient enrollment code at the center). Enrollment numbers will start at 300 in each center and go up sequentially (eg, at Center 01, patients will be assigned enrollment numbers E0101300, E0101301, etc). This number is the patient's unique identifier and is used to identify the patient on the electronic case report forms (eCRFs) and in vendor systems/tools. This "E#" is required prior to submission of the tumor sample for PD-L1 testing.

3. Obtain tumor sample and send for PD-L1 expression status evaluation

To complete screening procedures (Days -28 to -1), the Investigators or suitably trained delegate will:

1. Ensure the patient's PD-L1 status is available

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

3. Obtain signed informed consent for all main study procedures

4. Obtain signed informed consent for genetic research study (optional)

At randomization, once the patient is confirmed to be eligible, the Investigator or suitably trained delegate will:

1. Call the IVRS/IWRS to assign the eligible patient to 1 of the 3 treatment arms.

If the patient is ineligible and not randomized, the IVRS/IWRS should be contacted to terminate the patient in the system.

Patients will begin treatment on Day 0. Patients must not be treated unless all eligibility criteria have been met.

If a patient withdraws from participation in the study, then his or her enrollment/randomization code or patient identification number cannot be reused.

The IVRS/IWRS may be closed after the 12-month analysis. In this case a manual process will be followed.

3.4 Procedures for handling incorrectly enrolled patients

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

If a patient does not meet all the eligibility criteria but is randomized in error or incorrectly started on treatment, the Investigator should inform the Study Physician immediately, and the Study Physician and the Investigator should discuss whether to continue or discontinue the patient from treatment. The Study Physician must ensure that all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

The actual treatment given to patients will be determined by the randomization scheme in the IVRS/IWRS. The randomization scheme will be produced by a computer software program that incorporates a standard procedure for generating randomization numbers. One randomization list will be produced for each of the randomization strata. A blocked randomization will be generated, and all centers will use the same list in order to minimize any imbalance in the number of patients assigned to each treatment group.

Patients will be identified to the Centralized Randomization Center per country regulations. Randomization codes will be assigned strictly sequentially, within each stratum, as patients become eligible for randomization. The IVRS/IWRS Centralized Randomization Center will inform the pharmacist of the kit identification number to be allocated to the patient at the randomization visit.

3.6 Methods for ensuring blinding

Not applicable; this study is not blinded.

3.7 Methods for unblinding

Not applicable; this study is not blinded.

3.8 Restrictions

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

1. Females of childbearing potential who are sexually active with a non-sterilized male partner must use 2 methods of effective contraception (Table 4) from the time of screening and must agree to continue using such precautions for 90 days (MEDI4736 monotherapy and tremelimumab monotherapy) or 180 days (MEDI4736 + tremelimumab combination therapy) after the final dose of IP; cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

   – Females of childbearing potential are defined as those who are not surgically sterile (ie, those who had bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or those who are post-menopausal (defined as amenorrheic for 12 months without an alternative medical cause).

   – Patients must use 2 acceptable methods of effective contraception as described in Table 4.

2. Non-sterilized males who are sexually active with a female partner of childbearing potential must use 2 acceptable methods of effective contraception (see Table 4) from screening through 90 days (MEDI4736 monotherapy and tremelimumab monotherapy) or 180 days (MEDI4736 + tremelimumab combination therapy) after receipt of the final dose of IP.

3. Patients should not donate blood while participating in this study and for 3 months following the last dose of study treatment.

Restrictions relating to concomitant medications are described in Section 7.7.

Table 4 Effective methods of contraception (2 methods must be used)

Barrier methods	Intrauterine device methods	Hormonal methods
Male condom plus spermicide	Copper T	Implants
Cap plus spermicide	Progesterone T[a]	Hormonal shot or injection
Diaphragm plus spermicide	Levonorgestrel-releasing intrauterine system (eg, Mirena®)[a]	Combined pill Minipill Patch

[a] This is also considered to be a hormonal method.

3.9 Discontinuation of investigational product

An individual patient will not receive any further IP (MEDI4736, tremelimumab, or MEDI4736 + tremelimumab combination) if any of the following occur in the patient in question:

- Withdrawal of consent from further treatment with IP. The patient is at any time free to discontinue treatment, without prejudice to further treatment. A patient who discontinues treatment is normally expected to continue to participate in the study unless they specifically withdraw their consent to further participation in any study procedures and assessments (see Section 3.10).
- An AE that, in the opinion of the Investigator or the Sponsor, contraindicates further dosing
- Any AE that meets criteria for discontinuation as defined in Section 6.7
- Pregnancy or intent to become pregnant
- Non-compliance with the study protocol that, in the opinion of the Investigator or Sponsor, warrants withdrawal from study treatment (eg, refusal to adhere to scheduled visits)
- Initiation of alternative anticancer therapy including another investigational agent
- Confirmed PD and Investigator determination that the patient is no longer benefiting from treatment with IP

3.9.1 Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue IP without prejudice to further treatment. A patient who decides to discontinue IP will always be asked about the reason(s) for discontinuation and the presence of any AE. If possible, they will be seen and assessed by an Investigator. AEs will be followed-up (see Section 6). The Study Physician should be notified of any ongoing AE that may delay treatment or necessitate permanent discontinuation of treatment.Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment. Patients who are permanently discontinued because of toxicity or withdrawal of consent from treatment, and in the absence of PD, will be asked to come in for every protocol-specified visit and will follow all protocol procedures with the exception of dosing (see Table 5). Patients permanently discontinued due to PD will enter into follow-up (see Table 5). All patients will be followed for survival until the end of the study. Patients who decline to return to the site for evaluations should be contacted by telephone every 3 months as an alternative.

An individual patient will be considered to have completed the study if the patient completes the initial 12-month treatment period (Table 5).

3.10 Criteria for withdrawal of the patient from the study

3.10.1 Screen failures

Screen failures are patients who do not fulfill the eligibility criteria for the study, and therefore must not be enrolled and randomized. These patients should have the reason for study withdrawal recorded as "Screen failures" (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (ie, patients who are not enrolled). Patients may be re-screened a single time, but they may not be re-randomized.

3.10.2 Withdrawal of the informed consent

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

Patients who withdraw consent for further study drug administration will not receive any further IP but will continue with post-discontinuation study assessments and follow-up for survival, per Table 3 and Table 4, which will continue until patient death, withdrawal of consent for ongoing follow-up, or the end of the study, whichever comes first. If the patient has expressly withdrawn their consent for ongoing study assessments or survival follow-up, this should clearly be noted in the source documentation. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

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

If a patient withdraws from participation in the study, then his or her enrollment or patient identification number cannot be reused. Withdrawn patients will not be replaced.

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed (see Section 9.3), such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and evaluations should resume according to the protocol.

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of the Sponsor or the IDMC, study patients are placed at undue risk because of clinically significant findings that meet any of the following criteria:

- Meet individual stopping criteria or are otherwise considered significant
- Are assessed as causally related to study drug

- Are not considered to be consistent with continuation of the study

In addition, the study may be stopped based on the findings of the interim safety analysis conducted by the IDMC (see Section 6.8).

Regardless of the reason for termination, all data available for the patients at the time of discontinuation of follow-up must be recorded in the eCRFs. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests. If this study is discontinued, all other studies involving MEDI4736 or tremelimumab will remain open to enrollment and screening, if deemed appropriate by the Sponsor.

4. STUDY PLAN AND TIMING OF PROCEDURES

The procedures for PD-L1 testing, screening, and the 12-month treatment period in this study are presented in Table 5. The procedures for the follow-up period are presented in Table 6 and Table 7. All visits must be conducted within 7 days of the originally scheduled visit unless otherwise indicated in Table 5 through Table 7 below. Patient may postpone dosing by 7 days and resume subsequent dosing per the original schedule. All laboratory procedures required for dosing should be performed within 3 days prior to dosing. Imaging and procedures performed before signing the ICF may be used for screening purposes if the patient consents. Dosing must occur within 28 days of screening procedures. Screening procedures required for Cycle 1, Day 0 need not be repeated if they were performed within 3 days of Cycle 1, Day 0.

Table 8 shows the schedule of assessments for patients continuing on or entering into retreatment during the OS Extension period, and Table 9 shows the schedule of assessments for all patients in follow-up during the OS Extension period.

Table 5 Schedule of assessments for the treatment period (12 months)

	PD-L1 testing	Screen-ing	C1		C2		C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	
Visit	**Prior to Day 0**	**Day -28 to -1**	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Week			**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**50**
Informed consent																		
Consent: IHC PD-L1 expression[a]	X																	
Consent: genetic sample and analysis		X																
Informed consent: study procedures		X																
Study procedures																		
Physical exam: height		X																
Physical exam (not including height, including weight[b])		X	X		X		X	X	X	X	X	X	X	X	X	X	X	
Vital signs: BP, pulse, body temperature, respiratory rate, and oxygen saturation[c]		X	BP, pulse, respiratory rate, oxygen saturation, and body temperature will all be taken before the infusion or at a minimum of every 4 weeks when there is no infusion; BP and pulse will also be taken during and after each infusion or at a minimum of every 4 weeks when there is no infusion (see Section 5.2.4).															
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Demography, disease status, HPV status, and anatomical site		X																
Medical/surgical history		X																
Tobacco use and/or smoking		X																
Eligibility criteria		X																
Laboratory assessments																		
Clinical chemistry[c,d]		X	Pre-dose prior to each infusion or at a minimum of every 4 weeks when there is no infusion															
Hematology[c,d]		X	Pre-dose prior to each infusion or at a minimum of every 4 weeks when there is no infusion															
TSH and reflex free T_3 or free T_4, only if TSH is abnormal[c]		X	X		X		X	X	X	X	X	X	X	X	X	X	X	
Urinalysis		X	X		X		X	X	X	X	X	X	X	X	X	X	X	

	PD-L1 testing	Screen-ing	C1		C2		C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	
Visit	**Prior to Day 0**	**Day -28 to -1**	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Week			**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**50**
Hepatitis B and C and HIV		X																
Pregnancy test (for women of childbearing potential)		X	X		X		X	X	X	X	X	X	X	X	X	X	X	X
Other laboratory assessments and assays																		
Immunogenicity assessment (ADA sampling to identify ADA responses in patient circulation)			X					X			X			X			X	
sPD-L1 (serum)			X					X			X						X	
Circulating soluble factors (plasma)			X	X	X			X										
PBMC collection			X	X					X									
miRNA/mRNA analysis (blood)			X					X									X	
Tumor biopsy or obtain archival tumor tissue <3 years old for PD-L1 status	X																	
Tumor evaluation (CT or MRI) (RECIST 1.1)[e,f,g]		X					X		X		X		X		X		X	
PGx sample (optional DNA element)		X																
Pharmacokinetics																		
Tremelimumab PK sample (serum)			X[h]					X[h]			X[h]			X[h]			X[h]	
MEDI4736 PK sample (serum)			X[h]					X[h]			X[h]			X[h]			X[h]	
Other safety examinations																		
ECG[p]		X[i]	X[i]	Week 12 and as clinically indicated														
Monitoring																		
WHO/ECOG performance status		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE assessment[q]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	PD-L1 testing	Screen-ing	C1		C2		C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	
Visit	**Prior to Day 0**	**Day -28 to -1**	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Week			**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**50**
Drug accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP administration																		
MEDI4736 monotherapy			Every 2 weeks															
Tremelimumab monotherapy[j]			X		X		X	X	X	X	X			X			X	
MEDI4736 (in combination with Tremelimumab)[k]			X		X		X	X	Every 2 weeks									
Tremelimumab (in combination with MEDI4736)[l]			X		X		X	X										
Patient-reported outcomes assessments[m]																		
EORTC QLQ-C30		X	X		X		X		X		X		X		X		X	X
EORTC QLQ-H&N35		X	X		X		X	X	X	X	X	X	X	X	X	X	X	X

[a] PD-L1 testing will be done from a newly acquired tumor biopsy (preferred) or archival tissue (<3 years old).

[b] Weight should be measured in kg with 1 decimal place at a minimum q4w before infusion.

[c] Results for urea and electrolytes, full blood count, and liver function tests must be available before commencing an infusion. Reflex free T_3 or T_4 are only needed if TSH is abnormal. All laboratory procedures required for dosing should be performed within 3 days prior to dosing. Creatinine clearance, gamma-glutamyltransferase, magnesium, and uric acid testing are to be performed at Screening, on Day 0, and as clinically indicated. Activated partial thromboplastin time testing is to be conducted at Screening only, unless clinically indicated. All other clinical chemistry assessments as detailed in Table 10 are conducted at Screening; on Day 0; Weeks 2, 4, 6, and 8; and thereafter at each infusion.

[d] If screening assessments are performed within 3 days prior to Week 0, Day 0 (first infusion day) they do not need to be repeated at Day 0.

[e] RECIST 1.1 assessments will be performed using CT/MRI assessments of the neck (from base of skull) though the chest and abdomen (including liver and adrenals). Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before start of study treatment and ideally should be performed as close as possible to the start of study treatment. Imaging and procedures performed before signing the ICF may be used for screening purposes if the patient consents. Follow-up assessments will be performed q8w for the first 48 weeks (relative to the date of the first infusion of the assigned IP) and then q12w thereafter until confirmed objective disease progression per RECIST 1.1. The confirmatory scans should preferably be performed at the next scheduled visit (relative to the date of the first infusion) and no less than 4 weeks after the initial assessment of CR/PR and PD (in the absence of clinically significant deterioration). If an unscheduled scan is performed in the absence of suspicion of progression within 2 weeks of a scheduled scan, the scan does not need to be repeated. However, every attempt should be made to follow the original scan schedule. All confirmatory scans should be recorded in the database and submitted to the independent reviewer. Scans following Cycle 1 can be ±7 days of the scheduled visit. For all patients who are treated through progression, the Investigator should ensure patients do not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient, and that the patient still fulfils the eligibility criteria for this study, including re-consenting to continue treatment. Patients with rapid tumor progression or with

symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) will not be eligible to continue to receive study treatment.

[f] Patients who achieve and maintain disease control (ie, CR, PR, or SD) through to the end of the assigned IP 12-month treatment period may restart treatment with the IP upon evidence of PD, with or without confirmation, during follow-up. Before restarting their assigned IP, the Investigator should ensure patients do not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient, and that the patient still fulfils the eligibility criteria for this study, including re-consenting to restart MEDI4736 and tremelimumab. To restart treatment, the patient must not have received an intervening systemic anticancer therapy after their assigned IP discontinuation. Patients should have a baseline tumor assessment within 28 days of restarting their assigned IP treatment; all further scans should occur q8w (relative to the date of restarting treatment) until study treatment is stopped (maximum of 12 months of further treatment). If a patient derives clinical benefit from the combination of MEDI4736 and tremelimumab, per judgment of the Investigator, and subsequently progresses while undergoing treatment with MEDI4736 alone, tremelimumab induction may be reinstituted for 4 doses one time only (follow the same treatment guidelines as during the first 12 months).

[g] Patients with confirmed PD who continue to receive their assigned IP at the discretion of the Investigator can receive treatment for a maximum of 12 months. Patients will have scans q8w while on treatment (relative to the date of the first infusion) until study treatment is stopped. Patients with rapid tumor progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) will not be eligible to continue to receive study treatment. IP should be discontinued if there is confirmed PD following a previous response (complete response or partial response) to IP (ie, the response and progression events both occurred while receiving active IP during the same treatment period in the target lesions).

[h] Week 0, Week 12 and Week 24 samples collected up to 60 minutes pre-dose and within 10 minutes of end of infusion. Week 36 and 48 samples are collected up to 60 minutes pre-dose only. In the combination arm, tremelimumab samples do not need to be collected after Week 12 during the 12-month dosing period (this applies to the immunogenicity assessments as well).

[i] Refer to Section 5.2.3 for timing.

[j] 10 mg/kg of tremelimumab q4w for 7 doses, then q12w for 2 additional doses (up to 9 doses in total).

[k] 20 mg/kg of MEDI4736 q4w for 4 doses. Four weeks after the last combination dose, MEDI4736 will be administered at 10 mg/kg q2w for a total 12-month period (ie, up to an additional 18 doses with the final dose at Week 50).

[l] 1 mg/kg of tremelimumab is administered q4w for a total of 4 doses.

[m] PRO assessments may be conducted within ±7 days of the scheduled visit. Note: All assessments on treatment days are to be performed prior to infusion, unless otherwise indicated.

ADA Anti-drug antibody; AE Adverse event; BP Blood pressure; C Cycle; CR Complete response; CT Computed tomography; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; Exam Examination; HIV Human immunodeficiency virus; HPV Human papillomavirus; ICF Informed consent form; IHC Immunohistochemistry; IP Investigational product; miRNA Micro ribonucleic acid; MRI Magnetic resonance imaging: mRNA Messenger ribonucleic acid; PBMC Peripheral blood mononuclear cell; PD Progressive disease; PD-L1 Programmed cell death ligand 1; PGx Pharmacogenetic research; PK Pharmacokinetic; PR Partial response; PRO Patient-reported outcomes; q2w Every 2 weeks; q4w Every 4 weeks; q8w Every 8 weeks; q12w Every 12 weeks; QLQ-C30 30-Item core quality of life questionnaire; QLQ-H&N35 35-Item head and neck quality of life questionnaire; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1; SAE Serious adverse event; SD Stable disease; sPD-L1 Soluble programmed cell death ligand 1; TSH Thyroid-stimulating hormone; T_4 Thyroxine; T_3 Triiodothyronine; V Visit; WHO World Health Organization.

Table 6 Schedule of assessments for patients who have completed 12 months of treatment or who have discontinued treatment for toxicity reasons (no confirmed progression)

	Time since last dose of IP							
	Day (±3)	Months (±1 week)						12 months and every 6 months (±2 weeks)
Evaluation	**30**	**2**	**3**	**4**	**6**	**8**	**10**	
Physical examination	X							
Vital signs (temperature, respiratory rate, blood pressure, pulse, and oxygen saturation; see Section 5.2.4)	X							
Weight	X							
AE/SAE assessment	X	X	X					
Concomitant medications	X	X	X					
WHO/ECOG performance status	X	X	X					
Subsequent anticancer therapy	X	X	X	X	X	X	X	X
Survival status: phone contact with patients who refuse to return for evaluations and agree to be contacted		X	X	X	X	X	X	X (every 3 months)
Hematology	X	X	X					X
Clinical chemistry	X	X	X					

	Time since last dose of IP							
	Day (±3)	Months (±1 week)						12 months and every 6 months (±2 weeks)
Evaluation	**30**	**2**	**3**	**4**	**6**	**8**	**10**	
TSH and reflex free T_3 or free T_4, only if TSH is abnormal	X							
Pharmacokinetic assessment			X					
Immunogenicity assessment (ADA sampling) to identify ADA responses in patient circulation			X		X			
sPD-L1 concentration (to assess target engagement)			X					
Circulating soluble factors (plasma)	X							
PBMC collection	X							
EORTC QLQ-C30[a]	For patients who **achieve disease control following 12 months of treatment**, patient-reported outcomes (EORTC QLQ-C30 and EORTC QLQ-H&N35) should be completed q12w relative to the date of **last infusion** and thereafter until confirmed PD. Following confirmed PD, if patients are receiving retreatment, all questionnaires should be completed q8w for up to 12 months during retreatment. If patients are not receiving retreatment, all questionnaires should be completed at Day 30, Month 2, and Month 3 from the date of confirmed PD and then stopped. For patients who discontinue MEDI4736 for reasons other than disease progression (eg, due to toxicity or symptomatic deterioration), all questionnaires should be completed relative to the date of **first infusion** as follows: q8w up to Week 48 (per Table 5), then q12w until confirmed PD.							
EORTC QLQ-H&N35[a]								

	Time since last dose of IP							
	Day (±3)	Months (±1 week)						12 months and every 6 months (±2 weeks)
Evaluation	**30**	**2**	**3**	**4**	**6**	**8**	**10**	
Tumor assessment (CT or MRI)[b]	For patients who **achieve disease control following 12 months of treatment**, tumor assessments should be performed every 12 weeks relative to the date of **last infusion** thereafter until confirmed PD by RECIST 1.1 by investigational site review. Please refer to Table 5 for timings of confirmatory scans. For patients who **discontinue their assigned IP due to toxicity (or symptomatic deterioration)**, tumor assessments should be performed relative to the date of **first infusion** as follows: q8w for the first 48 weeks (per Table 5), then q12w until confirmed PD by RECIST 1.1 by investigational site review. Please refer to Table 5 for timings of confirmatory scans. Upon confirmed PD, scans should be conducted according to local standard clinical practice and submitted for central review until a new treatment is started (these scans are optional).							

[a] PRO assessments may be conducted within ±7 days of the scheduled visit.
[b] RECIST 1.1 assessments will be performed using CT/MRI assessments of the neck (from base of skull) through the chest and abdomen (including liver and adrenals). Additional anatomy should be imaged based on signs and symptoms of individual patients.ADA Antidrug antibody; AE Adverse event; CT Computed tomography; ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; IP Investigational product; MRI Magnetic resonance imaging; PD Progressive disease; PBMC Peripheral blood mononuclear cell; PRO Patient-reported outcomes; q8w Every 8 weeks; q12w Every 12 weeks; QLQ-C30 30-Item core quality of life questionnaire; QLQ-H&N35 35 Item head and neck quality of life questionnaire; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1; SAE Serious adverse event; sPD-L1 Soluble programmed death ligand 1; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone; WHO World Health Organization.

Table 7 Schedule of assessments for patients who have had confirmed progression

	Time since last dose of IP							
Evaluation	**Day (±3)**	**Months (±1 week)**						**12 months and every 6 months (±2 weeks)**
	30	**2**	**3**	**4**	**6**	**8**	**10**	
Physical examination	X							
Vital signs (temperature, respiratory rate, blood pressure, pulse, and oxygen saturation; see Section 5.2.4)	X							
Weight	X							
AE/SAE assessment	X	X	X					
Concomitant medications	X	X	X					
WHO/ECOG performance status	X							
Subsequent anticancer therapy	X	X	X	X	X	X	X	X
Survival status: phone contact with patients who refuse to return for evaluations and agree to be contacted		X	X	X	X	X	X	X (every 3 months)
Hematology	X	X	X					
Clinical chemistry	X	X	X					
TSH and reflex free T_3, or free T_4, only if TSH is abnormal	X							
Pharmacokinetic assessment			X					
Immunogenicity assessment (ADA sampling) to identify ADA responses in patient circulation			X					
sPD-L1 concentration (to assess target engagement)			X					

	Time since last dose of IP							
Evaluation	**Day (±3)**	**Months (±1 week)**						**12 months and every 6 months (±2 weeks)**
	30	**2**	**3**	**4**	**6**	**8**	**10**	
Circulating soluble factors (plasma)	X							
PBMC collection	X							
EORTC QLQ-C30[a]	X	X	X					
EORTC QLQ-H&N35[a]	X	X	X					
Tumor assessment (CT or MRI)	For patients who **continue on their assigned IP post-confirmed progression** at the Investigator's discretion (following consultation with the Sponsor), tumor assessments should be performed relative to the date of **first infusion** per Table 5 until IP is stopped. For patients who **discontinue their assigned IP following confirmed progression, scans should be conducted according to local clinical practice** and submitted for central review until a new treatment is started (these scans are optional).							

[a] PRO assessments may be conducted within ±7 days of the scheduled visit.

ADA Antidrug antibody; AE Adverse event; CT Computed tomography; ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; IP Investigational product; MRI Magnetic resonance imaging; PRO Patient-reported outcomes; QLQ-C30 30-Item core quality of life questionnaire; QLQ-H&N35 35-Item head and neck quality of life questionnaire; SAE Serious adverse event; sPD-L1 Soluble programmed death ligand 1; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone; WHO World Health Organization.

Table 8 Schedule of assessments for patients continuing on or entering into retreatment during the overall survival extension period

	OS Extension Period															
	C1		C2		C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	
Visit	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Week	**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**50**
Informed consent																
Informed consent: study procedures	X[a]															
Study procedures[b]																
Physical exam (not including height, including weight[c])	X		X		X	X	X	X	X	X	X	X	X	X	X	
Vital signs: BP, pulse, body temperature, respiratory rate, and oxygen saturation	BP, pulse, respiratory rate, oxygen saturation, and body temperature will all be taken before the infusion or at a minimum of every 4 weeks when there is no infusion; BP and pulse will also be taken during and after each infusion or at a minimum of every 4 weeks when there is no infusion (see Section 5.2.4).															
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments[b]																
Clinical chemistry[d,e]	Pre-dose prior to each infusion or at a minimum of every 4 weeks when there is no infusion															
Hematology[d,e]	Pre-dose prior to each infusion or at a minimum of every 4 weeks when there is no infusion															
TSH and reflex free T_3 or free T_4, only if TSH is abnormal[d,e]	X		X		X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X		X		X	X	X	X	X	X	X	X	X	X	X	
Hepatitis B and C and HIV	X[a]															
Pregnancy test (for women of childbearing potential)	X[a]		X		X	X	X	X	X	X	X	X	X	X	X	X
Other safety examinations[b]																
ECG	As clinically indicated															
Monitoring																
WHO/ECOG performance status	X[a]															

	OS Extension Period															
	C1		C2		C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	
Visit	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Week	**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**50**
AE/SAE assessment[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug accountability	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP administration (retreatment patients only)[a]																
MEDI4736 monotherapy	Every 2 weeks															
Tremelimumab monotherapy[g]	X		X		X	X	X	X	X			X			X	
MEDI4736 (in combination with Tremelimumab)[h]	X		X		X	X	Every 2 weeks									
Tremelimumab (in combination with MEDI4736)[i]	X		X		X	X										

[a] Patients will only undergo retreatment with their previously-assigned study treatment if they complete the retreatment informed consent and fulfil the retreatment eligibility criteria (Section 3.1).

[b] Assessments should be conducted in such a way as to allow the Investigator to assess per-protocol retreatment eligibility. Patients with confirmed PD who are continuing to receive study treatment will receive scans/RECIST assessments as per local standard of care. Patients continuing on the study who remain potentially eligible for future retreatment should receive scans/RECIST assessments as per local standard of care, but in such a way that will allow confirmation of retreatment eligibility criteria.

[c] Weight should be measured in kg with 1 decimal place at a minimum q4w before infusion.

[d] If retreatment eligibility assessments are performed within 3 days prior to Week 0, Day 0 (first infusion day) they do not need to be repeated at Day 0.

[e] Results for urea and electrolytes, full blood count, and liver function tests must be available before commencing an infusion. Reflex free T3 or T4 are only needed if TSH is abnormal. All laboratory procedures required for dosing should be performed within 3 days prior to dosing. Creatinine clearance, gamma-glutamyltransferase, magnesium, and uric acid testing are to be performed when assessing eligibility for retreatment, on Day 0, and as clinically indicated. Activated partial thromboplastin time testing is to be conducted when assessing eligibility for retreatment only, unless clinically indicated. All other clinical chemistry assessments as detailed in Table 10 are conducted when assessing eligibility for retreatment; on Day 0; Weeks 2, 4, 6, and 8; and thereafter at each infusion.

[f] AEs and SAEs will be recorded until 90 days after the patient's final dose of study treatment, and are to be reported as described in Section 6.4. AEs not meeting SAE criteria that occur during the progression follow-up outside of the 90-day post final dose reporting window, or retreatment after the OS Extension DCO will be followed up at the Investigator's discretion and reported as described in Section 6.4.

[g] 10 mg/kg of tremelimumab q4w for 7 doses, then q12w for 2 additional doses (up to 9 doses in total).

[h] 20 mg/kg of MEDI4736 q4w for 4 doses. Four weeks after the last combination dose, MEDI4736 will be administered at 10 mg/kg q2w for a total 12-month period (ie, up to an additional 18 doses with the final dose at Week 50).

[i] 1 mg/kg of tremelimumab is administered q4w for a total of 4 doses.

AE Adverse event; BP Blood pressure; C Cycle; DCO Data cutoff; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; HIV Human immunodeficiency virus; ICF Informed consent form; IP Investigational product; OS Overall survival; PD Progressive disease; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1; SAE Serious adverse event; TSH Thyroid-stimulating hormone; T_3 Triiodothyronine; T_4 Thyroxine; V Visit; WHO World Health Organization.

Table 9 Schedule of follow-up assessments for all patients in survival follow-up during the overall survival extension period

	Time since last dose of IP							
	Day (±3)	Months (±1 week)						12 months and every 6 months (±2 weeks)
Evaluation[a]	**30**	**2**	**3**	**4**	**6**	**8**	**10**	
Physical examination	X							
Vital signs (temperature, respiratory rate, blood pressure, pulse, and oxygen saturation; see Section 5.2.4)	X							
Weight	X							
AE/SAE assessment[b]	X	X	X					
Concomitant medications	X	X	X					
Survival status: phone contact with patients who agree to be contacted		X	X	X	X	X	X	X (every 3 months)
Hematology	X	X	X					X[c]
Clinical chemistry	X	X	X					
TSH and reflex free T_3 or free T_4, only if TSH is abnormal	X							

[a] Patients with confirmed PD who are continuing to receive study treatment will receive scans/RECIST assessments as per local standard of care. Patients continuing on the study who remain potentially eligible for future retreatment should receive scans/RECIST assessments as per local standard of care, but in such a way that will allow confirmation of retreatment eligibility criteria.

[b] AEs and SAEs will be recorded until 90 days after the patient's final dose of study treatment, and are to be reported as described in Section 6.4. AEs not meeting SAE criteria that occur during the progression follow-up outside of the 90-day post final dose reporting window, or retreatment after the OS Extension DCO will be followed up at the Investigator's discretion and reported as described in Section 6.4.

[c] Assessment not to be conducted for patients who have had confirmed progression.

AE Adverse event; DCO Data cutoff; IP Investigational product; OS Overall survival; PD Progressive disease; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1; SAE Serious adverse event; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone.

4.1 Enrollment/screening period

All screening and enrollment procedures will be performed according to the assessment schedule in Table 5. Screening evaluations may be performed over multiple visits. Procedures required for screening that were performed prior to the patient signing informed consent can be used for screening if the patient consents; however, dosing must occur within 28 days of screening procedures. Procedures required for Cycle 1, Day 0 need not be repeated if they were performed for screening purposes within 3 days of Cycle 1, Day 0.

Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including the PD-L1 testing and screening evaluations. All patients will be required to provide consent to supply a sample of their tumor (newly acquired biopsy or archival) for entry into this study.

The PD-L1 testing is intended for determination of the patient's tumoral PD-L1 expression status. If the patient's PD-L1 status has already been assessed using the analytically validated Ventana SP263 assay as a part of the screening process for D4193C00001 or another AstraZeneca/MedImmune study, this test result can be used for the determination of eligibility. A patient does not need to re-consent to PD-L1 testing if his or her PD-L1 status was determined previously on another AstraZeneca/MedImmune study.

HPV status of the SCCHN can be collected from historical medical records of any age. For patients whose HPV status of the SCCHN is not already available, HPV status should be assessed in a licensed clinical laboratory according to local standard procedures. If local testing is not available then central testing can be performed on formalin-fixed archival or newly acquired tumor tissue.

Patients who are progression-free following randomized treatment and potentially eligible for retreatment are to undergo sampling for local laboratory assessments (Table 9), and in such a way that continued per-protocol retreatment eligibility can be properly determined.

4.2 Treatment period

All procedures to be conducted during the 12-month treatment period will be performed according to the assessment schedule (see Table 5).

Whenever vital signs, ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: ECG, vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the exact nominal time.

4.3 Follow-up period

All procedures to be conducted during the 12-month follow-up period will be performed according to the assessment schedule (see Table 6 and Table 7).

Whenever vital signs, ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: ECG, vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the exact nominal time.

4.4 Overall survival extension period

Table 8 shows the schedule of assessments for patients continuing on or entering into retreatment during the OS Extension period. Table 9 shows the schedule of assessments for all patients in follow-up during the OS Extension period.

5. STUDY ASSESSMENTS

A Web Based Data Capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRFs as specified in this study protocol and in accordance with the instructions provided.

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

During the OS Extension period, all patients will be followed for survival. Overall survival, safety-related data and IP administration details will be collected in the clinical database.

5.1 Efficacy assessments

RECIST 1.1 criteria will be used to assess patient response to treatment by determining ORR, DoR, DCR, BoR, and PFS. The RECIST 1.1 guidelines for measurable, non-measurable, target, and non-target lesions and the objective tumor response criteria (CR, PR, SD, or PD) are presented in Appendix E. Overall survival will also be evaluated.

The methods of assessment of tumor burden used at baseline are CT and/or MRI scans of the neck (including the base of skull) through chest and abdomen (including the liver and adrenals). Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients. The method of assessment should remain consistent over the life of the patient's involvement unless in a situation where a specific form of imaging is not clinically appropriate.

The baseline assessment should be performed no more than 28 days before the start of IP treatment and ideally as close as possible to the start of the assigned IP. Scans required for screening that were performed for other reasons prior to the patient signing informed consent can be used for the baseline assessment if the patient consents; however, dosing must occur within 28 days of screening procedures. Efficacy for all patients will be assessed by objective tumor assessments q8w for the first 48 weeks (relative to the date of the first MEDI4736 or tremelimumab infusion; Table 5) and then q12w after discontinuation of assigned IP in

patients who have disease control after 12 months of treatment (Table 6) until confirmed objective disease progression as defined by RECIST 1.1 (irrespective of the reason for stopping treatment). If an unscheduled scan is performed in the absence of suspicion of progression within 2 weeks of a scheduled scan, the scan does not need to be repeated. However, every attempt should be made to follow the original scan schedule.

Disease progression requires confirmation, the confirmatory scan should occur preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Treatment with IP will continue between the initial assessment of progression and confirmation for progression.

Only patients who the Investigator determines do not have any significant, unacceptable, or irreversible toxicities and would continue to receive benefit from therapy can continue therapy through progression during the initial 12 months of therapy or restart a second 12 months of retreatment upon suspicion of PD. The Investigator should also ensure that the patient still meets all of the inclusion criteria and none of the exclusion criteria for this study, including re-consenting to continue or restart treatment. Patients with rapid tumor progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) will not be eligible to continue to receive study drug. Patients with confirmed progression in the MEDI4736 monotherapy arm, tremelimumab monotherapy arm, or in the combination portion of therapy in the MEDI4736 + tremelimumab arm cannot continue therapy or obtain retreatment if the progression occurred during dosing and after confirmed response in the target lesions (ie, the response and progression events both occurred while receiving active IP during the same treatment period in the target lesions).

Progression would be considered confirmed if the following criteria are met:

- ≥20% increase in the sum diameters of target lesions compared with the nadir at 2 consecutive visits with an absolute increase of 5 mm(1)
- And/or significant progression (worsening) of non-target lesions or new lesions at the confirmatory PD timepoint compared with the first timepoint where progression of non-target lesions or new lesions was identified
- And/or additional new unequivocal lesions at the confirmatory PD timepoint compared with the first timepoint at which new lesions were identified.

(1) The assessment of progression requires a ≥20% increase in the sum diameters of target lesions at the first progression timepoint relative to the nadir. The nadir is the smallest sum of diameters, and this may be at baseline or subsequent follow-up assessments. The confirmatory scan confirms the persistence of the ≥20% increase relative to the nadir. The minimum absolute increase in the sum of diameters of target lesions is at least 5 mm at both assessments.

In the absence of clinically significant deterioration, the Investigator should continue study treatment until progression is confirmed.

If progression is not confirmed, then the patient should continue on study treatment and on treatment assessments.

If a patient discontinues treatment prior to progression, then the patient should still continue to be followed until confirmed objective disease progression by radiographic documentation of PD.

Categorization of objective tumor response assessment will be based on the RECIST 1.1 criteria of response: CR, PR, SD, and PD. Target lesion progression will be calculated in comparison to when the tumor burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of progression, tumor response (CR or PR) and SD will be calculated in comparison to the baseline tumor measurements obtained before starting treatment.

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

If the Investigator is in doubt as to whether progression has occurred, particularly with response to non-target lesion or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated and reassess the patient's status. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.

To achieve "unequivocal progression" on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of 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 one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

Following confirmed progression, patients should continue to be followed up for survival as outlined in the study plan (Table 7). An exception are patients with confirmed PD who continue to receive IP at the discretion of the Investigator (after consultation with the Sponsor); these patients can receive treatment for a maximum of 12 months and will have scans for RECIST 1.1 assessments every 8 weeks (q8w) (relative to the date of the first infusion per Table 5) until study treatment is stopped, and then every 3 months until disease progression.

Patients with confirmed PD who discontinue IP should have scans conducted according to local practice and submitted for BICR until the patient commences a new treatment (these scans are optional; see Table 7).

Patients who achieve and maintain disease control (ie, CR, PR, or SD) through to the end of the 12-month IP treatment period may restart treatment with MEDI4736, tremelimumab, or

MEDI4736 + tremelimumab combination upon evidence of PD, with or without confirmation, during follow-up. To restart treatment, the patient must not have received an intervening systemic anticancer therapy post-IP discontinuation. Patients who restart MEDI4736, tremelimumab, or MEDI4736 + tremelimumab combination must have a baseline tumor assessment within 28 days of restarting treatment with IP; all further scans should occur q8w (relative to the date of restarting treatment) until study treatment is stopped (maximum of 12 months of further treatment). During and after the OS Extension period, all patients should receive scans/RECIST assessments as per the local standard of care.

Patients with confirmed progression in the MEDI4736 monotherapy arm or in the combination portion of therapy in the MEDI4736 + tremelimumab arm cannot continue therapy or obtain retreatment if the progression occurred during dosing and after confirmed response in the target lesions (ie, the response and progression events both occurred while receiving active IP during the same treatment period in the target lesions). Patients in the MEDI4736 + tremelimumab group who are eligible for retreatment will receive 20 mg/kg MEDI4736 via IV infusion q4w for 4 months (up to 4 doses) and 1 mg/kg tremelimumab via IV infusion q4w for 4 months (up to 4 doses in total). After completion of the initial 4 doses of combination therapy, single agent MEDI4736 will continue at 10 mg/kg q2w to complete 12 months of therapy (up to an additional 18 doses with the final dose at Week 50). The first MEDI4736 dose at 10 mg/kg q2w will be 4 weeks after the final dose of the combination of tremelimumab and MEDI4736 at 20 mg/kg.

It is important to follow the assessment schedule as closely as possible. Please refer to the study plans (Table 5 [screening and the treatment period], Table 6 [for follow-up of patients achieving disease control or who are discontinued due to toxicity in the absence of confirmed PD], and Table 7 [for follow-up of patients discontinuing due to confirmed PD]) and Appendix E. However, if an unscheduled scan is performed in the absence of suspicion of progression within 2 weeks of a scheduled scan, the scan does not need to be repeated. All patients will be followed up for disease progression and survival.

5.1.1 Central reading of scans

A BICR of all scans used in the assessment of tumors using RECIST 1.1 modified for confirmation of progression and irRECIST 1.1 will be conducted (see Section 8.4.1.1 for the analysis methods). All imaging assessments including unscheduled visit scans will be collected on an ongoing basis and sent to an AstraZeneca-appointed Contract Research Organisation for central analysis. Results of these independent reviews will not be communicated to Investigators, and the management of patients will be based solely upon the results of the RECIST 1.1 assessment conducted by the Investigator.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the assessment schedules (see Table 5, Table 6, and Table 7).

Clinical laboratory safety tests, including serum pregnancy tests, will be performed in a licensed clinical laboratory. Hematology, clinical chemistry, and urinalysis tests will be performed by the hospital's local laboratory. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. Urine pregnancy tests may be performed at the site using a licensed test (dipstick). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

During the OS Extension period, laboratory assessments should be conducted as detailed in Table 8 and Table 9, and in such a way that per-protocol retreatment eligibility can be determined.

For patients receiving retreatment after the OS Extension DCO, it is recommended that Investigators monitor the patient's safety laboratory assessments prior to and periodically during study treatment in order to manage AEs in accordance with the toxicity management guidelines (Table 13).

The laboratory variables to be measured are presented in Table 10 (clinical chemistry), Table 11 (hematology), and Table 12 (urinalysis).

Table 10 Clinical chemistry

Alanine aminotransferase[a]	Glucose
Albumin	Lactate dehydrogenase
Alkaline phosphatase[a]	Lipase
Amylase	Magnesium[b]
Aspartate aminotransferase[a]	Potassium
Bicarbonate	Sodium
Calcium	Total bilirubin[a]
Chloride	Total protein
Creatinine (creatinine clearance)[b]	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyltransferase[b]	Uric acid[b]

[a] Tests for alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently.
[b] Creatinine clearance, gamma glutamyltransferase, magnesium, and uric acid testing are to be performed at Screening, on Day 0, and as clinically indicated.
Note: Clinical chemistry assessments are to be performed at each visit and when clinically indicated.

Table 11 Hematology

Activated partial thromboplastin time[a]	Mean corpuscular hemoglobin concentration
Basophils	Mean corpuscular volume
Eosinophils	Monocytes
Hematocrit	Neutrophils
Hemoglobin	Platelet count
International normalized ratio[a]	Red blood cell count
Lymphocytes	Total white cell count
Mean corpuscular hemoglobin	

[a] Activated partial thromboplastin time and the international normalized ratio will be determined at Screening only, unless clinically indicated.
Note: Hematology assessments (absolute counts, as appropriate) are to be performed at each visit and when clinically indicated.

Table 12 Urinalysis

Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

Note: Urinalysis is to be performed at Screening, Day 0, every 4 weeks after Day 0 (ie, every second dosing visit), and when clinically indicated.

If a patient shows an AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN, refer to Appendix D for further instructions. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's Law case or if any of the individual liver test parameters fulfill any of the SAE criteria. All patients with an elevated AST, ALT, or bilirubin value (the latter at ≥1.5 × ULN) at the time of the last dose of study treatment should have a further liver chemistry profile (AST, ALT, bilirubin, and alkaline phosphatase) performed 30 days (±3 days) after permanent discontinuation of study treatment.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 6.3.7.

All patients with Grade 3 or 4 laboratory values at the time of completion or discontinuation from study treatment must have further tests performed until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

5.2.2 Physical examination

Physical examinations will be performed according to the assessment schedules (see Table 5, Table 6, and Table 7) and will include assessments of the head, eyes, ears, nose, and throat

and the respiratory, cardiovascular, GI, and hematologic/lymphatic systems at a minimum. Height will be measured at Screening only. Situations in which physical examination results should be reported as AEs are described in Section 6.3.7.

5.2.3 Electrocardiograms

Resting 12-lead ECGs will be recorded at Screening, on Day 0, at Week 12, and as clinically indicated throughout the study (see Table 5). ECGs should be obtained after the patient has been in a supine or reclining position and using a Sponsor-provided device.

At Screening, a mean QT interval corrected for Fridericia's formula (QTcF) will be calculated using 3 ECGs approximately 5 minutes apart. The mean QTcF must be <470 ms for the patient to meet eligibility criteria. On Day 0, ECGs must be performed prior to infusion and within 30-minutes post-infusion. At Week 12, ECGs are conducted post-dose.

In case of clinically significant ECG abnormalities, including a QT interval corrected for Fridericia's formula (QTcF) value ≥470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm prolongation.

Situations in which ECG results should be reported as AEs are described in Section 6.3.7.

During and after the OS Extension period, ECGs will be collected locally and as clinically indicated.

5.2.4 Vital signs

Vital signs (BP, pulse, temperature, respiration rate, and oxygen saturation) will be evaluated according to the assessment schedules (see Table 5, Table 6, and Table 7). On infusion days, patients will be monitored during and after infusion of IP as follows. Supine or reclining BP will be measured using a semi-automatic BP recording device with an appropriate cuff size, after the patient has rested for at least 5 minutes. BP and pulse will be collected from patients in the MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, and tremelimumab monotherapy treatment groups before, during, and after the infusion of each agent at the following times (based on a 60-minute infusion):

- At the beginning of the infusion (at 0 minutes but no more than 30 minutes prior to infusion)
- Every 30 minutes during the infusion (±5 minutes)
- At the end of the infusion (±5 minutes)
- A 1-hour post-infusion observation period at 30 (±5) and 60 (±5) minutes after the infusion ends is required after the first infusion of tremelimumab or MEDI4736. For the combination therapy group, these assessments should be followed for each of the 2 component infusions. If no infusion reactions are observed during or after the first cycle, subsequent infusion

observation periods can be at the Investigator's discretion (suggested approximately 30 minutes after the infusion).

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. The date and time of collection and measurement will be recorded on the appropriate eCRF. Additional monitoring with assessment of vital signs is at the discretion of the Investigator per standard clinical practice or as clinically indicated.

Situations in which vital signs results should be reported as AEs are described in Section 6.3.7.

5.2.5 Other safety assessments

Pregnancy tests on either urine (human chorionic gonadotropin [hCG]) or blood (serum β-hCG) samples will be performed for pre-menopausal women of childbearing potential at the times specified in the assessment schedule (see Table 5). Tests will be performed by the hospital's local laboratory. If results are positive, the patient is ineligible and must be discontinued from the study. In the event of a suspected pregnancy during the study, the test should be repeated.

Other safety tests to be performed at Screening include assessment for hepatitis B surface antigen, hepatitis C antibodies, and HIV antibodies.

5.3 Other assessments

These assessments will not be performed during the OS Extension period.

5.3.1 Patient-reported outcomes

The EORTC QLQ-C30 (core questionnaire) and QLQ-H&N35 (head and neck-specific questionnaire) are self-administered questionnaires to be completed by the patient without the assistance of the investigational site personnel using the site pad provided by AstraZeneca-selected vendor. All questionnaires should be completed according to the assessment schedules (see Table 5, Table 6, and Table 7). It is preferred that questionnaires be completed before any other study procedures (laboratory tests or imaging) are conducted for a given visit. However, if questionnaires cannot be administered prior to study procedures for a given visit, all questionnaires must be completed prior to the patient receiving any results of laboratory tests or imaging or meeting with their study nurse or physician. For the screening visit ONLY, PRO questionnaires can be collected anytime during the screening window. It takes approximately 20 to 30 minutes for patients to complete both questionnaires; therefore, the burden to the patient is moderate. If patients have missed a scheduled data collection visit, PRO questionnaires should continue to be administered at the following visit. Study coordinators will need to document a reason why a particular questionnaire or visit was missed.

5.3.1.1 EORTC QLQ-C30

The EORTC QLQ-C30 is a 30-item self-administered questionnaire (see Appendix F). There are 9 multiple item scales: 5 scales that assess aspects of functioning (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), and a global health status/QoL scale. There are 5 single-item measures assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation, and diarrhea) and a single item concerning the perceived financial impact of the disease. All but 2 questions have 4-point scales: "Not at all," "A little," "Quite a bit," and "Very much." The 2 questions concerning global health status and QoL have 7-point scales with ratings ranging from "Very poor" to "Excellent." For each of the 15 domains (9 multiple-item scales, and 6 single item scales), final scores are transformed such that they range from 0 to 100 where higher scores indicate greater functioning, greater QoL, or greater level of symptoms (Aaronson et al 1993).

5.3.1.2 EORTC QLQ-H&N35

The EORTC QLQ-H&N35 module is a 35-item self-administered questionnaire (see Appendix F). There are 7 multiple item scales that assess pain in the mouth, problems with swallowing, senses, speech, social eating, social contact, and sexuality. There are 11 single-item measures assessing additional symptoms commonly reported by head and neck cancer patients, including problems with teeth, problems with mouth opening, dry mouth, sticky saliva, coughing, feeling ill, use of analgesics, use of nutritional supplements, use of a feeding tube, weight gain, and weight loss. All but 5 questions have 4-point scales: "Not at all," "A little," "Quite a bit," and "Very much." The 5 questions concerning use of analgesics, use of nutritional supplements, use of a feeding tube, weight gain, and weight loss have 2-point scales ("Yes" or "No"). For each of the 18 domains (7 multiple-item scales and 11 single item scales), final scores are transformed such that they range from 0 to 100, where higher scores indicate greater level of symptoms (Singer et al 2013).

5.3.2 Administration of the patient-reported outcome questionnaires

Patients will complete the PRO assessments by using a handheld electronic device.

Each center must allocate the responsibility for the administration of the PRO instruments to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a back-up person to cover if that individual is absent. The PRO questionnaires must be administered and completed at the clinic as per the schedule of assessments. The PRO questionnaires will be administered on the days specified in the schedules of assessments (see Table 5, Table 6, and Table 7). The EORTC QLQ-C30 should always be completed prior to the QLQ-H&N35 module.

It is important that the significance and relevance of the data are explained carefully to participating patients so that they are motivated to comply with data collection.

The following best practice guidelines should be followed when collecting PRO data via an electronic device:

- It is preferred that PRO questionnaires are completed prior to any other study procedures (following informed consent) and before discussion of disease progress to avoid biasing the patient's responses to the questions. For the screening visit ONLY, PRO questionnaires can be collected anytime during the screening window.

- PRO questionnaires must be completed in private by the patient.

- The patient should be given sufficient time to complete the PRO questionnaires at their own speed.

- The patient should not receive help from relatives, friends, or clinic staff to answer the PRO questionnaires. If a patient uses visual aids (eg, spectacles or contact lenses) for reading, they should be reminded to bring them to the appointment.

- As a general rule, site staff should not read or complete the PRO questionnaires on behalf of the patient. For patients who cannot read for any reason, site staff can read the questions and response options **verbatim** and record the responses for the patient. The questions and response options should not be paraphrased or interpreted for the patient. It should be documented that a patient received assistance during that visit.

- On completion of the PRO questionnaires, it should be handed back to the person responsible for PRO questionnaires, who should make sure that all questionnaires for that visit were completed.

5.3.3 WHO/ECOG performance status

WHO/ECOG performance status will be assessed at the times specified in the assessment schedules (see Table 5, Table 6, and Table 7) based on the following:

0. Fully active; able to carry out all usual activities without restrictions

1. Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature, eg, light housework or 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; unable to carry out any self-care and totally confined to bed or chair

Any significant changes from baseline or screening must be reported as an AE.

5.4 Pharmacokinetics

5.4.1 Collection of samples and determination of drug concentration

Blood samples for determination of MEDI4736 and tremelimumab concentration in serum will be obtained according to the assessment schedules (see Table 5, Table 6, and Table 7).

Samples for determination of MEDI4736 and tremelimumab concentration in serum will be analyzed by a designated third party on behalf of AstraZeneca. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual. Full details of the analytical method used will be described in a separate Bioanalytical Validation Report.

Pharmacokinetic assessments will not be conducted during or after the OS Extension period.

5.4.2 Collection of samples to measure for the presence of ADAs

The presence of ADA will be assessed in serum samples taken according to the assessment schedules (see Table 5, Table 6, and Table 7).

Samples will be measured for the presence of ADAs for both IPs (MEDI4736 and tremelimumab) using validated assays. Tiered analysis will be performed to include screening, confirmatory, and titer assay components, and positive-negative cut points previously statistically determined from drug-naïve validation samples will be employed. Samples will be collected and stored for potential neutralizing ADA analysis in the future when the method is available.

ADA assessments will not be conducted during or after the OS Extension period.

5.4.3 Storage and destruction of pharmacokinetic/ADA samples

PK and ADA samples will be disposed of 5 to 10 years after the IPs are approved for marketing.

PK and ADA samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Results from such analyses may be reported separately from the 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 Validation Report.

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

5.5 Pharmacogenetics

Refer to Appendix C for details of the genetic research (optional DNA component).

Pharmacogenetic assessments will not be conducted during or after the OS Extension period.

5.6 Biomarker analysis

The patient's consent to the use of donated biological samples is mandatory.

Mandatory tumor and blood biomarkers to be evaluated for the purposes of patient selection and for exploratory analyses are described in Section 5.6.1. Exploratory biomarkers may be evaluated as determined by additional data (see Section 5.6.2). Samples will be taken according to the assessment schedules (see Table 5, Table 6, and Table 7).

Biomarker assessments will not be conducted during or after the OS Extension period.

Biomarkers that have demonstrated the potential to identify patients who are likely to respond to treatment with IP (from other MEDI4736 + tremelimumab studies) may be investigated to determine a patient's biomarker status and for possible correlation with efficacy endpoints in an exploratory analysis outside the scope of the CSR.

Exploratory biomarker research will not form part of the CSR. The results may be pooled with biomarker data from other MEDI4736 + tremelimumab studies to test existing hypotheses or to generate hypotheses to be tested in future studies.

5.6.1 Collection of patient samples for PD-L1 status identification

There is 1 mandatory provision of formalin-fixed and paraffin-embedded tissue to be used for determination of eligibility.

- MANDATORY: Provision of a newly acquired tumor sample (preferred) **OR** archival tissue obtained within 3 years. ONLY 1 sample (either newly acquired or archival tissue) will be used to assess PD-L1 status for purposes of eligibility. Where multiple samples have been submitted for the same patient, the initial result will inform patient status for eligibility.

Samples should be collected via a core needle of 18 gauge or larger or be collected as an excisional tumor biopsy sample.

Where institutional practice, in this setting, uses a smaller gauge needle, samples should be submitted in sufficient number to ensure that a valid result can be achieved.

When tissue is newly obtained using an 18-gauge needle for the purpose of entry into this study, 2 cores should be placed in formalin and processed to a single paraffin-embedded block, as described in the Pathology Manual. When a smaller gauge needle is used, the number of cores rises to 3 or 4.

The tumor specimen submitted to establish eligibility should be of sufficient quantity to allow for PD-L1 IHC analysis (see the Pathology Manual). Samples with limited tumor content and fine needle aspirates are inadequate for defining tumor PD-L1 status.

- Tumor lesions used for newly acquired biopsies should not be the same lesions used as RECIST 1.1 target lesions, unless there are no other lesions suitable for biopsy. OPTIONAL: If archival tissue (<3 years old) is submitted for PD-L1 analysis as an assessment for eligibility, an optional additional newly acquired biopsy is strongly encouraged, which will be used to assess exploratory endpoints. Please consult the Laboratory Manual for further details on how this sample should be processed.

    - OPTIONAL: The collection of additional archived tumor tissue block (formalin-fixed paraffin-embedded) is highly encouraged, where such samples exist in a quantity sufficient to allow for analysis. This specimen may be supplied at any time during the study. Tumor tissue block is preferred. If a tissue block is unavailable, unstained sections from the tissue block may be submitted. Please consult the Pathology Manual for specific instructions and guidelines regarding sections.

    - OPTIONAL: The collection of tumor biopsies prior to retreatment, if feasible or clinically indicated.

    - OPTIONAL: Additional tumor biopsies collected as part of clinical care (eg, for mixed responses or upon PD) can be submitted for further analysis.

See the Pathology and Laboratory Manuals for further details of requirements, including sample quality control and shipping.

A brief description of exploratory tumor markers likely to be explored by IHC or RNA analysis is provided in Section 5.6.2. The analytically validated Ventana PD-L1 SP263 IHC assay will be used to determine PD-L1 IHC status in this study for the analysis of the original diagnostic sample.

To meet the requirement of Food and Drug Administration (FDA) approval of a companion diagnostic, sections of the tumor will be retained at the Ventana-approved laboratory for potential additional studies, as requested by the FDA, to support potential test approval.

5.6.2 Collection of exploratory biomarker data

5.6.2.1 Blood-borne biomarkers

Blood samples may be analyzed to evaluate protein, nucleic acid, and cellular biomarkers that relate to IP treatment.

Blood (mononuclear cell) samples collected for the analysis of immune cell gene expression profiles and the quantities and phenotypes of lymphocyte subsets such as T cells may be evaluated for any relationship with efficacy endpoints.

Blood (plasma) samples will be collected for possible analysis of circulating soluble factors in relation to immune status at baseline and in response to treatment. Factors to be analyzed may include, but are not limited to: the presence of interferon-γ tumor necrosis factor (TNF)-α, IL-2, IL-6, IL-10, IL-8, and IL-12 and the levels of sPD-L1 and antibodies against tumor, self, or viral antigens.

5.6.2.2 Tumor samples

The expression and localization of other immune-related or response-related markers by IHC may also include, but may not be limited to, CTLA-4, CD3, CD4, CD8, CD45RO, forkhead box P3, granzyme B, OX40, PD-1, cleaved caspase 3, and Ki67. Archived material or newly acquired biopsies may also be analyzed for the presence of key mutations which may include, but are not limited to: epidermal growth factor receptor (EGFR), K-ras, N-ras, B-raf, anaplastic lymphoma kinase, and met proto oncogene to evaluate their potential relevance and correlations with response to IP treatment. Analysis of messenger RNA (mRNA) and/or micro-RNA (miRNA) in archival and/or newly acquired tumor tissue may be performed to evaluate the association with response to MEDI4736 + tremelimumab treatment.

5.6.2.3 Pharmacogenomics (RNA)

Whole blood and tumor samples will be collected for mRNA and/or miRNA analyses and stored for future analyses. RNA analyses will be conducted to generate hypotheses associated with the mechanisms of action of MEDI4736 and tremelimumab and to evaluate the utility of gene expression profiling to identify subsets of patients responsive to IP.

5.6.3 Management of biomarker data

The biomarker data will have unknown clinical significance. AstraZeneca will not provide biomarker research results to patients, their family members, any insurance company, an employer, clinical study investigator, general physician, or any other third party, unless required to do so by law. The patient's samples will not be used for any purpose other than those described in the study protocol.

Individual patients will not be identified in any report or publication resulting from this work. The data and results of this research may be reviewed with collaborators and published, but neither the patient's name nor any other personal identifiers will appear in any publication or report.

5.6.4 Storage, re-use, and destruction of biological samples

Samples will be stored for a maximum of 15 years from the end of study, after which they will be destroyed. The results of this biomarker research may be reported in the CSR itself, as an addendum, or separately in a scientific report or publication. The results of this biomarker

research may be pooled with biomarker data from other studies involving MEDI4736 and tremelimumab to generate hypotheses to be tested in future research.

5.6.5 Labeling and shipment of biological samples

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

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

5.6.6 Chain of custody of biological samples

A full chain of custody will be maintained for all samples throughout their life cycle.

The Principal Investigator at each center will keep full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate) and will keep documentation of receipt of arrival.

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

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

Samples retained for further use will be registered in the AstraZeneca Biobank during the entire life cycle.

5.6.7 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of or destroyed and the action documented. If samples have already been analyzed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator will:

- Ensure that AstraZeneca is immediately notified of the patients' withdrawal of informed consent to the use of donated samples
- Ensure that biological samples from that patient, if stored at the study site, are immediately identified, disposed of or destroyed and the action documented

- Ensure that the laboratory(ies) holding the samples is/are immediately informed about the withdrawn consent and that samples are disposed of or destroyed, the action is documented, and the signed document is returned to the study site

- Ensure that the patient and AstraZeneca are informed about the sample disposal

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. Safety guidelines around SAE reporting described within the protocol will remain in effect during and after the OS Extension period.

6.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition during or following exposure to a pharmaceutical product, whether or not the condition is considered to be causally related to the product. An undesirable medical condition can be a symptom (eg, nausea or chest pain), sign (eg, tachycardia or enlarged liver), or the abnormal result of an investigation (eg, laboratory findings or ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term 'AE' is used to include both serious and non-serious AEs.

6.2 Definitions of serious adverse event

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

- Results in death

- Is immediately life-threatening

- Requires in-patient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions

- Is a congenital abnormality or birth defect

- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

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

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse events and SAEs will be collected from the time the informed consent is signed through 90 days after the last dose of the last study treatment or until another therapy has been initiated.

For screen failure patients, AEs and/or SAEs must be collected from time of first informed consent to time of withdrawal. If a patient signs consent, and did not get dosed (is withdrawn), there is no requirement to collect AEs and/or SAEs after the patient has been withdrawn.

During the OS Extension period, AEs/SAEs will be monitored and recorded in the clinical database.

After the OS Extension period DCO, AEs not meeting SAE criteria will be followed-up at the Investigator's discretion. Any SAEs occurring whilst the patient is either still receiving study treatment (ie, retreatment patients) or in the 90-day safety follow-up period after receiving the last dose of IP should be reported to the AstraZeneca representative following the procedures outlined in Section 6.4.

6.3.2 Follow-up of unresolved adverse events

During the course of the study, all AEs and SAEs should be proactively followed up for each patient. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation or study completion.

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

6.3.3 Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- The maximum CTCAE grade reported
- Whether the AE is serious or not
- Investigator causality rating against the IPs (yes or no)

- Action taken with regard to IPs
- Administration of treatment for the AE
- Whether the AE caused the patient's withdrawal from the study (yes or no)
- Outcome

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

- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Seriousness criteria fulfilled
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Description of the AE

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but it is 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 it would be an SAE if it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

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

For SAEs, causal relationship will also be assessed for other medications 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 A.

6.3.5 Relationship to protocol procedures

The Investigator is also required to provide an assessment of the relationship of SAEs to protocol procedures on the SAE report form. This includes both non-treatment-emergent (ie, SAEs that occur prior to the administration of IP) and treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection). The following guidelines should be used by Investigators to assess the relationship of SAEs to the protocol:

- Protocol related: The event occurred due to a procedure or intervention that was described in the protocol for which there is no alternative etiology present in the patient's medical record.
- Not protocol related: The event is related to an etiology other than the procedure or intervention that was described in the protocol. The alternative etiology must be documented in the study patient's medical record.

6.3.6 Adverse events based on signs and symptoms

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

6.3.7 Adverse events based on examinations and tests

The results from protocol-mandated tests and vital signs measurements will be summarized in the CSR. Deterioration as compared to baseline in protocol-mandated test values and vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IPs.

If deterioration in a test value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated test result or vital sign will be considered as additional information. Whenever possible, the reporting Investigator should use the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AEs.

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

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

6.3.8 Hy's Law

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

6.3.9 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression should not be reported as an AE during the study.

6.3.10 New cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study.

6.3.11 Deaths

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

- Death clearly resulting from disease progression should be reported to the Study Physician at the next monitoring visit and should be documented in the eCRF. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the Study Physician as an SAE within 24 hours. The report should contain a

comment regarding the co-involvement of PD, if appropriate, and should assign main and contributory causes of death.

- Deaths with an unknown cause should always be reported as an SAE. A post-mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Drug Safety or its representative within the usual timeframes.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IPs or to any study procedure.

If any SAE occurs in the course of the study, then the Investigator or other site personnel should inform the appropriate AstraZeneca representatives (PRA Health Sciences [PRA] Drug Safety Center) within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work 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 in which important or relevant information is missing, active follow-up is undertaken immediately. The Investigator or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigator or other site personnel indicates that an AE is serious in the WBDC system, an automated e-mail alert is sent to the designated AstraZeneca representative.

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

The AstraZeneca representative will advise the Investigator or study site personnel how to proceed.

The reference documents for the definition of expectedness or listedness are the IBs for MEDI4736 and tremelimumab.The Principal Investigator 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.**

Name	Role in the study	Address & telephone number
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

6.5 Overdose

Use of IP in doses in excess of that specified in the protocol per the dosing instructions in Section 7.1 is considered to be an overdose. There is currently no specific treatment in the event of overdose of IP, and possible symptoms of overdose are not established.

- An overdose with associated AEs will be recorded as the AE diagnosis or symptoms in the relevant AE modules of the eCRF and in the Overdose eCRF module.
- An overdose without associated symptoms will only be reported in the Overdose eCRF module.

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

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the AstraZeneca representative.

6.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the IPs should be discontinued immediately.

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

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform the appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 to 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy, and the PREGOUT is used to report the outcome of the pregnancy.

6.6.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 90 days (MEDI4736 monotherapy and tremelimumab monotherapy) or 180 days (MEDI4736 +tremelimumab combination therapy) following the last dose.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should, if possible, be followed up and documented.

The outcome of any conception occurring from the date of the first dose until 90 days (180 days if on MEDI4736+tremelimumab combination therapy) after the last dose should be followed up and documented. Information on the pregnancy of a patient's partner must be obtained directly from the patient's partner. Therefore, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner.

6.7 Management of IP-related toxicities

The following general guidance should be followed for management of toxicities.

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity if required).

- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned IP along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted (see Sections 6.7.1 and Table 13).

- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

All toxicities will be graded according to CTCAE version 4.03.

In addition, there are certain circumstances in which MEDI4736 and tremelimumab should be permanently discontinued (see and Section 3.9 and Table 13).

Following the first dose of IP, subsequent administration of MEDI4736 and tremelimumab can be modified based on toxicities observed as described in Table 13. These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, or tremelimumab monotherapy by the reporting investigator.

Dose reductions are not permitted. In case of doubt, the Investigator should consult with the Study Physician.

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize 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.

6.7.1 Adverse events of special interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to the understanding of the IP and may require close monitoring and rapid communication by the Investigator to the Sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of these IPs.

AESIs for MEDI4736 or 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 MEDI4736 monotherapy and combination therapy. An immune-related adverse event (irAE) is defined as an AE that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE

diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

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

AESIs observed with MEDI4736 and/or tremelimumab include:

- Colitis
- Pneumonitis
- ALT/AST increases/hepatitis/hepatotoxicity
- Neuropathy/neuromuscular toxicity (ie, events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)
- Endocrinopathy (ie, events of hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism)
- Dermatitis
- Nephritis
- Pancreatitis (or labs suggestive of pancreatitis, including increased serum lipase or increased serum amylase)

Further information on these risks (eg, presenting symptoms) can be found in the current versions of the MEDI4736 and tremelimumab Investigator's Brochures.

6.7.2 Immune-related adverse events

Because MEDI4736 and/or tremelimumab administration leads 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 and MDX-1106 including immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies (Brahmer et al 2012, Hodi et al 2010). Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (eg, infection or PD), the AE should be considered to be immune-related. For guidance regarding specific immune related toxicity management, refer to Table 13.

Table 13 applies specifically to AEs related to the study drug/study regimen. It is important to note that these guidelines prepared by the Sponsor are to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities.

Table 13 Dosing modification and toxicity management guidelines for immune-mediated, infusion related, and nonimmune-mediated reactions (MEDI4736 monotherapy or combination therapy with tremelimumab or tremelimumab monotherapy)

Dose modifications	Toxicity management
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03. In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/study regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing **Grade 1** No dose modification **Grade 2** Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per Investigator or treating physician's clinical judgement. 3. Doses of prednisone are at ≤10 mg/day or equivalent. **Grade 3** Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below. **Grade 4** Permanently discontinue study drug/study regimen. Note: For Grade ≥3 asymptomatic amylase or lipase levels, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. Note: For Grade 3 and above asymptomatic amylase or lipase levels hold	It is recommended that management of irAEs follows the guidelines presented in this table: – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, concomitant medications, and infections). – In the absence of a clear alternative etiology, all events should be considered potentially immune related. – Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events. – For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [eg, up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper). – More potent immunosuppressives such as TNF inhibitors (eg, infliximab) (also refer to the individual sections of the irAE for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. – Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (eg, inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit/risk analysis for that patient.

Dose modifications	Toxicity management
study drug/regimen and if complete work up shows no evidence of pancreatitis, may continue or resume study drug/regimen	

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

Specific immune-mediated reactions

Adverse events	Severity grade of the event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
Pneumonitis/ILD	**Any Grade**	General Guidance	**For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high-resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider pulmonary and infectious disease consult.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1,	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (eg, prednisone 1 to

Specific immune-mediated reactions

Adverse events	Severity grade of the event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
		then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If still no improvement within 3 to 5 days despite IV methylprednisone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[a] – Consider pulmonary and infectious disease consult. – Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain pulmonary and infectious disease consult. – Hospitalize the patient. – Supportive care (eg, oxygen). – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment

Specific immune-mediated reactions

Adverse events	Severity grade of the event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
	intervention indicated [eg, tracheostomy or intubation])		with additional immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. − Once the patients is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation).[a]
Diarrhea/Enterocolitis	**Any Grade**	General Guidance	**For Any Grade:** − Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). − Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. − Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event. − Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1 (stool frequency of	No dose modifications.	**For Grade 1:** − Monitor closely for worsening symptoms.

Specific immune-mediated reactions

Adverse events	Severity grade of the event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
	<4 over baseline per day)		– Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
	Grade 2 (stool frequency of 4 to 6 over baseline per day)	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeksa. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consult study physician if no resolution to Grade ≤1 in 3 to 4 days. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of

Specific immune-mediated reactions

Adverse events	Severity grade of the event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
			cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3: stool frequency of ≥7 over baseline per day; Grade 4: life threatening consequences)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (eg infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis.	**Any Grade**	General Guidance	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications).
	Grade 1 AST or ALT > to 3 ×	No dose modifications. • If it worsens, then treat as Grade	**For Grade 1:** – Continue LFT monitoring per protocol.

Specific immune-mediated reactions

Adverse events	Severity grade of the event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
	ULN and/or TB > to 1.5 × ULN)	2 event.	
	Grade 2 (AST or ALT > 3 to 5 × ULN and/or TB >1.5 to 3.0 × ULN)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Regular and frequent checking of LFTs (eg, every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to Grade ≤1 in 1 to 2 days, discuss with study physician. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil)[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3: AST or	**For Grade 3:** For elevations in transaminases	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone at 1

Specific immune-mediated reactions

Adverse events	Severity grade of the event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
	ALT >5 to 20 × ULN and/or TB >3.0 to 10 × ULN) (Grade 4: AST or ALT >20 × ULN and/or TB >10 × ULN)	≤8 × ULN, or elevations in bilirubin ≤5 × ULN: • Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (ie, elevated alkaline P04) and in the absence of any alternative cause.[b] **For Grade 4:** Permanently discontinue study drug/study regimen.	to 4 mg/kg/day or equivalent. – If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Perform hepatology consult, abdominal workup, and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific immune-mediated reactions

Adverse events	Severity grade of the event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade**	General Guidance	**For Any Grade:** – Consult with nephrologist. – Monitor for signs and symptoms that may be related to changes in renal function (eg, routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression or infections). – Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.
	Grade 1 (Serum creatinine > 1 to 1.5 × baseline; > ULN to 1.5 × ULN)	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
	Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted.

Specific immune-mediated reactions

Adverse events	Severity grade of the event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
		or baseline, then resume study drug/study regimen after completion of steroid taper.	– Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: serum creatinine >3.0 × baseline; >3.0 to 6.0 × ULN; Grade 4: serum creatinine >6.0 × ULN)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine on daily basis. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started.

Specific immune-mediated reactions

Adverse events	Severity grade of the event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
			– Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Rash (excluding bullous skin formations)	**Any Grade** (refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash)	General Guidance	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED.**
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, discuss with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent.

Specific immune-mediated reactions

Adverse events	Severity grade of the event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
			– Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Discuss with study physician.
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, hypopituitarism, and adrenal insufficiency)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	General Guidance	**For Any Grade:** – Consult endocrinologist. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including brain metastases, or infections).

Specific immune-mediated reactions

Adverse events	Severity grade of the event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
			– Monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine labs depending on suspected endocrinopathy. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
	Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** – Monitor patient with appropriate endocrine function tests. – If TSH < 0.5 × LLN, or TSH >2 × ULN or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider endocrinology consult.
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until patient is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated	**For Grade 2 (including those with symptomatic endocrinopathy):** – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids. – Initiate hormone replacement as needed for management. – Evaluate endocrine function, and as clinically indicated, consider pituitary scan. – For patients with abnormal endocrine work up, except for those with isolated hypothyroidism, consider short-term corticosteroids (eg, 1 to

Specific immune-mediated reactions

Adverse events	Severity grade of the event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
		with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (eg, levothyroxine, hydrocortisone, or sex hormones). - – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper.	**For Grade 3 or 4:** – Consult endocrinologist. – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – Administer hormone replacement therapy as necessary. – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Once the patient is improving, gradually taper immunosuppressive steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections

Specific immune-mediated reactions

Adverse events	Severity grade of the event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
			[Category 2B recommendation]).[a] – Discuss with study physician.
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	General Guidance	**For Any Grade:** – Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (eg, electromyogram and nerve conduction investigations). – Perform symptomatic treatment with neurological consult as appropriate.
	Grade 1	No dose modifications.	**For Grade 1:** – See "Any Grade" recommendations above.
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of	**For Grade 2:** – Discuss with the study physician. – Obtain neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (eg, IV IG).

Specific immune-mediated reactions

Adverse events	Severity grade of the event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
		steroid taper.	
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 irAE does not resolve to Grade ≤1 within 30 days. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Discuss with study physician. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (eg, IV IG). – Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade**	General Guidance	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying

Specific immune-mediated reactions

Adverse events	Severity grade of the event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
			cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (eg, electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 1	No dose modifications.	**For Grade 1:** – Discuss with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult unless the symptoms are very minor and stable.
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2:** – Discuss with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult

Specific immune-mediated reactions

Adverse events	Severity grade of the event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
			– Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

Specific immune-mediated reactions

Adverse events	Severity grade of the event (NCI CTCAE version 4.03)	Dose modifications	Toxicity management
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 irAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Discuss with study physician. – Recommend hospitalization. – Monitor symptoms and obtain neurological consult. *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. o If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

[a] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.
[b] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

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

irAE Immune-related adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PCP ; PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Infusion-related reactions

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

CTCAE Common Terminology Criteria for Adverse Events; IM Intramuscular; IV Intravenous; NCI National Cancer Institute.

Non-immune-mediated reactions

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

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

6.8 Study governance and oversight

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance this could involve amendments to the study protocol and letters to Investigators.

An IDMC will be comprised of independent experts and will be conducted when the 20th patient has been randomized or 3 months after the 1st patient has been randomized, whichever occurs first, followed by 2 meetings for safety analysis 3 months apart, and subsequent meetings 6 months apart, to perform an interim assessment of the safety of MEDI4736 + tremelimumab combination therapy in this population. Following the meeting, the IDMC will report to the Sponsor and may recommend changes in the conduct of the study.

Full details of the IDMC procedures and processes can be found in the IDMC Charter.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

AstraZeneca will supply MEDI4736 and tremelimumab (Table 14).

Table 14 List of investigational products for this study

Investigational product	Dosage form and strength	Manufacturer
MEDI4736	500 mg/vial solution for infusion	MedImmune
Tremelimumab	20 mg/mL, solution, IV	MedImmune

IV Intravenous.

7.1.1 MEDI4736

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

Preparation of MEDI4736 doses for administration with an IV bag

The dose of MEDI4736 for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the MEDI4736 vial to the start of administration should not exceed:

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

A dose of 10 mg/kg will be administered using an IV bag containing 0.9% (weight/volume) saline or 5% (weight/volume) dextrose, with a final MEDI4736 concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter.

Patient weight at baseline should be used for dosing calculations unless there is a ≥10% change in weight. A volume equal to the calculated volume of MEDI4736 to be added to the IV bag should be removed from the bag prior to addition of MEDI4736. The calculated volume of MEDI4736 is then added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

Standard infusion time is 1 hour; however, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. Table 15 summarizes time allowances and temperatures.

Table 15 MEDI4736 infusion times

Maximum time from needle puncture to start of administration	4 hours at room temperature, 24 hours at 2°C to 8°C
Maximum time for IV bag infusion, including interruptions	8 hours at room temperature

IV Intravenous.

In the event that either preparation time or infusion time exceeds the time limits outlined in Table 15, a new dose must be prepared from new vials. MEDI4736 does not contain preservatives, and any unused portion must be discarded. All details can be found in the Drug Handling Instructions.

Dose calculation

The volume of MEDI4736 (in mL) to add to the IV bag is calculated as follows:

10 or 20 mg/kg × patient weight (kg) ÷ MEDI4736 concentration (nominal: 50 mg/mL)

Example: For a patient weighing 80 kg, dosed at 10 mg/kg, 16 mL [10 mg/kg × 80 kg divided by 50 mg/mL] of MEDI4736 is to be diluted in an IV bag. The bag is mixed by gentle

inversion to ensure homogeneity of the dose in the bag and the diluted MEDI4736 is administered as described above.

7.1.2 Tremelimumab

Tremelimumab will be supplied as a sterile solution, packaged in 20-mL clear glass vials with a rubber stopper and aluminum seal. Each vial contains 20 mg/mL of tremelimumab (with a nominal fill of 400 mg per vial) in 20 mM histidine buffer, pH 5.5, with 84 mg/mL of trehalose dihydrate, 0.2 mg/mL polysorbate 80, and 0.1 mg/mL disodium-EDTA dihydrate.

The standard supply of tremelimumab is delivered in a white carton with 16 vials of tremelimumab within foam inserts.

Standard infusion time is 1 hour.

The volume of tremelimumab (mL) to add to the IV bag is calculated as follows:

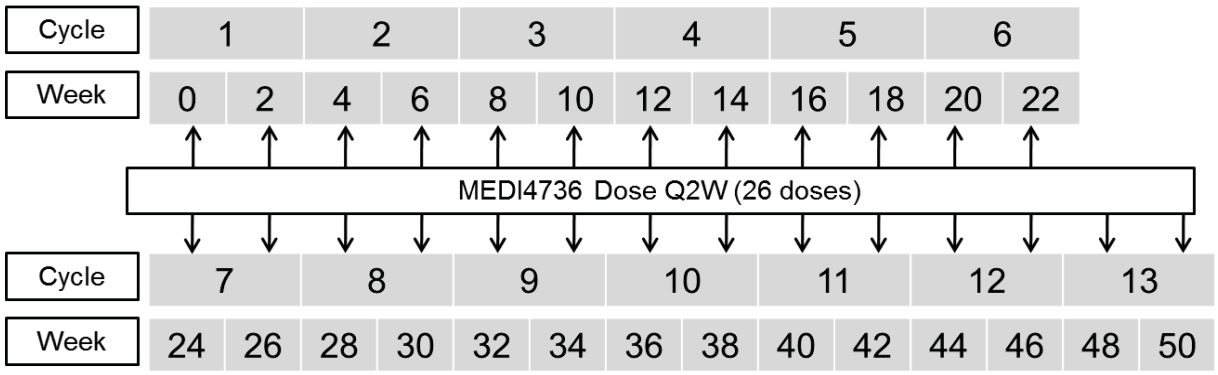
[1 mg/kg] × patient weight (kg) ÷ tremelimumab concentration (nominal: 20 mg/mL)

7.2 Dose and treatment regimens

Patients will be randomized in a 1:1:2 ratio to receive treatment with MEDI4736 monotherapy, tremelimumab monotherapy, or MEDI4736 + tremelimumab combination therapy.

Patients in the MEDI4736 monotherapy treatment group will receive 10 mg/kg MEDI4736 via IV infusion q2w for up to 12 months (up to 26 doses) (Figure 3).

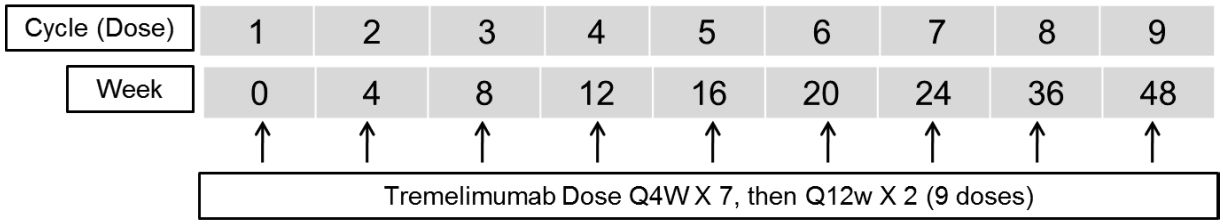
Figure 3 Dosing scheme for MEDI4736 monotherapy



Q2W Every 2 weeks.

Patients in the tremelimumab monotherapy treatment group will receive 10 mg/kg tremelimumab via IV infusion q4w for 7 doses then q12w for 2 additional doses for up to 12 months (up to 9 doses in total) (Figure 4).

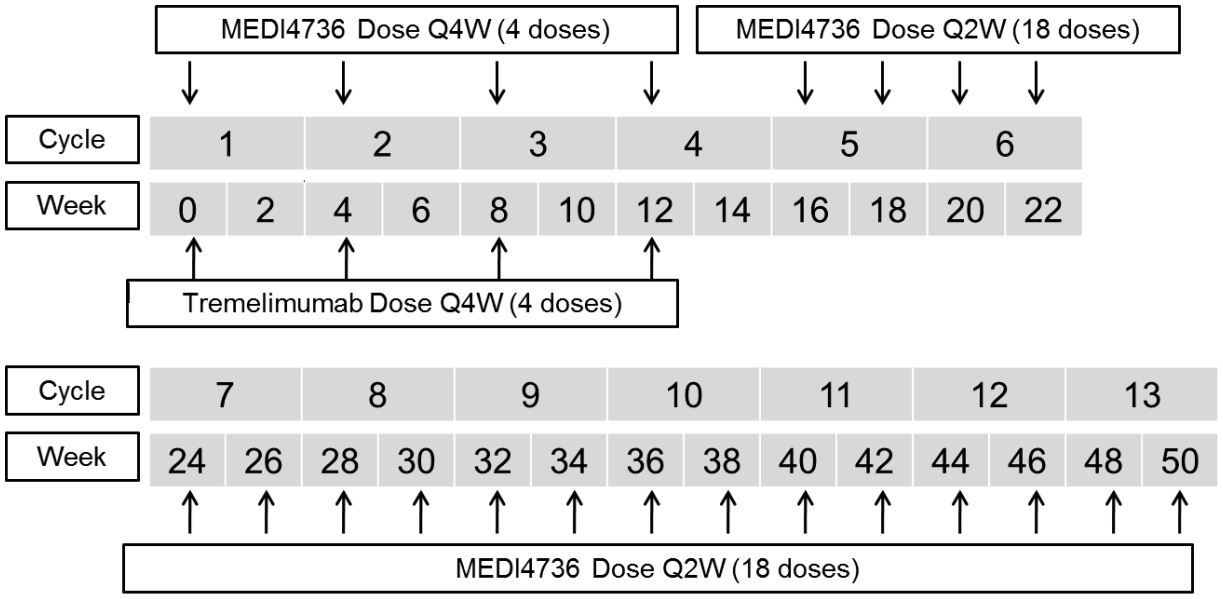
Figure 4 Dosing scheme for tremelimumab monotherapy



Q4W Every 4 weeks; Q12w Every 12 weeks.

Patients in the MEDI4736 + tremelimumab group will receive 20 mg/kg MEDI4736 via IV infusion q4w for 4 months (up to 4 doses) and 1 mg/kg tremelimumab via IV infusion q4w for 4 months (up to 4 doses in total). After completion of the initial 4 doses of combination therapy, single agent MEDI4736 will continue at 10 mg/kg q2w to complete 12 months of therapy (up to an additional 18 doses with the final dose at Week 50). The first MEDI4736 dose at 10 mg/kg q2w will be 4 weeks after the final dose of the combination of tremelimumab and MEDI4736 at 20 mg/kg (see Figure 5). The total treatment period will be 12 months. Tremelimumab will be administered first. MEDI4736 infusion will start approximately 1 hour after the end of tremelimumab infusion for the first infusion only. Infusions may be administered consecutively at subsequent infusions at the Investigator's discretion. The duration will be approximately 1 hour for each infusion.

Figure 5 Dosing scheme for MEDI4736 + tremelimumab combination therapy



Q2W Every 2 weeks; Q4W Every 4 weeks.

Patients will be treated with the assigned IP for 12 months or until confirmed PD (unless, in the Investigator's opinion, the patient continues to receive benefit from the treatment and after discussion with the Sponsor), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or another treatment discontinuation criterion is met (see Section 3.9), whichever occurs first.

Disease progression requires confirmation. All scans showing PD should be confirmed, preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of PD in the absence of clinical deterioration. Treatment with the assigned IP will continue between the initial assessment of progression and its confirmation. Patients with clinical evidence of progression who do not meet PD criteria by RECIST 1.1 should have radiographic documentation of PD. If progression is not confirmed, then the patient should continue receiving study treatment and participating in study assessments.

Patients with confirmed PD who, in the Investigator's opinion, continue to receive benefit from the assigned IP treatment and who meet the criteria for treatment in the setting of PD (see Section 3.1) may continue to receive treatment for a maximum of 12 months, after consultation with the Sponsor and at the Investigator's discretion. Patients with confirmed progression in the MEDI4736 monotherapy arm, the tremelimumab monotherapy arm, or in the combination portion of therapy in the MEDI4736 + tremelimumab arm cannot continue therapy if progression occurred after confirmed response in the target lesions (CR or PR) to IMT treatment (ie, the response and progression events both occurred while receiving active IP during the same treatment period in the target lesions).

Patients who the Sponsor and Investigator determine may not continue treatment after confirmed PD during the 12-month initial treatment period or in the 12-month retreatment period will enter follow-up (Table 7). Patients who have discontinued treatment due to toxicity or symptomatic deterioration, or who have commenced subsequent anticancer therapy, will be followed up until confirmed disease progression and death.

Patients who have a dose interruption due to toxicity at any point during the first 12 months of treatment may resume treatment and complete the 12-month treatment period.

Patients who achieve and maintain disease control (ie, CR, PR, or SD) through the end of the 12-month treatment period will enter follow-up (see Table 6).

Patients are eligible for a second additional 12 month period of retreatment with the same treatment guidelines followed during the initial 12-month treatment period (see Table 5 and Table 6) if the following criteria are met:

- They have evidence of PD, with or without confirmation during follow-up after the initial therapy and meet the criteria for treatment in the setting of PD (see Section 3.1),
- They are in the MEDI4736 + tremelimumab arm and are in the monotherapy portion of therapy and have evidence of PD.

Retreatment in the combination arm can only occur if PD occurs during the monotherapy portion or after completion of 12 months of therapy. Patients who discontinue treatment in 1 treatment group may not switch to treatment in a different group.

7.3 Labeling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into the local language.

The label will include the following information:

- Name of the Sponsor (AstraZeneca)
- IP dosage form, route of administration, and quantity of dosage units
- Storage conditions
- Study code
- Enrollment code
- Directions for use
- The name of the Principal Investigator, where applicable (this may be pre-printed or added to the label when the IP is dispensed)
- The period of use (eg, expiry date)
- Product lot identifier
- Medication identity number
- The following standard statements:

– "For clinical study use only"

– "Keep out of reach of children," if the study treatment is to be taken home by the patient

Labels will be provided as either single panel label or as multi-language booklet labels.

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The IP label on the pack/bottle/carton specifies the appropriate storage. Storage is also described in the IBs.

7.5 Compliance

The administration of all study drugs (including IP) should be recorded in the appropriate sections of the eCRF.

Treatment compliance will be assured by site reconciliation of the medication dispensed and returned.

7.6 Accountability

The study drug provided for this study will be used only as directed in the study protocol. The study personnel will account for all study drugs.

Drug accountability should be performed until the patient stops study treatment completely. Study site personnel will account for all study drugs received at the site, for all unused study drugs, and for appropriate destruction of study drugs. Certificates of delivery, destruction, and return should be signed.

7.7 Concomitant and other treatments

The Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF.

Restricted, prohibited, and permitted concomitant medications are described in the following tables. Refer to Section 6.7 for guidance on management of IP-related toxicities.

Prohibited medication/class of drug:	**Usage:**
Any investigational cancer therapy other than those under investigation in this study	Should not be given during the study
Any concurrent chemotherapy, local therapy (except palliative radiotherapy for non-target lesions, eg, radiotherapy, surgery, radiofrequency ablation), biologic therapy, or hormonal therapy for cancer treatment	Should not be given during the study. (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable.)
Immunosuppressive medications, including, but not limited to: systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-α blockers	Should not be given during the study. (Use of immunosuppressive medications for the management of IP-related AEs or in patients with contrast allergies is acceptable. In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. Temporary use of corticosteroids for concurrent illnesses [eg, food allergies or CT scan contrast hypersensitivity] is acceptable upon discussion with the Study Physician.)

Prohibited medication/class of drug:	Usage:
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP during the study
Herbal and natural remedies	Should be avoided during the study

AE Adverse event; CT Computed tomography; IP Investigational product; TNF tumor necrosis factor.

Rescue/supportive medication/class of drug:	Usage:
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary by the Investigator to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited" as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy, etc])	Should be used when necessary for all patients

7.7.1 Other concomitant treatment

Medications other than those described in Section 7.7 that are considered necessary for the patient's safety and well-being may be given at the discretion of the Investigator and should be recorded in the appropriate sections of the eCRF.

7.8 Post study access to study treatment

After the final analysis, AstraZeneca will continue to supply open-label drug to patients receiving the assigned IP as long as, in the Investigator's opinion, the patient is gaining clinical benefit from active treatment. Patients will only be able to restart treatment once; thus, a maximum of two 12-month treatment periods will be allowed (see Section 7.2).

In the event that a roll-over or safety extension study becomes available, patients currently receiving treatment with study drug or patients who are progression-free following randomized treatment and potentially eligible for retreatment may be transitioned to such a study, and the current study would end. The roll-over or safety extension study would ensure treatment continuation with visits and assessments per its protocol. Any patient that would be proposed to move to such a study would be asked to sign a new ICF. Following the OS Extension DCO, investigators who intend to commence or continue retreatment with IP should continue to monitor patients' safety laboratory assessments so as to ensure that no laboratory abnormalities or AEs that could potentially result in IP discontinuation are overlooked. All data will be recorded in the patients' charts but will not be otherwise documented for the purposes of this study.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

All statistical analyses will be performed by AstraZeneca or its representatives.

A comprehensive statistical analysis plan (SAP) will be prepared prior to 1st patient enrolled, and any subsequent amendments will be documented, with final amendments completed prior to reporting of the data.

8.2 Sample size estimate

The study will screen approximately 384 patients to identify a total of approximately 240 patients who have PD-L1-negative disease, and are suitable for enrollment and randomization (in a 1:1:2 fashion) in order to obtain at least 208 evaluable patients for the primary and the key secondary endpoints. Patients will be randomized to MEDI4736 monotherapy (60 randomized, 52 evaluable patients), tremelimumab monotherapy (60 randomized, 52 evaluable patients), and MEDI4736 + tremelimumab combination therapy (120 randomized, 104 evaluable patients).

The primary objective of the study is to estimate the ORR in all response-evaluable patients. The primary objective of the study is to assess the efficacy of MEDI4736 + tremelimumab combination, in terms of ORR. If the true ORR is 27%, a sample size of 104 patients will provide a precision of ±8.5% around this estimate, using a 95% confidence interval (CI).

Although no formal statistical comparisons are planned, a sample size of 104 patients will provide adequate power to test the hypothesis H_0: ORR ≤13% versus H_1: ORR >13%. If the ORR is 27%, then the study will provide 92% power to reject the null hypothesis (H_0) at the 1-sided 0.025 alpha level (or, equivalently, 2-sided 0.05 alpha level) using an exact binomial test.

To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared with a) MEDI4746 monotherapy and b) tremelimumab monotherapy in terms of ORR, a sample size of 156 evaluable patients (52 versus 104 for MEDI4736 monotherapy or tremelimumab monotherapy versus MEDI4736 + tremelimumab combination therapy) will be required. This sample size will provide 90% power to demonstrate a statistically significant difference in ORR at a 2-sided 0.05 significance level assuming a true ORR difference of 22% in ORR (5% on monotherapy and 27% on combination therapy). Based on the assumptions above, the minimum difference in ORR that would be statistically significant at the 0.05 level is 10.4%.

To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared with a) MEDI4746 monotherapy and b) tremelimumab monotherapy in terms of PFS, 116 PFS events (74% maturity) need to be observed in the 156 evaluable patients (52 versus 104 for MEDI4736 monotherapy or tremelimumab monotherapy versus MEDI4736 + tremelimumab combination therapy). If the true HR is 0.60 (15 versus 37% PFS rates at 6 months), 116 PFS events provide 80% power to demonstrate a statistically significant difference in PFS at a 0.05 two-sided significance level, with the smallest treatment difference that could be statistically

significant being an average HR of 0.70. With an assumed 10-month recruitment period and an assumed minimum follow-up period of 6 months, it is anticipated that this analysis will be performed 16 months after the first patient has been recruited.

To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared with a) MEDI4746 monotherapy and b) tremelimumab monotherapy in terms of OS, 125 death events (80% maturity) need to be observed in 156 evaluable patients (52 or 104 for MEDI4736 or tremelimumab, respectively, versus MEDI4736 + tremelimumab). If the true HR is 0.60 (10% versus 31% survival rates at 18 months), 125 death events will provide 80% power to demonstrate a statistically significant difference in OS at a 0.05 two-sided significance level, with the smallest treatment difference that could be statistically significant being an average HR of 0.70. With an assumed 10-month recruitment period and an assumed minimum follow-up period of approximately 18 months, it is anticipated that this analysis will be performed 28 months after the first patient has been recruited.

8.3 Definitions of analysis sets

Definitions of the analysis sets for each outcome variable are provided in Table 16.

Table 16 Summary of outcome variables and analysis populations

Outcome variable	Populations
Efficacy Data	
ORR[1], TTR[1], DCR1, BoR[1], DoR[1]	Evaluable Analysis Set[1]
ORR[2,3], BoR, PFS[2], OS	Full Analysis Set
Demography, WHO performance status	Full Analysis Set
EORTC QLQ-C30 and QLQ-H&N35	Full Analysis Set
PK data	PK Analysis Set
Safety Data	
Exposure	Safety Analysis Set
Adverse events	Safety Analysis Set
Laboratory measurements	Safety Analysis Set
Vital signs	Safety Analysis Set

[1]ORR, DCR, BoR, and DoR will be analyzed on the Evaluable Analysis Set using BICR data.
[2]ORR, DoR, and PFS will also be analyzed on FAS using site Investigator data.
[3]ORR will also be analyzed on FAS using the BICR data.
BoR Best objective response; DCR Disease control rate; DoR Duration of response; EORTC European Organisation for Research and Treatment of Cancer; FAS Full Analysis Set; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; PK Pharmacokinetic; QLQ C30 30-Item core quality of life questionnaire; QLQ-H&N35 35-Item head and neck quality of life questionnaire; TTR Time to recurrence; WHO World Health Organization.

8.3.1 Full Analysis Set

The Full Analysis Set (FAS) will include all randomized patients. Treatment groups will be compared on the basis of randomized study treatment, regardless of the treatment actually received. Patients who were randomized but did not subsequently go on to receive study treatment are included in the analysis in the treatment group to which they were randomized.

8.3.2 Evaluable Analysis Set

The Evaluable Analysis Set will include all treated patients (ie, received at least 1 dose of IP) who have measurable disease at baseline according to BICR.

8.3.3 Safety Analysis Set

The Safety Analysis Set will consist of all patients who received at least 1 dose of study treatment. Safety data will not be formally analyzed but summarized using the SAS according to the treatment received, that is, erroneously treated patients (eg, those randomized to treatment A but actually given treatment B) will be summarized according to the treatment they actually received.

8.3.4 PK Analysis Set

All patients who receive at least 1 dose of either MEDI4736 or tremelimumab per the protocol for whom any post-dose data are available and who do not violate or deviate from the protocol in ways that would significantly affect the PK analyses will be included in the PK Analysis Set.

8.4 Outcome measures for analyses

8.4.1 Calculation or derivation of efficacy variables

8.4.1.1 RECIST 1.1-based endpoints

Blinded Independent Central Review (BICR) of RECIST 1.1-based assessments

The BICR of all radiological imaging data will be carried out using RECIST 1.1, RECIST 1.1 modified for confirmation of progression, and irRECIST 1.1. All radiological scans for all patients (including those at unscheduled visits or outside visit windows) will be provided to the BICR. The imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1 and will be adjudicated, if required. For each patient, the BICR will define the overall visit response data (CR, PR, SD, PD, or not evaluable [NE]) and the relevant scan dates for each timepoint (ie, for visits where response or progression is/is not identified). If a patient has had a tumor assessment that cannot be evaluated then the patient will be assigned a visit response of NE (unless there is evidence of progression, in which case the response will be assigned as PD). Endpoints (of ORR, DoR, DCR, BoR, and PFS) will be derived from the overall visit response date and the scan dates.

Further details of the BICR will be documented in the Imaging Charter.

Investigator RECIST 1.1-based assessments

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

At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, or PD depending on the status of their disease compared with baseline and previous assessments. Baseline will be assessed within the 28 days prior to enrollment. If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of NE (unless there is evidence of progression in which case the response will be assigned as PD). Imaging and procedures performed before signing the ICF may be used for screening purposes if the patient consents.

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

8.4.1.2 Primary endpoint (objective response rate)

The primary endpoint is ORR. ORR (per RECIST 1.1 as assessed by the BICR) is defined as the number (%) of patients with a confirmed overall response of CR or PR and will be based on all treated patients who have measurable disease at baseline per BICR (Evaluable Analysis Set). A confirmed response of CR/PR means that a response of CR/PR is recorded at one visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. Therefore, data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Any patient who discontinues treatment without progression, receives a subsequent therapy, and then responds will not be included as responders in the ORR.

Additionally, ORR will also be assessed using irRECIST 1.1 data obtained from BICR. Responses of CR/PR need confirmation under this approach.

For sensitivity analysis, ORR will be assessed using tumor data recorded by the Investigator according to RECIST 1.1, and the denominator will be all randomized patients. ORR (per RECIST 1.1 as assessed by the BICR) will also be analyzed using the FAS population (all randomized patients) with treated patients with measurable disease at baseline per the site Investigator.

8.4.1.3 Secondary endpoints

Duration of response

DoR (per RECIST 1.1 as assessed by the BICR) will be defined as the time from the date of first documented response until the first date of documented progression or death in the absence of disease progression. The end of response should coincide with the date of progression or death from any cause used for the RECIST 1.1 PFS endpoint. The denominator for DoR will be defined as described for ORR (see Section 8.4.1.2).

The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of CR or PR. If a patient does not progress following a response, then their DoR will be censored at the PFS censoring time. DoR will not be defined for those patients who do not have documented response.

DoR will also be assessed using RECIST 1.1 data obtained from the site Investigator.

Disease control rate

DCR at 4, 6, or 12 months is defined as the percentage of patients who have a BoR of CR or PR in the first 4, 6, or 12 months, respectively, or who have demonstrated SD for a minimum interval of 16, 24, or 48 weeks, respectively (-7 days, ie, 105, 161, or 329 days, respectively), following randomization.

As additional analysis, DCR at 6 months will also be assessed as percentage of patients who have a BoR of CR or PR in the first 6 months or who have demonstrated SD for a minimum interval of 12 weeks (-7 days, ie, 77 days) following randomization.

DCR will be determined programmatically based on RECIST 1.1 using BICR data using all data up until the first progression event. DCR will also be assessed using the irRC data obtained from BICR.

DCR will also be assessed using RECIST 1.1 data obtained from the site Investigator.

Progression-free survival

PFS (per RECIST 1.1 as assessed by the BICR) will be defined as the time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment. If the patient has no evaluable visits or does not have baseline data they will be censored at 0 days unless they die within 2 visits of baseline.

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

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

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

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

For sensitivity analyses, PFS will be assessed using the RECIST 1.1 BICR tumor data following a modification where any objective progression requires confirmation. Therefore, data obtained up until confirmed progression, or the last evaluable assessment in the absence of a confirmed progression, will be included in the assessment of ORR. Note that the response may be after an unconfirmed progression. Additionally, PFS will also be assessed using irRECIST 1.1 data obtained from BICR. Objective disease progressions also require confirmation under this approach.

For sensitivity analyses, PFS will be assessed using tumor data recorded by the Investigator according to RECIST 1.1.

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

Overall survival

OS is defined as the time from the date of randomization until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

Note: Survival calls will be made in the week following the date of DCO for the analysis, and if patients are confirmed to be alive or if the death date is post the DCO date, these patients will be censored at the date of DCO. Death dates may be found by checking publicly available death registries.

No OS data will be recorded in the study database after the OS Extension DCO, but such information may continue to be collected for operational purposes.

Best objective response

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

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

CR or PR must be confirmed. BoR will be determined programmatically based on RECIST 1.1 using BICR data using all data up until the first progression event. It will also be assessed using the irRECIST 1.1 data obtained from BICR.

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

For patients who die with no evaluable RECIST 1.1 assessments, if the death occurs ≤17 weeks (ie, 16 weeks ±7 days) after enrollment, then BoR will be assigned to the

progression (PD) category. For patients who die with no evaluable RECIST 1.1 assessments, if the death occurs >17 weeks (ie, 16 weeks ±7 days) after the date of enrollment then BoR will be assigned to the NE category.

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

8.4.2 Calculation or derivation of safety variables

8.4.2.1 Adverse events

Data from all cycles of treatment will be combined in the presentation of safety data. AEs (both in terms of Medical Dictionary for Regulatory Activities [MedDRA] preferred terms and CTCAE grade) will be listed individually by patient.

Any AE occurring before treatment with IP will be included in the data listings but will not be included in the summary tables of AEs. Any AE occurring within 90 days of discontinuation of IP (ie, the last dose of MEDI4736 in combination with tremelimumab or only MEDI4736) may be included in the AE summaries, but the majority of those summaries will omit those AEs observed after a patient has received further therapy for cancer. Further details will be provided in the SAP. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of IP) will be flagged in the data listings.

A separate data listing of AEs occurring more than 90 days after discontinuation of MEDI4736 in combination with tremelimumab or only MEDI4736 will be produced. These events will not be included in AE summaries.

8.4.2.2 Safety assessments

For the change from baseline summaries for vital signs, laboratory data, ECGs, and physical examination, the baseline value will be the latest result obtained prior to the start of study treatment.

QTcF will be derived during creation of the reporting database using the reported ECG values (RR and QT).

QTcF = QT/RR^ (1/3) where RR is in seconds

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

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

The denominator used in laboratory summaries will only include evaluable patients, in other words those who had sufficient data to have the possibility of an abnormality.

For example:

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

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

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

8.4.3 Calculation or derivation of patient-reported outcome variables

PRO questionnaires will be assessed using the EORTC QLQ-C30 and EORTC QLQ-H&N35. All items/questionnaires will be scored according to published scoring guidelines. All PRO analyses will be based on the FAS.

8.4.3.1 EORTC QLQ-C30

The EORTC QLQ-C30 consists of 30 questions that can be combined to produce 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), and a global measure of health status. The EORTC QLQ-C30 will be scored according to the EORTC QLQ-C30 scoring manual (Fayers et al 1999). An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales, each of the functional scales, and the global health status scale in the EORTC QLQ-C30 according to the EORTC QLQ-C30 Scoring Manual. Higher scores on the global health status and functioning scales indicate better health status/function, but higher scores on symptom scales represent greater symptom severity.

The change from baseline in health-related QoL will be assessed using the EORTC QLQ-C30 global QoL scale, which includes 2 items from the EORTC QLQ-C30: "How would you rate your overall health during the past week? (Item 29)" and "How would you rate your overall QoL during the past week? (Item 30)."

Definition of clinically meaningful changes

Changes in score compared with baseline will be evaluated. A minimum clinically meaningful change is defined as an absolute change in the score from baseline of ≥10 for scales from the EORTC QLQ-C30 (Osoba et al 1998). For example, a clinically meaningful improvement in physical function (as assessed by EORTC QLQ-C30) is defined as an increase in the score from baseline of ≥10, whereas a clinically meaningful deterioration is defined as a decrease in the score from baseline of ≥10. At each post-baseline assessment, the change in symptoms/functioning from baseline will be categorized as improvement, no change or deterioration as shown in Table 17.

Table 17 Mean change and visit response in health related quality of life

Score	Change from baseline	Visit response
EORTC QLQ-C30 Global quality of life score	≥+10	Improvement
	≤-10	Deterioration
	Otherwise	No change
EORTC QLQ-C30 symptom scales/items	≥+10	Deterioration
	≤-10	Improvement
	Otherwise	No change
EORTC QLQ-C30 functional scales	≥+10	Improvement
	≤-10	Deterioration
	Otherwise	No change

EORTC European Organisation for Research and Treatment of Cancer; QLQ-C30 30-item core quality of life questionnaire.

For each subscale, if <50% of the subscale items are missing, then the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscales (Fayers et al 1999). If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded. If there is evidence that the missing data are systematic, missing values will be handled to ensure that any possible bias is minimized.

Time to symptom deterioration

For each of the symptoms scales in the EORTC QLQ-C30, time to symptom deterioration will be defined as the time from randomization until the date of the first clinically meaningful symptom deterioration (an increase in the score from baseline of ≥10) or death (by any cause) in the absence of a clinically meaningful symptom deterioration, regardless of whether the patient withdraws from study treatment or receives another anticancer therapy prior to symptom deterioration. Death will be included as an event only if the death occurs within 2 visits of the last PRO assessment where the symptom change could be evaluated.

Patients whose symptoms (as measured by EORTC QLQ-C30) have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the symptom could be evaluated. Also, if symptoms deteriorate after 2 or more missed PRO assessment visits or the patient dies after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where the symptom could be evaluated. If a patient has no evaluable visits or does not have baseline data they will be censored at 0 days. The population for the analysis of time to symptom deterioration will include a subset of the FAS who have baseline scores of ≤90.

Time to QoL/Function deterioration

For QoL, time to deterioration will be defined as the time from the date of randomization until the date of the first clinically meaningful deterioration (a decrease in the function scales or the global health status/QoL from baseline of ≥10) or death (by any cause) in the absence of a clinically meaningful deterioration, regardless of whether the patient withdraws from study treatment or receives another anticancer therapy prior to QoL/function deterioration. Death will be included as an event only if the death occurs within 2 visits of the last PRO assessment where the QoL/function change could be evaluated.

Patients whose QoL (as measured by EORTC QLQ-C30) have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the QoL/function could be evaluated. Also, if QoL deteriorates after 2 or more missed PRO assessment visits or the patient dies after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where QoL/function could be evaluated. If a patient has no evaluable visits or does not have baseline data they will be censored at 0 days. The population for the analysis of time to QoL/function deterioration will include a subset of the FAS who have baseline scores of ≥10.

Symptom improvement rate

The symptom improvement rate will be defined as the number (%) of patients with 2 consecutive assessments at least 14 days apart that show a clinically meaningful improvement (a decrease from baseline score ≥10 for EORTC QLQ-C30 symptom scales) in that symptom from baseline. The denominator will consist of a subset of the FAS who have a baseline symptom score ≥10.

QoL/function improvement rate

The QoL/function improvement rate will be defined as the number (%) of patients with 2 consecutive assessments at least 14 days apart that show a clinically meaningful improvement (an increase from baseline score ≥10 for EORTC QLQ-C30 functional scales and global health status/QoL) in that scale from baseline. The denominator will consist of a subset of the FAS who have a baseline QoL/function score ≥10.

8.4.3.2 EORTC QLQ-H&N35

The QLQ-H&N35 is a head and neck cancer-specific module from the EORTC for head and neck cancer comprising 35 questions to assess head and neck cancer symptoms. The head and neck cancer module includes 11 single items and 7 multi-item scales that assess pain, swallowing, senses (taste and smell), speech, social eating, social contact, and sexuality. For all items and scales, high scores indicate increased symptomatology/more problems.

The scoring approach for the QLQ-H&N35 is identical in principle to that for the symptom scales/single items of the EORTC QLQ-C30. As the wording is reversed on the QLQ-H&N35, higher scores represent greater symptom severity.

Definition of clinically meaningful changes

Changes in score compared with baseline will be evaluated. A minimum clinically meaningful change is defined as a change in the score from baseline of >10 for scales/items from QLQ-H&N35 (Bjordal et al 2000). For example, a clinically meaningful deterioration or worsening in dry mouth (as assessed by QLQ-H&N35) is defined as an increase in the score from baseline of ≥10. At each post-baseline assessment, the change in symptoms/functioning from baseline will be categorized as improved, no change, or deterioration, as shown in Table 18.

Table 18 Visit response for HRQoL and disease-related symptoms

Score	Change from baseline	Visit response
H&N35 symptom scales and items	≥+10	Deterioration
	≤-10	Improved
	Otherwise	No change

HRQoL Health-related quality of life; H&N35 Head and neck cancer module.

Time to symptom deterioration

For each of the symptom scales/items in the QLQ-H&N35, time to symptom deterioration will be defined as the time from the date of the first dose until the date of the first clinically meaningful symptom deterioration (an increase in the score from baseline of ≥10) or death (by any cause) in the absence of a clinically meaningful symptom deterioration, regardless of whether the patient withdraws from study treatment or receives another anticancer therapy prior to symptom deterioration. Death will be included as an event only if the death occurs within 2 visits of the last PRO assessment where the symptom change could be evaluated.

Patients whose symptoms (as measured by the QLQ-H&N35) have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the symptom could be evaluated. Also, if symptoms progress after 2 or more missed PRO assessment visits or the patient dies after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where the symptom could be evaluated. If a patient has no evaluable visits or does not have baseline data, they will be censored at 0 days. The population for analysis of time to symptom deterioration will include a subset of the FAS population who have baseline scores ≤90.

Symptom improvement rate

The symptom improvement rate will be defined as the number (%) of patients with 2 consecutive assessments at least 14 days apart that show a clinically meaningful improvement (a decrease from baseline score >10 for QLQ-H&N35 scales/items) in that symptom from baseline.

8.4.4 Calculation or derivation of pharmacokinetic variables

8.4.4.1 Population pharmacokinetics and exposure-response/safety analysis

A population PK model will be developed using a non-linear mixed-effects modelling approach. The impact of physiologically-relevant patient characteristics (covariates) and disease on PK will be evaluated. The relationship between PK exposure and the effect on safety and efficacy end points will be evaluated. The results of such an analysis will be reported in a separate report.

8.4.4.2 Pharmacokinetic non-compartmental analysis

The actual sampling times will be used in the PK calculations. MEDI4736 and tremelimumab concentration data and summary statistics will be tabulated. Individual and mean blood MEDI4736 and tremelimumab concentration-time profiles will be generated. PK parameters will be determined using standard non-compartmental methods. The following PK parameters will be determined after the first and steady-state doses: peak and trough concentration (as data allow).

8.4.4.3 Immunogenicity analysis

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable ADAs for MEDI4736 and tremelimumab. The immunogenicity titer will be reported for samples confirmed positive for the presence of ADAs. The effect of immunogenicity on PK, pharmacodynamics, efficacy, and safety will be evaluated.

8.4.5 Calculation or derivation of biomarker variables

Biomarker status will be assessed for evaluable patients according to pre-specified criteria that will be detailed in the SAP.

8.4.6 Calculation or derivation of pharmacogenetic variables

In the case of genetic data, only the date the patient gave consent to participation in the genetic research and the date the blood sample was taken from the patient will be recorded in the eCRF and database. The genetic data generated from the study will be stored in the AstraZeneca LIMS database or other appropriate system. This database is a secure database, which is separate from the database used for the main study. Some or all of the dataset from the main study may be duplicated within the AstraZeneca LIMS database for exploratory genetic analysis. Data will be reported outside the CSR (please see Appendix C).

8.5 Methods for statistical analyses

The DCO for primary analysis will take place approximately 6 months after the last patient is first dosed. All study endpoints will be analyzed at this time. However, if the required number of PFS events are not observed, only descriptive analyses of PFS and OS will be presented at this time. A further analysis of efficacy will take place approximately 12 months after the last patient is dosed or after the occurrence of approximately 116 PFS events between

the MEDI4736 + tremelimumab therapy group and the MEDI4736 monotherapy group, whichever occurs first.

The final analysis of OS will be conducted following the OS Extension DCO, which will occur approximately 30 months after LPD, or when 85% OS event maturity is reached, whichever occurs first.

Kaplan-Meier plots and median DoR, PFS, BoR, and OS will be presented. Also, summaries (ie, number of patients [%]) of PFS, death events, and DCR will be provided. Formal analysis of PFS and OS will only be done when approximately 116 PFS events and 125 death events are observed or 18 months after the last patient is dosed, whichever comes first, for MEDI4736 + tremelimumab combination therapy versus MEDI4736 monotherapy.

Descriptive statistics will be used for all variables, as appropriate, and will be presented by treatment group. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total.

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

All data collected will be listed. Efficacy data will be summarized and analyzed based on either the Evaluable Set or the FAS (see Table 16). PK data will be summarized and analyzed based on the PK Analysis Set. Safety data will be summarized based on the Safety Analysis Set.

Table 19 details which endpoints are to be subject to formal statistical analysis, together with pre-planned sensitivity analyses making clear which analysis is regarded as primary for that endpoint.

Table 19 Statistical analyses to be conducted and pre-planned sensitivity analyses

Endpoints Analyzed	Notes
Objective Response Rate	Primary objective (assess efficacy of MEDI4736 + tremelimumab combination) • Primary analysis - 95% CI using exact binomial test, BICR data (RECIST 1.1) • Secondary analysis using BICR data (irRECIST 1.1) • Sensitivity analyses using 1) site Investigator tumor data (RECIST 1.1) Secondary objective (assess efficacy of MEDI4736 + tremelimumab combination therapy compared with a) MEDI4736 monotherapy and b) tremelimumab monotherapy, in terms of ORR) • Primary analysis – Logistic regression using BICR data (RECIST 1.1) • Secondary analysis - Logistic regression using BICR data (irRECIST 1.1) • Sensitivity analysis using • site Investigator tumor data (RECIST 1.1)
Time to Treatment Response	Secondary analysis • Kaplan-Meier plots using BICR data (RECIST 1.1) • Sensitivity analysis using 1. site Investigator data (RECIST 1.1)
Duration of Response	Secondary analysis • Kaplan-Meier plots using BICR data (RECIST 1.1) • Sensitivity analysis using 1) site Investigator data (RECIST 1.1)
Disease Control Rate	Secondary analysis • N (%), using BICR data (RECIST 1.1) • Sensitivity analysis using • site Investigator data (RECIST 1.1)
Progression-Free Survival	Secondary objective (assess efficacy of MEDI4736 + tremelimumab combination therapy compared with a) MEDI4736 monotherapy and b) tremelimumab monotherapy, in terms of PFS) • Stratified log-rank test using BICR data (RECIST 1.1) • Stratified log-rank test using BICR data (irRECIST 1.1) • Kaplan-Meier plots using BICR data (RECIST 1.1) • Kaplan-Meier plot using BICR data (irRECIST 1.1) • Sensitivity analyses using 1) site Investigator tumor data (RECIST 1.1)
Overall Survival	Secondary analysis • Kaplan-Meier plots of OS
Best Objective Response	Secondary analysis 1) N (%), using BICR data (RECIST 1.1)

BICR Blinded Independent Central Review; CI Confidence interval; irRECIST 1.1 Immune-related RECIST 1.1; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1; OS Overall survival.

8.5.1 Analysis of the primary variable(s)

8.5.1.1 Primary objective (assess the efficacy of MEDI4736 + tremelimumab combination therapy, in terms of ORR)

The primary endpoint, ORR, will be estimated with 95% exact CIs. The primary analysis will be based on the programmatically derived ORR based on BICR assessments, and using all scans regardless of whether they were scheduled or not. An additional analysis will be conducted using irRECIST 1.1 data obtained from the BICR.

An analysis of ORR using the results of the programmatically derived RECIST 1.1 using the site Investigator tumor data from all scans will be conducted as a sensitivity analysis to confirm the results of the primary analysis using data derived from the eCRFs. The primary analysis population for ORR will be the Evaluable Analysis Set, but ORR will also be analyzed using the FAS population.

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

Overall visit response data will be listed and summarized over time for all evaluable patients (ie, evaluable).

8.5.1.2 Secondary objective (assess the efficacy of MEDI4736 + tremelimumab combination therapy compared with a) MEDI4736 monotherapy and b) tremelimumab, in terms of ORR, PFS, and OS)

Overall Response Rate

ORRs will be compared between the three treatment groups, using logistic regression. The comparisons will include the following:

- MEDI4736 + tremelimumab combination therapy versus MEDI4736 monotherapy
- MEDI4736 + tremelimumab combination therapy versus tremelimumab monotherapy

Evaluable patients data analysis for the MEDI4736 or tremelimumab monotherapy versus MEDI4736 + tremelimumab combination groups will be based on the programmatically derived ORR using BICR assessments (RECIST 1.1). The logistic regression models adjusting for stratification variables (HPV status and smoking status), and results of the analyses will be presented in terms of odds ratios together with their associated profile likelihood 95% CIs, and p-values (based on twice the change in log-likelihood resulting from

the addition of a treatment factor to the model). The covariates in the statistical modelling will be based on the values entered into IVRS at randomization, even if it is subsequently discovered that these values were incorrect.

All scans for evaluable patients will be used for the analysis, regardless of whether or not they were scheduled. An additional analysis will be conducted using irRECIST 1.1 data obtained from the BICR.

Sensitivity analysis will be performed on programmatically derived ORR using site Investigator tumor data (RECIST 1.1). Summaries will present the number and percentage of patients with a tumor response (CR/PR). The number (%) of patients with a confirmed response and the number (%) of patients with a single visit response (ie, an unconfirmed response) will also be presented.

Overall visit response data will be listed and summarized over time for all evaluable patients (ie, Evaluable Set).

Progression-free survival

PFS will be compared between the three treatment groups (MEDI4736 + tremelimumab vs MEDI4736 monotherapy and MEDI4736 + tremelimumab vs tremelimumab monotherapy) using stratified log rank test adjusting for HPV status (positive versus negative) and smoking status (>10 versus ≤10 pack-years) for generation of the p-value and using the Breslow approach for handling ties (Breslow, 1974).

The HR and CI can be estimated from the stratified log-rank as follows (Berry et al 1991, Collett 2003, Selke and Siegmund 1983):

$$HR = \exp\left(\frac{U}{V}\right)$$

$$95\%\ \text{CI for HR} = \left(\exp\left\{\frac{U}{V} - \frac{1.96}{\sqrt{V}}\right\}, \exp\left\{\frac{U}{V} + \frac{1.96}{\sqrt{V}}\right\}\right)$$

Where $U = \sum_k U_k = \sum_k \sum_i (d_{1ki}, -e_{1ki})$ $U = \sum_k U_k = \sum_k \sum_i (d_{1ki}, -e_{1ki})$ is the stratified log-rank test statistic obtained from the SAS LIFETEST procedure, $\sqrt{V} = \sqrt{\sum_k V_k}$, is its standard deviation, k denotes the stratum, and d_{1ki} and e_{1ki} are the observed and expected events in Group 1, stratum k, with event time.

Kaplan-Meier plots of PFS will be presented per treatment arm. Summaries of the number and percentage of patients experiencing a PFS event, and the type of event (RECIST 1.1 or death) will be provided along with median PFS.

PFS at 6 months and at 12 months will be summarized (using the Kaplan-Meier curve) and presented by treatment arm. Each will be compared between treatments by using the Kaplan-Meier estimator of PFS at 6 months and 12 months for each treatment to obtain the HR. The HR and CI will be presented using the following approach (Klein et al 2007).

- The *HR(group1:group2)* is estimated as $\frac{\ln \hat{S}_1(t)}{\ln \hat{S}_2(t)}$
- The variance for *ln(HR)* is estimated as $\frac{\hat{\sigma}_1(t)^2}{\ln^2 S_1(t)} + \frac{\hat{\sigma}_2(t)^2}{\ln^2 S_2(t)}$

where $\hat{\sigma}_i(t)^2 = \sum_{t_i \le t} \frac{d_i}{n_i(n_i - d_i)}$ is the variance for *ln{S(t)* derived from Greenwood's formula for the variance of *S(t)* and can be estimated from standard software packages, and where d_i and n_i refer to the number of events and patients at risk for each risk set. The *ln(HR)* and its variance in each strata will be estimated and combined by weighting inversely proportionately according to each within-stratum variance (Whitehead and Whitehead 1991).

The assumption of proportionality will be assessed. Proportional hazards will be tested first by examining plots of complementary log-log (event times) versus log (time) and, if these raise concerns, by fitting a time-dependent covariate to assess the extent to which this represents random variation. If a lack of proportionality is evident, the variation in treatment effect will be described by presenting piecewise HR calculated over distinct time periods. In such circumstances, the HR can still be meaningfully interpreted as an average HR over time unless there is extensive crossing of the survival curves. If lack of proportionality is found, this may be a result of treatment-by-covariate interactions, which will be investigated.

Cox proportional hazards modelling will be employed to assess the effect of covariates on the HR estimate. Details will be presented in the SAP.

Additionally, summaries and Kaplan-Meier plots of PFS will also be provided using the irRECIST 1.1 data obtained from BICR. A sensitivity analysis of PFS using the site Investigator tumor data will also be performed.

Overall survival

The analysis of OS will be done using stratified log-rank test, using the same methodology described for the PFS endpoint.

The effect of treatment will be estimated by the HR together with its corresponding CI and p-value.

Kaplan-Meier plots of OS will be presented per treatment arm. Summaries of the number and percentage of patients who have died, are still in survival follow-up, are lost to follow-up, or have withdrawn consent will be provided along with median OS for each treatment group.

Details of the analysis will be presented in the SAP.

8.5.2 Analysis of the secondary variable(s)

Duration of response

Kaplan-Meier plots of DoR based on the BICR assessment of RECIST 1.1 will be presented per treatment arm. Median DoR will be summarized for only patients who have a response. This will be repeated for DoR using the irRECIST 1.1 data obtained from BICR. Sensitivity analyses will be performed using the RECIST 1.1 data obtained from the site Investigator.

Best objective response and disease control rate

BoR will be summarized by n (%) for each category (CR, PR, SD, PD, and NE), per treatment arm.

The DCR will be summarized (ie, number of patients [%]) per treatment arm. Sensitivity analyses will be performed using the RECIST 1.1 data obtained from the site Investigator.

Health-related quality of life and symptoms

QLQ-C30

Time to symptom deterioration will be analyzed for each of the 3 symptom scales (fatigue, pain, and nausea/vomiting) and the 5 individual symptom items (dyspnea, insomnia, appetite loss, constipation, and diarrhea). Time to health-related QoL/function deterioration will be analyzed for the 5 function scales (physical, role, emotional, cognitive, and social) and global health status/QoL.

Time to deterioration will be presented using a Kaplan-Meier plot for each of the 3 symptom scales (fatigue, pain, and nausea/vomiting), 5 individual symptom items (dyspnea, insomnia, appetite loss, constipation, and diarrhea), 5 functional scales (physical, role, emotional, cognitive, and social), and global health status/QoL. Summaries of the number and percentage of patients experiencing a clinically meaningful deterioration or death as well as who were censored will be provided along with the median time to deterioration or death for each treatment arm.

A summary of the symptom improvement rate (along with a 95% CI using the Newcombe-Wilson method) for each of the 3 symptom scales and the 5 individual symptom items will be produced. Similarly, a summary of QoL/function improvement rate for each of the 5 function scales (physical, role, emotional, cognitive, and social) and global health status/QoL will be produced.

Summaries of absolute and change from baseline values of each symptom scale/item, the global health-related QoL score, and each functional domain will be reported by visit for each treatment arm. Graphical presentations may also be produced as appropriate. Summaries of the number and percentage of patients in each response category at each visit for each ordinal

item (in terms of the proportion of patients in the categories of improvement, no change, and deterioration) will also be produced for each treatment arm.

QLQ-H&N35

For each of the symptom scales/items in the H&N35, time to deterioration in symptoms will be presented using a Kaplan-Meier plot. Summaries of the number and percentage of patients experiencing a clinically meaningful deterioration or death, and the median time to deterioration, will also be provided for each treatment group.

A summary of the symptom improvement rate (along with a 95% CI using the Newcombe-Wilson method) for each of the symptom scales/items will be produced.

Summaries of absolute and change from baseline values of each symptom scale/item will be reported by visit for each treatment group. Graphical presentations may also be produced as appropriate. Summaries of the number and percentage of patients in each response category at each visit for each ordinal symptom item (in terms of the proportion of patients in the categories of improvement, no change, and deterioration) will also be produced for each treatment group.

8.5.3 Subgroup analysis (if applicable)

The analysis of ORR based upon BICR RECIST assessments will also be presented by subgroup. The subgroups are defined as follows:

- Smoking status (>10 years versus ≤10 years)
- HPV status (positive versus negative)

8.5.4 Interim analysis

No interim analysis for futility or superiority is planned for this study. Interim safety assessment will be conducted when the 20th patient has been randomized or 3 months after the 1st patient has been randomized, whichever occurs first, followed by 2 meetings for safety analysis 3 months apart, and subsequent meetings 6 months apart. Details of the interim safety assessment will be documented in an IDMC charter.

8.5.5 Sensitivity analysis (if applicable)

Sensitivity analyses from BICR (according to RECIST 1.1 modified for confirmation of progression) and from RECIST 1.1 measurements per the site Investigator will be performed on selected efficacy variables (see Table 19, Section 8.5.1, and Section 8.5.2).

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first patient is enrolled in the study, an AstraZeneca (or delegated) representative will review and discuss the requirements of the clinical study protocol and related documents with the investigational staff and train them in any study-specific procedures and IVRS, WBDC, ECG machine, and any electronic PRO systems to be utilized.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff and 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 and their project-specific training completed (medical, nursing, and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca (or delegated) representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, data are being accurately and timely recorded in the eCRFs, biological samples are handled in accordance with the Laboratory Manual, and study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice and other records relevant to the study), including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure that withdrawal of informed consent for the use of the patient's biological samples is reported, biological samples are identified and disposed of or destroyed accordingly, and the action is documented, and reported to the patient

The AstraZeneca (or delegated) representative will be available between visits if the Investigators or other staff at the centers need information and advice about the study conduct.

9.2.1 Source data

Refer to the CSA for location of source data.

9.2.2 Study agreements

The Principal Investigator at each center should comply with all the terms, conditions, and obligations of the CSA for this study. In the event of any inconsistency between this clinical study protocol and the CSA, the terms of clinical study protocol shall prevail with respect to the conduct of the study and the treatment of patients. In all other respects not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca (or delegate) and the Principal Investigator should be in place before any study-related procedures can take place, or before any patients are enrolled.

9.2.3 Archiving of study documents

The Investigator will follow the principles outlined in the CSA.

9.3 Study timetable and end of study

The study will continue until the last patient completes 90 days of follow-up after retreatment or the last patient withdraws from the progression-free follow-up (so no further patients are eligible for retreatment), whichever occurs first (estimated to be the end of Q3 2018).

In the event that a roll-over or safety extension study will become available, patients currently receiving treatment with study drug or patients who are progression-free following randomized treatment and potentially eligible for retreatment may be transitioned to such a study, and the current study would end. The roll-over or safety extension study would ensure treatment continuation with visits and assessments per its protocol. Any patient that would be proposed to move to such a study would be asked to sign a new ICF.

The study may be terminated at individual centers if the study procedures are not being performed according to Good Clinical Practice (GCP), or when there are no longer any patients being treated, or within 90 days post treatment discontinuation, or followed for potential retreatment eligibility once the DCO for final OS analysis has occurred. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with MEDI4736 or tremelimumab (see Section 3.11 for further details).

After the OS Extension period, patients in progression follow-up will be withdrawn from the study. Patients who are progression-free following randomized treatment and potentially eligible for retreatment may decide to continue in the study in follow-up. These patients would therefore remain eligible for possible future retreatment upon progression if they meet retreatment criteria and the Investigator believes that the patient will gain clinical benefit.

Patients who are receiving treatment at the time of the OS Extension DCO may continue receiving IP if the Investigator believes that they are gaining clinical benefit.

9.4 Data management by AstraZeneca

Data management will be performed by a chosen vendor according to the Data Management Plan. AEs and medical/surgical history will be classified according to the terminology of the latest version of MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary. Classification coding will be performed by the chosen vendor.

The data collected through third party sources will be obtained and reconciled against study data.

Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Quality 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 Quality 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 be added thereafter, 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 in the AstraZeneca genotyping database or other appropriate secure system within AstraZeneca and/or a third party contracted to work with AstraZeneca to analyze samples. The results from this genetic research may be reported in the CSR for the main study or in a separate report, as appropriate.

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 human biological samples will be transferred from laboratories internal or external to AstraZeneca.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation

(ICH)/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

The ICFs will incorporate wording that complies with relevant data protection and privacy legislation. In some cases, such wording will be in a separate accompanying document.

AstraZeneca will not provide individual genotype results to patients, their family members, their general physician, any insurance company, any employer, or any other third party, unless required to do so by law**.**

Precautions are taken to preserve confidentiality and prevent genetic data from 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 might also have access to his or 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.

10.3 Ethics and regulatory review

An Ethics Committee (EC)/Institutional Review Board (IRB) should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable EC/IRB and to the study site staff.

The opinion of the EC/IRB should be given in writing. The Investigator should submit the written approval to AstraZeneca (or delegate) before enrollment of any patient into the study.

The EC/IRB should approve all advertising used to recruit patients for the study.

AstraZeneca (or delegate) should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC/IRB annually.

Before enrollment of any patient into the study, the final study protocol, including the final version of the ICF, should be approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca (or delegate) will handle the distribution of these documents to the national regulatory authorities.

AstraZeneca (or delegate) will provide Regulatory Authorities, ECs/IRBs, and Principal Investigators with safety updates or reports according to local requirements.

Each Principal Investigator is responsible for providing the EC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca (or delegate) 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 center 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
- Ensure that each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure that each patient provides a signed and dated informed consent before conducting any procedure specifically for the study
- Ensure that the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure that a copy of the signed ICF is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an EC/IRB.
- Document in the patient's source documents the time, date, name of the ICF, and name of individual involved in the Informed Consent Process.
- Patients who are eligible for retreatment at any time including after the OS Extension period must sign the retreatment ICF prior to restarting their originally-assigned study treatment. Copies of the informed consent must be maintained with the patient's medical records.

10.5 Changes to the 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 study protocol, then these changes will be documented in a study protocol amendment and, where required, in a new version of the study protocol (revised clinical study protocol).

The amendment is to be approved by the relevant EC/IRB and, if applicable, the national regulatory authority, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca (or delegate) will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator. For distribution to EC/IRB see Section 10.3.

If a protocol amendment requires a change to a center's ICF, AstraZeneca (or delegate) and the center's EC/IRB are to approve the revised ICF before the revised form is used.

If required by local regulations, any administrative change will be communicated to or approved by each EC/IRB.

10.6 Audits and inspections

Authorized representatives of AstraZeneca, a third party, a regulatory authority, or an EC/IRB may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and to determine if data were recorded, analyzed, and accurately reported according to the protocol, GCPs, ICH guidelines, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

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Appendix A Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability, or incapacity but may jeopardize the patient or may require medical intervention to prevent 1 or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, or other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where 1 or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

MEDI4736 AND TREMELIMUMAB

There is no information to date on drug-drug interactions with MEDI4736 or tremelimumab either pre-clinically or in patients. As MEDI4736 and tremelimumab are monoclonal antibodies and therefore proteins, they will be degraded to small peptides and amino acids and will be eliminated by renal and reticuloendothelial clearance. It is therefore not expected that MEDI4736 or tremelimumab will induce or inhibit the major drug metabolizing cytochrome P450 pathways. As a result, there are no expected pharmacokinetic drug-drug interactions.

No formal drug-drug interaction studies have been conducted with tremelimumab. However, in renal cell carcinoma studies, acute renal failure has been reported with the combination of tremelimumab and sunitinib. It is unknown whether a similar reaction will be observed when tremelimumab is combined with other tyrosine kinase inhibitors.

The mechanism of action of MEDI4736 involves binding to PD-L1, and the mechanism of action of tremelimumab involves binding to CTLA-4; therefore, significant pharmacodynamic drug interactions with the commonly administered concomitant medications are not expected. Despite this, appropriate clinical monitoring in all of the planned clinical studies will be conducted to evaluate any potential drug-drug interactions.

Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

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 (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B, or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening, or fatal disease in otherwise healthy humans or animals. Category A pathogens are, eg, Ebola, Lassa fever virus:

- Are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- Are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(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 C Pharmacogenetics Research

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
DNA	Deoxyribonucleic acid
LIMS	Laboratory information management system
SCCHN	Squamous cell carcinoma of the head and neck

BACKGROUND AND RATIONALE

AstraZeneca intends to perform genetic research in the MEDI4736 + tremelimumab clinical development program to explore how genetic variations may affect the clinical parameters associated with this drug combination. Collection of DNA samples from populations with well-described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Future research may suggest other genes or gene categories as candidates for influencing not only response to MEDI4736 + tremelimumab, but also susceptibility to SCCHN. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to SCCHN and MEDI4736 + tremelimumab treatment.

GENETIC RESEARCH OBJECTIVES

The objective of this research is to collect and store DNA, derived from a blood sample, for future exploratory research into genes/genetic variations that may influence response, ie, distribution, safety, tolerability, and efficacy of MEDI4736 + tremelimumab, and/or susceptibility to SCCHN.

GENETIC RESEARCH PLAN AND PROCEDURES

Selection of genetic research population

Study selection record

All enrolled patients who take part in the main study will be asked to participate in this genetic research. Participation is voluntary, and if a patient declines to participate, there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

Inclusion criteria

For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Discontinuation of patients from this genetic research

Specific reasons for discontinuing a patient from this genetic research are:

Withdrawal of consent for genetic research: patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 3.9 of the main Clinical Study Protocol.

Collection of samples for genetic research

Blood samples will ideally be collected during the screening/baseline period. If for any reason the sample is not drawn during the screening/baseline period, it should be taken as soon as possible, but not later than the last study visit. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event, as these patients would be important to include in any genetic analysis. Only 1 sample should be collected per patient for genetics during the study.

If the patient agrees to participate, an 8.5-mL blood sample will be collected into a tube containing reagents that coagulate blood and stabilize blood cell DNA and gently inverted a minimum of 5 times to mix thoroughly. Tubes will be identified with the protocol study number, center number, enrollment code, and date of sample collection. No personal identifiers (patient name, initials, or date of birth) will be placed on the tube or accompanying documentation. A record of the date of the patient consent to the host genetic research and the date of the blood sample collection will be recorded.

AstraZeneca/MedImmune, or its designee, will act as the central laboratory for sample logistics. This will include the supply of site material and all transport arrangements.

A single blood sample will be stored frozen (-20°C or below) at the site and sent to the central laboratory. The central laboratory will then send the samples to AstraZeneca/MedImmune, or its designee laboratory, for DNA extraction. Samples must remain frozen at all times. Further details on the processing of the samples are outlined in the Laboratory Manual for Investigators.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years from the date of the last patient's last visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca/MedImmune genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca/MedImmune 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 enrollment/randomization code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analyzed.

ETHICAL AND REGULATORY REQUIREMENTS

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 10 of the main Clinical Study Protocol.

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/Good Clinical Practice, applicable regulatory requirements, and the AstraZeneca policy on Bioethics.

Informed consent

The portion of this study evaluating genetic alterations in blood samples is optional, and the patient may participate in other components of the main study without participating in this specific genetic analysis. To participate in this genetic component of the study, the patient must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study center. The principal investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue from the genetic aspect of the study at any time.

Subject data protection

AstraZeneca/MedImmune will not provide individual genotype results to patients, any insurance company, any employer, their family members, their 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. Individual patients will not be identified in any report or publication resulting from this work. The data and results of this study may be reviewed with collaborators and published, but neither the patient's name nor any other personal identifiers will appear in any publication or report. 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/MedImmune physician or an investigator might know a patient's identity and also have access to his or her genetic data. Regulatory authorities may also require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

DATA MANAGEMENT

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/MedImmune to analyze the 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.

STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

LIST OF REFERENCES

None

Appendix D Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

Introduction

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

A Potential Hy's Law (PHL) case is defined as a study patient with an increase in serum Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3 × Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥2 × ULN, irrespective of serum Alkaline Phosphatase (ALP), at any point during the study following the start of study medication.

Hy's Law (HL)

A Hy's Law (HL) case is defined as a study patient with an increase in serum AST or ALT ≥3 × ULN together with TBL ≥2 × ULN, where no other reason can be found to explain the combination of increases, eg, elevated serum ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL to be met the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of potential Hy's law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3 × ULN
- AST ≥3 × ULN

- TBL ≥2 × ULN

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 "Definitions" of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

Follow-up

Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment in the presence of liver metastases (see Section "Actions required when potential Hy's law criteria are met before and after starting study treatment")
- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss, and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the 3 Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

Review and Assessment of potential Hy's law cases

The instructions in this section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there **is** an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.

  - The 'Medically Important' serious criterion should be used if no other serious criteria apply

  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

Actions required when potential Hy's law criteria are met before and after starting study treatment

This section is applicable to patients who meet PHL criteria on study treatment (including the 30-day follow-up period post discontinuation of 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 "Potential Hy's Law Criteria met" of this Appendix

[#] A 'significant' change in the patient's condition refers to a subsequent clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms such as fatigue, vomiting, rash, right upper quadrant pain, jaundice, or eosinophilia. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

Actions required for repeat episodes of potential Hy's law

This section is applicable when a patient meets PHL criteria on study treatment (including the 30-day follow-up period) 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 chronic or progressing malignant 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 "Actions required when potential Hy's law criteria are met before and after starting study treatment"?

If No: follow the process described in Section "Potential Hy's Law Criteria met" of this Appendix

If Yes:

Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section "Potential Hy's Law Criteria met" of this Appendix

[#] A 'significant' change in the patient's condition refers to a subsequent clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms, such as fatigue, vomiting, rash, right upper quadrant pain, jaundice, or eosinophilia. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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

INTRODUCTION

This appendix details the implementation of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines (Eisenhauer et al 2009) for the D4193C00003 study with regards to Investigator assessment of tumor burden including protocol-specific requirements for this study.

DEFINITION OF MEASURABLE, NON-MEASURABLE, TARGET AND NON-TARGET LESIONS

Only patients with measurable disease at baseline should be included in the study. Measurable disease is defined by the presence of at least one measurable (by RECIST 1.1) lesion which has not been previously irradiated. A tumor lesion in a previously irradiated field can be assessed as measurable disease provided the lesion has been deemed to demonstrate progression.

Measurable:

A lesion, not previously irradiated per the protocol prior to enrollment, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements. A tumor lesion in a previously irradiated field can be assessed as measurable disease provided the lesion has been deemed to demonstrate progression.

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis at baseline[1]).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease,

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

lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.

- Lesions <2 cm biopsied within the screening period (fresh tumor biopsy)
- Previously irradiated lesions that have not demonstrated progression[2]
- 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 (TLs).

Target lesions:

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TLs at baseline.

Non-target lesions:

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

METHODS OF ASSESSMENT

The same method of assessment and the same technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits.

[2] Localized post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated and have not demonstrated progression will not be considered measurable and must be selected as NTL at baseline and followed up as part of the NTL assessment.

A summary of the methods to be used for RECIST assessment is provided in Table 20, and those excluded from tumor assessments for this study are highlighted with the rationale provided.

Table 20 Summary of methods of assessment

Target lesions	Non-target lesions	New lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Clinical examination	Clinical examination
	X-ray, Chest X-ray	X-ray, Chest X-ray
		Ultrasound
		Bone scan
		FDG-PET

CT Computed tomography; FDG-PET 18-Fluoro-deoxyglucose positron emission tomography; MRI Magnetic resonance imaging.

CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and identification of any new lesions.

In the D4193C00003 study, the methods of assessment of tumor burden used at baseline and follow-up visits are CT / MRI of the neck (including the base of skull) through chest and abdomen (including the liver). Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients. CT examination with intravenous contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For brain lesion assessment, MRI is the preferred method.

Clinical examination

In the D4193C00003 study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as TLs if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

X-ray

Plain X-ray

In the D4193C00003 study plain X-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

Ultrasound

In the D4193C00003 study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumor size

and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

Endoscopy and laparoscopy

In the D4193C00003 study, endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor assessment.

Tumor markers

In the D4193C00003 study, tumor markers will not be used for tumor response assessments as per RECIST 1.1.

Cytology and histology

In the D4193C00003 study histology will not be used as part of the tumor response assessment as per RECIST 1.1.

Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

In the D4193C00003 study, isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and X-ray is recommended where bone scan findings are equivocal.

FDG-PET scan

In the D4193C00003 study, 18-Fluoro-deoxyglucose positron emission tomography (FDG-PET) scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive 18-Fluoro-deoxyglucose uptake[3] not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up

[3] A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

TUMOR RESPONSE EVALUATION

Schedule of evaluation

RECIST assessments will be performed using CT/MRI assessments of the neck (from base of skull) though the chest and abdomen (including liver). Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before start of study treatment, and ideally should be performed as close as possible to the start of study treatment (see Table 2 of the Clinical Study Protocol). Follow-up assessments will be performed every 8 weeks for the first 12 months (relative to first infusion), and then every 12 weeks thereafter until confirmed objective disease progression as defined by RECIST 1.1 (irrespective of the reason for stopping treatment and/or subsequent therapy).

Additional assessments will be performed post confirmed objective disease progression for patients remaining on study treatment, retreatment or until subsequent cancer therapy according to the clinical study protocol.

Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

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

Target lesions

Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts.
- If two or more TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention eg, radiotherapy, embolization, surgery, during the study, the size of the TL should still be provided where possible.

Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumor visit response for TL (see Table 21).

Table 21 Evaluation of target lesions

Complete Response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progression of disease (PD)	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
Not Evaluable (NE)	Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. Note: if the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response

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

Non-target lesions

Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit (see Table 22).

Table 22 Evaluation of non-target lesions

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

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

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

New lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor.

If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

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

Evaluation of overall visit response

The overall visit response will be derived using the algorithm shown in Table 23.

Table 23 Overall visit response

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

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

CONFIRMATION OF PROGRESSION

In the D4193C00003 study, imaging for confirmation of response (complete response or partial response) should be performed at next scheduled visit (and no less than 4 weeks) following the date the criteria for response were first met.

Disease progression requires confirmation, the confirmatory scan should occur preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of progression of disease (PD) in the absence of clinical deterioration.

Progression would be considered confirmed if the following criteria are met:

- ≥20% increase in the sum diameters of TLs compared with the nadir at 2 consecutive visits with an absolute increase of 5mm
- And/or significant progression (worsening) of NTLs or new lesions at the confirmatory PD time-point compared with the first time point where progression of NTLs or new lesions identified
- And/or additional new unequivocal lesions at the confirmatory PD time-point compared with the first time point new lesions identified.

In the absence of significant clinical deterioration the Investigator should continue study treatment until progression is confirmed.

If progression is not confirmed then the patient should continue on study treatment and on treatment assessments.

If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression then the patient should still continue to be followed until objective disease progression.

CENTRAL REVIEW

The Contract Research Organization appointed by AstraZeneca to perform the independent central review for this study will provide specification for radiological imaging protocols in standard acquisition guidelines documentation.

REFERENCES

Eisenhauer et al 2009

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

Appendix F Patient Reported Outcomes: EORTC QLQ-C30 and EORTC QLQ-H&N35

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____
Your birthdate (Day, Month, Year): ____
Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

ENGLISH

EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Have you had pain in your mouth?	1	2	3	4
32.	Have you had pain in your jaw?	1	2	3	4
33.	Have you had soreness in your mouth?	1	2	3	4
34.	Have you had a painful throat?	1	2	3	4
35.	Have you had problems swallowing liquids?	1	2	3	4
36.	Have you had problems swallowing pureed food?	1	2	3	4
37.	Have you had problems swallowing solid food?	1	2	3	4
38.	Have you choked when swallowing?	1	2	3	4
39.	Have you had problems with your teeth?	1	2	3	4
40.	Have you had problems opening your mouth wide?	1	2	3	4
41.	Have you had a dry mouth?	1	2	3	4
42.	Have you had sticky saliva?	1	2	3	4
43.	Have you had problems with your sense of smell?	1	2	3	4
44.	Have you had problems with your sense of taste?	1	2	3	4
45.	Have you coughed?	1	2	3	4
46.	Have you been hoarse?	1	2	3	4
47.	Have you felt ill?	1	2	3	4
48.	Has your appearance bothered you?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:		Not at all	A little	Quite a bit	Very much
49.	Have you had trouble eating?	1	2	3	4
50.	Have you had trouble eating in front of your family?	1	2	3	4
51.	Have you had trouble eating in front of other people?	1	2	3	4
52.	Have you had trouble enjoying your meals?	1	2	3	4
53.	Have you had trouble talking to other people?	1	2	3	4
54.	Have you had trouble talking on the telephone?	1	2	3	4
55.	Have you had trouble having social contact with your family?	1	2	3	4
56.	Have you had trouble having social contact with friends?	1	2	3	4
57.	Have you had trouble going out in public?	1	2	3	4
58.	Have you had trouble having physical contact with family or friends?	1	2	3	4
59.	Have you felt less interest in sex?	1	2	3	4
60.	Have you felt less sexual enjoyment?	1	2	3	4

During the past week:		No	Yes
61.	Have you used pain-killers?	1	2
62.	Have you taken any nutritional supplements (excluding vitamins)?	1	2
63.	Have you used a feeding tube?	1	2
64.	Have you lost weight?	1	2
65.	Have you gained weight?	1	2

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Statistical Analysis Plan

Drug Substance	MEDI4736 and tremelimumab
Study Code	D4193C00003
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A Phase II, Randomized, Open-Label, Multi-Center, Global Study of MEDI4736 Monotherapy, Tremelimumab Monotherapy, and MEDI4736 in Combination with Tremelimumab in Patients with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

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Global Product Statistician

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[redacted] Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	Antidrug antibody
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
Baseline	Refers to the last assessment prior to intake of the first dose of IP, except for Efficacy where baseline refers to the last visit prior to enrolment.
BICR	Blinded independent central review
BoR	Best objective response
CI	Confidence interval
CR	Complete response
CRA	Clinical Research Associate
eCRF	Case Report Form (electronic)
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4
CTM	Clinical team manager
CTMS	Clinical trial management system
DBP	Diastolic blood pressure
DCO	Data cut-off
DCR	Disease control rate
DoR	Duration of response
EAS	Evaluable analysis set
ECG	Electrocardiogram
EORTC	European Organisation for Research and Treatment of Cancer
FAS	Full analysis set

Abbreviation or special term	Explanation
HRQoL	Health-related quality of life
IDMC	Independent Data Monitoring Committee
IP	Investigational product
irAE	Immune-related adverse event
irRECIST 1.1	Immune-related response evaluation criteria in solid tumors version 1.1
ITT	Intent-to-treat
IV	Intravenous
KM	Kaplan-Meier
LD	Longest diameter
MD	Medical doctor
MedDRA	Medical Dictionary for Regulatory Activities
MEDI4736	Immune-mediated therapy
mg	Milli-gram
MMA	Medical monitoring associate
MRI	Magnetic resonance imaging
NA	Not applicable
NCI	National Cancer Institute
NE	Not evaluable
NED	No evidence of disease
NTL	Non-target lesions
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-L1	Programmed cell death ligand 1
PFS	Progression free survival
PK	Pharmacokinetic(s)
PR	Partial response

Abbreviation or special term	Explanation
PRO	Patient reported outcome
q2W	Every 2 weeks
q4W	Every 4 weeks
q12W	Every 12 weeks
QLQ-C30 v3	30-item core quality of life questionnaire, version 3
QLQ-H&N35	35-item head and neck quality of life questionnaire
QoL	Quality of life
QRS	ECG Q, R, S waves
QT	time between the start of the Q wave and the end of the T wave
QTcB	QT interval corrected for Bazzet's formula
QTcF	QT interval corrected for Fridericia's formula
RDI	Relative dose intensity
RECIST 1.1	Response Evaluation Criteria In Solid Tumors version 1.1
RR	Response rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable disease
SDV	Source data verify
SBP	Systolic blood pressure
TEAE	Treatment-emergent adverse event
TL	Target lesions
TSH	Thyroid-stimulating hormone
TTR	Time to treatment response
ULN	Upper limit of normal
WHO	World Health Organization

AMENDMENT HISTORY

Date	Brief description of change
	Sample size wording was updated in section 1.3 to be in line with protocol version 04 (09March2016).
	Sensitive analyses on DoR, TTR, BoR, DCR, and PFS analyzed by BICR using FAS were added to be in line with FDA's request.
28/OCT/2016	irRECIST was changed from secondary to exploratory analysis and analysis with irRECIST data was kept for only ORR and PFS.
	Listing of physical exams was removed.
	Dose intensity for the re-treatment was removed.
	Additional subgroups were added, including the new scoring for the biomarker.
	Timing of PFS and OS formal analyses was more accurately defined based on the number of events (i.e. 116 PFS events and 125 death events)
	Hazard ratio and confidence interval derived at landmarks as per Klein's method were removed.
	Non-compartment PK was removed.

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary Objective

Table 1 Primary Objective

Primary Objective:	Outcome Measure:
To assess the efficacy of MEDI4736 + tremelimumab combination therapy in terms of ORR	ORR using BICR assessments according to RECIST 1.1[a]

[a] Sensitivity analysis of ORR will be performed based on tumor information recorded in the clinical database by the Investigator according to RECIST 1.1 and will also be performed based on BICR assessment according to RECIST 1.1 modified for confirmation of progression.

BICR Blinded Independent Central Review; ORR Objective response rate; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1.

1.1.2 Secondary Objectives

Table 2 Secondary Objectives

Objective:	Outcome Measures:
To further assess the efficacy of MEDI4736 + tremelimumab combination therapy in terms of ORR, TTR, DoR, DCR, BoR, PFS, and OS.	TTR, DoR, DCR, BoR, and PFS a using BICR assessments according to RECIST 1.1 OS
To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared with a) MEDI4736 monotherapy and b) tremelimumab monotherapy, in terms of ORR, PFS, and OS	ORR and PFS using BICR assessments according to RECIST 1.1b OS
To assess disease-related symptoms and health-related quality of life (QoL) in patients treated with MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, and tremelimumab monotherapy using the EORTC QLQ-C30 v3 and the QLQ-H&N35 module	EORTC QLQ-C30: global health QoL, functioning (physical), and symptoms (fatigue) EORTC QLQ-H&N35: symptoms (pain and swallowing) Changes in WHO/ECOG performance status will also be assessed.

[a] Sensitivity analysis of PFS will be performed based on tumor information recorded in the clinical database by the Investigator according to RECIST 1.1.

[b] Sensitivity analyses of ORR will be performed based on tumor information recorded in the clinical database by the Investigator according to RECIST 1.1 and PFS will also be performed based on BICR assessment according to RECIST 1.1 modified for confirmation of progression.

BICR Blinded Independent Central Review; BoR Best objective response; DCR Disease control rate; DoR Duration of response; ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; QLQ-C30 v3 30-item core quality of life questionnaire, version 3; QLQ-H&N35 35-item head and neck quality of life questionnaire; QoL Quality of life; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1; TTR Time to treatment response; WHO World Health Organization.

1.1.3 Safety Objectives

Table 3 Safety Objectives

Safety Objective:	Outcome Measures:
To assess the safety and tolerability profile of MEDI4736 monotherapy, tremelimumab monotherapy, and MEDI4736 + tremelimumab combination therapy	AEs, physical examinations, laboratory findings (including clinical chemistry, hematology, and urinalysis), vital signs (including blood pressure, pulse respiratory rate, body temperature, and oxygen saturation), and ECGs

AE Adverse Event; ECG Electrocardiogram.

1.1.4 Exploratory Objectives

Table 4 Exploratory Objectives

Exploratory Objective:	Outcome Measures:
To further assess the efficacy of MEDI4736 + tremelimumab combination therapy in terms of ORR and PFS.	ORR and PFS using BICR assessments according to irRECIST 1.1
To assess the PK of MEDI4736 monotherapy, tremelimumab monotherapy, and MEDI4736 + tremelimumab combination therapy	Concentration of MEDI4736/tremelimumab in
To investigate the immunogenicity of MEDI4736 and tremelimumab	Presence of ADA for MEDI4736 and tremelimumab (confirmatory results: positive or negative; titers)
To collect blood and tissue samples for analysis of biomarkers	Biomarker analysis of blood and tissue to assess exploratory markers that may include but are not limited to: immune cell gene expression profiles within the peripheral and tumoral compartments; the presence of IFN-γ TNF-α, IL-2, IL-6, IL-10, IL-8, and IL-12 as well as antibodies against tumor, self, or viral antigens; expression of PD-L1; and the number and phenotype of immune cells such as T-cells
To explore the relationship(s) between a patient's biomarker status before and after treatment with MEDI4736 monotherapy, tremelimumab monotherapy, and MEDI4736 + tremelimumab and clinical outcomes, efficacy, AEs, and/or safety parameters	Biomarker status before and after treatment and relationship with clinical outcomes, efficacy, AEs, and/or safety parameters, as deemed appropriate
To explore potential biomarkers in residual biological samples (e.g., tumor, plasma, and/or serum) that may influence the progression of cancer (and associated clinical characteristics) and/or prospectively identify patients likely to respond to MEDI4736 and tremelimumab. This includes HPV status.	Correlation of biomarkers with response to MEDI4736 and tremelimumab and/or the progression of cancer

To collect and store DNA according to each country's local and ethical procedures for future exploratory research into genes/genetic variation that may influence response (i.e., distribution, safety, tolerability, and efficacy) to study treatments and/or susceptibility to disease (optional)	Correlation of polymorphisms with variation in PK, pharmacodynamics, safety, or response parameters observed in patients treated with MEDI4736 and tremelimumab and/or susceptibility to disease

Note: Exploratory objective analyses may be reported separately from the main clinical study report.

ADA Antidrug antibody; AE Adverse event; ECOG Eastern Cooperative Oncology Group; irRECIST 1.1 Immune-related Response Evaluation Criteria in Solid Tumors version 1.1; IFN Interferon; IL Interleukin; PD-L1 Programmed cell death ligand 1; PK Pharmacokinetics; TNF Tumor necrosis factor; WHO World Health Organization.

1.2 Study design

This is a randomized, open-label, multi-center, global, Phase II study to determine the efficacy and safety of MEDI4736 monotherapy, tremelimumab monotherapy, and MEDI4736 in combination with tremelimumab in the treatment of patients with recurrent or metastatic PD-L1-negative SCCHN who have progressed during or after treatment with only systemic palliative regimen for recurrent or metastatic disease that must have contained a platinum agent. A schematic diagram of the overall study design is shown in Figure 1, and a flow chart of the study design is presented in Figure 2.

Patients will undergo an assessment on their tumor tissue sample to determine PD-L1 status prior to treatment (Day 0). The tissue sample could be a newly acquired tumor tissue (preferred) or an archival tissue (≤3 years old) for the purpose of establishing PD-L1 status. Patients with tumoral PD-L1 expression below a pre-specified cut-off level, less than 25% of tumor cells with membrane staining, as determined by an immunohistochemistry assay (referred to hereafter as patients with PD-L1-negative tumors), will be enrolled in the study. If the patient's PD-L1 status has already been assessed using the analytically validated Ventana SP263 assay as a part of the screening process for D4193C00001 or another AstraZeneca/MedImmune study, this test result can be used for the determination of eligibility.

Patients will be randomized in stratified manner according to prognostic factors, human papillomavirus status and smoking status to achieve a balance between treatments for each of the factors. Patients will be randomized in a 1:1:2 fashion (60:60:120 patients) to receive MEDI4736 monotherapy, tremelimumab monotherapy, or MEDI4736 + tremelimumab combination therapy for a total of 208 evaluable patients (52 in MEDI4736 monotherapy, 52 in tremelimumab monotherapy, and 104 in MEDI4736 + tremelimumab combination arm).

Patients in the MEDI4736 monotherapy treatment group will receive 10 mg/kg MEDI4736 via intravenous (IV) infusion every 2 weeks (q2w) for up to 12 months (up to 26 doses). Patients in the tremelimumab monotherapy treatment group will receive 10 mg/kg tremelimumab via IV infusion every 4 weeks (q4w) for 7 doses then every 12 weeks for 2 additional doses for up to 12 months (up to 9 doses in total). Patients in the MEDI4736 + tremelimumab group will receive 20 mg/kg MEDI4736 via IV infusion q4w for 4 months (up to 4 doses) and 1 mg/kg tremelimumab via IV infusion q4w for 4 months (up to 4 doses in total). After completion of the initial 4 doses of combination therapy, single agent MEDI4736 will continue at 10 mg/kg

q2w to complete a total of 12 months of therapy (up to 18 additional doses with the final dose at Week 50). The first MEDI4736 dose at 10 mg/kg q2w will be 4 weeks after the final dose of the combination of tremelimumab and MEDI4736 at 20 mg/kg.

All treatments will be administered beginning on Day 1 for 12 months or until confirmed progression of disease (PD; unless, in the Investigator's opinion, the patient continues to receive benefit from the treatment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Patients with confirmed PD who, in the Investigator's opinion, continue to receive benefit from their assigned investigational product (IP) and who meet the criteria for treatment in the setting of PD may continue to receive their assigned IP treatment for a maximum of 12 months after consultation with the Sponsor and at the Investigator's discretion. IP should be discontinued if there is confirmed PD following a previous response (CR or PR) to IP in the target lesions. Patients who the Sponsor and Investigator determine may not continue treatment after confirmed PD during the 12-month initial treatment period or in the 12-month retreatment period will enter follow-up. Patients who have discontinued treatment due to toxicity, or who have commenced subsequent anticancer therapy, will be followed up until confirmed disease progression or death (whichever occurs first).

Tumor assessments will be performed using computed tomography or magnetic resonance imaging. Efficacy for all patients will be assessed by objective tumor assessments every 8 weeks (q8w) for the first 48 weeks (relative to the date of the first infusion) then q12w in patients who have disease control after 12 months until confirmed objective disease progression as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1; irrespective of the reason for stopping treatment or subsequent therapy). If an unscheduled scan is performed in the absence of suspicion of progression within 2 weeks of a scheduled scan, the scan does not need to be repeated. However, every attempt should be made to follow the original scan schedule.

Categorization of objective tumor response assessment will be based on RECIST 1.1: complete response (CR), partial response (PR), stable disease (SD), and PD. RECIST 1.1 measurements based on Independent Central Review (ICR) assessment will be used to programmatically derive the primary variable of objective response rate (ORR) and the secondary variables of duration of response (DoR), disease control rate (DCR), best objective response (BoR), and progression-free survival (PFS). Results of these independent reviews will not be communicated to the Investigators, and the management of patients will be based solely upon the results of the RECIST assessment conducted by the Investigator. ORR and PFS will also be assessed as exploratory variables using BICR assessment according to immune-related response criteria (irRECIST 1.1). While BICR assessment will be used to define study endpoints, determination of CR, PR, SD, and PD during the trial and subsequent appropriate management will be based on individual Investigator review of tumor response assessments as per RECIST 1.1. Additional secondary objectives will include overall survival (OS), safety and tolerability, and health-related quality of life. Exploratory objectives will also be assessed.

Objective tumor response (CR or PR) should be confirmed preferably at the next scheduled visit and no earlier than 4 weeks immediately prior assessment of PD in the absence of clinically significant deterioration. Treatment with IP will continue between the assessment of progression and its confirmation. If progression is not confirmed, then the patient should continue receiving study treatment and participating in study assessments.

Patients with clinical evidence of progression who do not meet PD criteria by RECIST 1.1 should have radiographic documentation of PD.

Patients who achieve and maintain disease control (i.e., CR, PR, or SD) through the end of the 12-month treatment period will enter follow-up. When these patients experience evidence of PD, with or without confirmation, during follow-up and meet the criteria for treatment in the setting of PD, they will be given the option to restart their assigned IP treatment for up to an additional 12 months with the same treatment guidelines followed during the initial 12-month treatment period. Patients should have a baseline tumor assessment within 28 days of restarting treatment with their assigned IP; all further scans should occur q8w (relative to the date of restarting treatment) until study treatment is stopped (maximum of 12 months of further treatment). Only patients who the Investigator determines do not have any significant, unacceptable, or irreversible toxicities, or would continue to receive benefit from therapy can restart a second 12 months of retreatment upon PD.

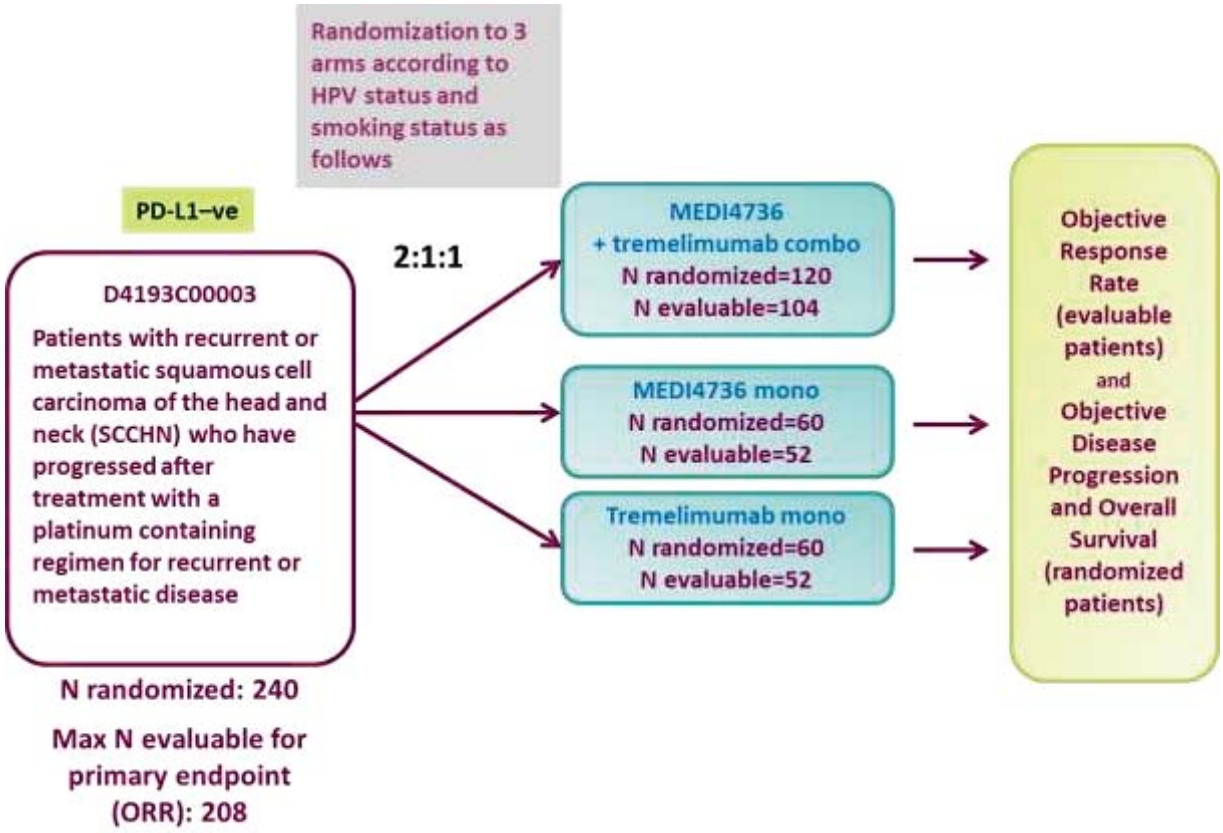
Patients with confirmed progression in the MEDI4736 monotherapy arm or in the combination portion of therapy in the MEDI4736 + tremelimumab arm cannot continue therapy or obtain retreatment if the progression occurred during dosing and after confirmed response in the target lesions (i.e., the response and progression events both occurred while receiving active IP during the same treatment period in the target lesions). Retreatment in the combination arm can only occur if PD occurs during the monotherapy portion or after completion of 12 months of therapy. During the retreatment period, the patient would resume MEDI4736 dosing at 20 mg/kg q4w as during the initial induction period, along with 1 mg/kg of tremelimumab q4w for 4 doses. Monotherapy with MEDI4736 would then resume at 10 mg/kg q2w 4 weeks after the last combination dose is administered for a total of up to 18 additional doses with the final dose at Week 50.

Patients with confirmed PD who continue to receive their assigned IP at the discretion of the Investigator (after consultation with the Sponsor) may do so for a maximum of 12 months.

Patients with confirmed PD who discontinue their assigned IP should have scans conducted according to local practice and submitted for BICR until the patient commences a new treatment (these scans are optional). Patients who discontinue treatment in 1 treatment group may not switch to treatment in a different group.

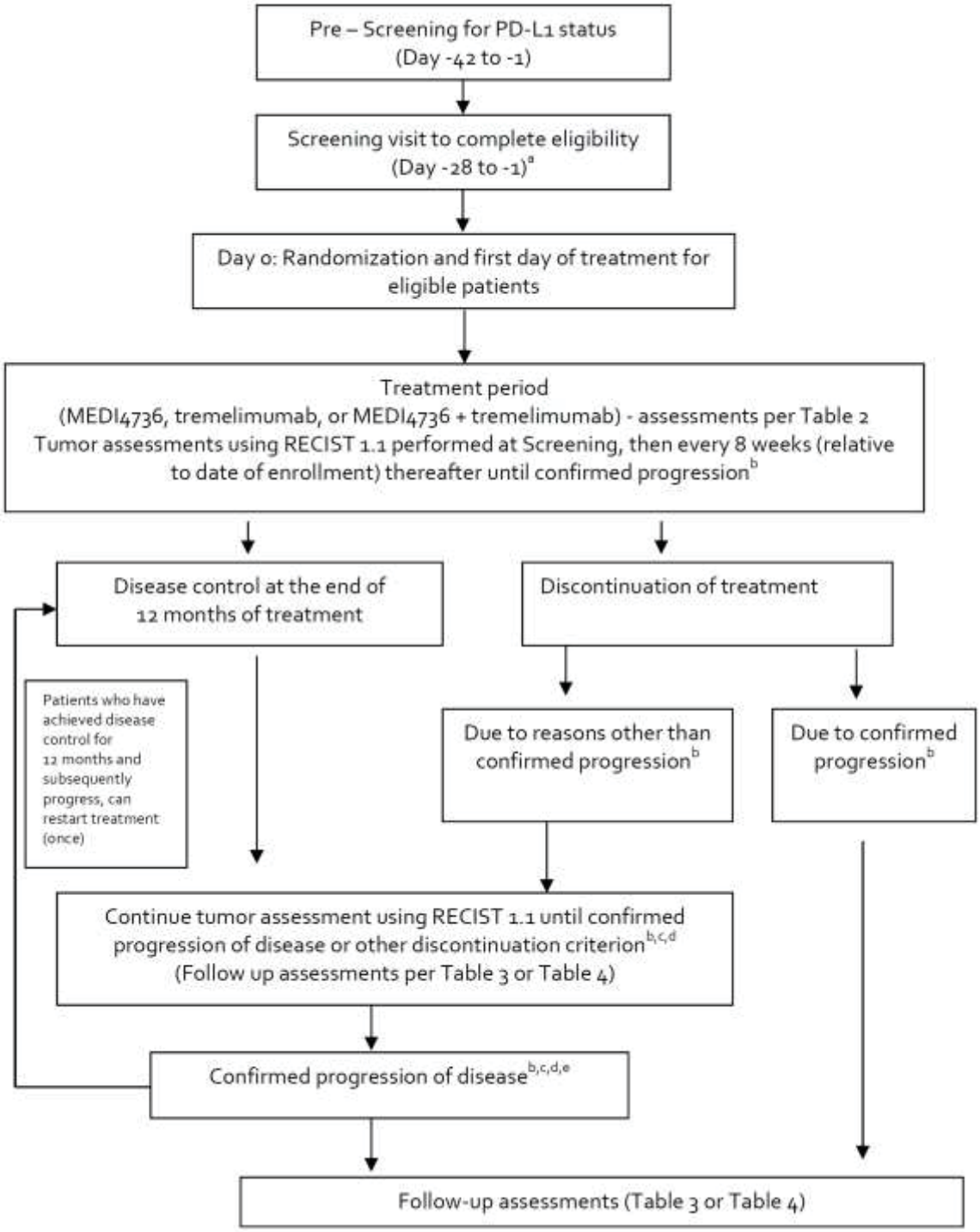
Following completion or discontinuation of treatment, patients will enter a follow-up period.

Figure 1 Overall study design



ORR Objective response rate; PD-L1-ve Programmed cell death ligand-1 negative.

Figure 2 Study flow chart



Screening assessments can be performed over multiple visits. Imaging and procedures performed before signing the ICF may be used for screening purposes if the patient consents. If the patient's PD-L1 status has already been assessed using the analytically validated Ventana assay as a part of the screening process for D4193C00001 or another AstraZeneca/MedImmune study, this test result can be used for the determination of eligibility.

[b] Disease progression needs to be confirmed. The confirmatory scan should occur preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of PD in the absence of clinical deterioration. Administration of

study treatment will continue between the initial assessment of progression and confirmation for progression. Patients with clinical evidence of progression who do not meet PD criteria by RECIST 1.1 should have confirmation of PD if clinically feasible no earlier than 4 weeks after the initial assessment of PD. For all patients who are treated through progression, the Investigator should ensure that patients do not have any significant, unacceptable, or irreversible toxicities that indicate that continuing treatment will not further benefit the patient, and that the patient still meets all of the inclusion criteria and none of the exclusion criteria for this study including re-consenting to continue treatment. Patients with rapid tumor progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) will not be eligible to continue to receive IP.

[c] Patients who achieve and maintain disease control (ie, CR, PR, or SD) through to the end of the 12-month treatment period may restart study treatment upon evidence of PD (with or without confirmation, according to RECIST 1.1) during follow-up. Before restarting study treatment, the Investigator should ensure that patients do not have any significant, unacceptable, or irreversible toxicities that indicate that continuing treatment will not further benefit the patient, and that the patient still meets all of the inclusion criteria and none of the exclusion criteria for this study including re consenting to restart treatment. To restart study treatment, the patient must not have received an intervening cancer therapy post study treatment discontinuation. Patients should have a baseline tumor assessment within 28 days of restarting study treatment; all further scans should occur q8w (relative to the date of restarting study treatment) (maximum of 12 months of further treatment). Patients with confirmed progression during dosing in the MEDI4736 or tremelimumab monotherapy arms or in the combination portion of therapy in the MEDI4736 + tremelimumab arm cannot continue therapy or obtain retreatment if progression occurred after confirmed response in the target lesions (ie, the response and progression events both occurred while receiving active IP during the same treatment period in the target lesions). Retreatment in the combination arm can only occur if PD occurs during the monotherapy portion or after completion of 12 months of therapy.

[d] Patients with confirmed PD who continue to receive study treatment at the discretion of the Investigator (following consultation with the Sponsor) can receive study treatment for a maximum of 12 months. This will not be considered retreatment but will be considered a part of the initial 12-month period of therapy. For all patients who are treated through progression, the Investigator should ensure that patients do not have any significant, unacceptable, or irreversible toxicities that indicate that continuing treatment will not further benefit the patient, and that the patient still meets all of the inclusion criteria and none of the exclusion criteria for this study including re-consenting to continue study treatment. The same exceptions as noted in footnote "b" apply. Patients will follow the assessments in Table 5 of the CSP including tumor assessments q8w (relative to the date of enrollment) until study treatment is stopped. IP should be discontinued if there is confirmed PD following a previous response in target lesions (CR or PR) to IP.

[e] Patients with confirmed PD or clinical progression who discontinue IP should have scans conducted according to local practice and submitted for Blinded Independent Central Review until the patient commences a new treatment (these scans are optional).

CR Complete response; ICF Informed consent form; IP Investigational product; PD Progressive disease; PD-L1 Programmed cell death ligand-1; PR Partial response; q8w Every 8 weeks; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1; SD Stable disease.

1.3 Number of subjects

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 8.2 of the CSP.

The study will screen approximately 384 patients to identify a total of approximately 240 patients who have PD-L1-negative disease, and are suitable for enrollment and randomization (in a 1:1:2 fashion) in order to obtain at least 208 evaluable patients for the primary and the key secondary endpoints. Patients will be randomized to MEDI4736 monotherapy (60 randomized, 52 evaluable patients), tremelimumab monotherapy (60 randomized, 52 evaluable patients), and MEDI4736 + tremelimumab combination therapy (120 randomized, 104 evaluable patients).

The primary objective of the study is to assess the efficacy of MEDI4736 + tremelimumab combination, in terms of ORR. If the true ORR is 27%, a sample size of 104 patients will provide a precision of ±8.5% around this estimate, using a 95% confidence interval (CI).

Although no formal statistical comparisons are planned, a sample size of 104 patients will provide adequate power to test the hypothesis H0: ORR ≤13% versus H1: ORR >13%. If the ORR is 27%, then the study will provide 92% power to reject the null hypothesis (H0) at the 1-sided 0.025 alpha level (or, equivalently, 2-sided 0.05 alpha level) using an exact binomial test.

To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared with a) MEDI4746 monotherapy and b) tremelimumab monotherapy in terms of ORR, a sample size of 156 evaluable patients (52 versus 104 for MEDI4736 monotherapy or tremelimumab monotherapy versus MEDI4736 + tremelimumab combination therapy) will be required. This sample size will provide 90% power to demonstrate a statistically significant difference in ORR at a 2-sided 0.05 significance level assuming a true treatment difference of 22% in ORR (5% on monotherapy and 27% on combination therapy). Based on the assumptions above, the minimum difference in ORR that would be statistically significant at the 0.05 level is 10.4%.

To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared with a) MEDI4746 monotherapy and b) tremelimumab monotherapy in terms of PFS, 116 PFS events need to be observed in the 156 evaluable patients (52 versus 104 for MEDI4736 monotherapy or tremelimumab monotherapy versus MEDI4736 + tremelimumab combination therapy). If the true HR is 0.60 (15 versus 37% PFS rates at 6 months), 116 PFS events provide 80% power to demonstrate a statistically significant difference in PFS at a 0.05 two-sided significance level. Based on the assumptions above, the critical HR that would be statistically significant at the 0.05 level is 0.70. With an assumed 10-month recruitment period and an assumed minimum follow-up period of 6 months, it is anticipated that this analysis will be performed 16 months after the first patient has been recruited.

To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared with a) MEDI4746 monotherapy and b) tremelimumab monotherapy in terms of OS, 125 death events (80% maturity) need to be observed in 156 evaluable patients (52 or 104 for MEDI4736 or tremelimumab, respectively, versus MEDI4736 + tremelimumab). If the true HR is 0.60 (10% versus 31% survival rates at 18 months), 125 death events will provide 80% power to demonstrate a statistically significant difference in OS at a 0.05 two-sided significance level, with the smallest treatment difference that could be statistically significant being an average HR of 0.70. With an assumed 10-month recruitment period and an assumed minimum follow-up period of approximately 18 months, it is anticipated that this analysis will be performed 28 months after the first patient has been recruited.

2. ANALYSIS SETS

2.1 Definition of analysis sets

Four analysis sets are defined for this study. Table 5 gives a summary of outcome variables and analysis populations.

2.1.1 Full analysis set (FAS)

The full analysis set (FAS) will include all randomized patients. Treatment groups will be compared on the basis of randomized study treatment, regardless of the treatment actually received. Patients who were randomized but did not subsequently go on to receive study treatment are included in the analysis in the treatment group to which they were randomized.

2.1.2 Evaluable analysis set (EAS)

All treated patients (ie, received at least 1 dose of IP) who have a baseline tumor assessment and have measurable disease at baseline according to a BICR.

2.1.3 Safety analysis set

The Safety Analysis Set will consist of all patients who received at least 1 dose of study treatment. Safety data will not be formally analyzed but summarized using the SAS according to the treatment received, that is, erroneously treated patients (e.g., those randomized to treatment A but actually given treatment B) will be summarized according to the treatment they actually received.

2.1.4 PK analysis set

All patients who receive at least 1 dose of either MEDI4736 or tremelimumab per the protocol for whom any post-dose data are available.

Table 5 Summary of Outcome Variables and Analysis Populations

Outcome variable	Populations
Efficacy Data	
ORR[1], TTR[1], DCR[1], BoR[1], DoR[1], PFS[1]	Evaluable analysis set[1]
ORR[2], TTR[2], DCR[2], BoR[2], DoR[2], PFS[2], OS	Full analysis set
Demography, WHO performance status	Full analysis set
EORTC QLQ-C30 and H&N35	Full analysis set
PK data	PK analysis set
Safety Data	
Exposure	Safety analysis set
Adverse events	Safety analysis set
Laboratory measurements	Safety analysis set
Vital Signs	Safety analysis set

[1]ORR, TTR, DCR, BoR, DoR and PFS will be analyzed on the evaluable analysis set, using BICR data.
[2]ORR, TTR, DCR, BoR, DoR and PFS will also be analyzed on FAS using BICR and the site investigator data.
BoR Best objective response; DCR Disease control rate; DoR Duration of response; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; PK Pharmacokinetic; WHO World Health Organization.

2.2 Violations and deviations

The important protocol deviations specified below will be listed and summarized. Deviation 1 below will lead to exclusion from the Evaluable and Safety analysis sets. None of the other deviations will lead to patients being excluded from the analysis sets described in section 2.1. If the deviations are serious enough to have the potential to impact the primary analysis, sensitivity analyses may be performed. Eligibility criteria deviations are deviations from the protocol inclusion and exclusion criteria. Post-entry deviations are deviations from the protocol that occurred after the patient was randomized to the study.

The following general categories will be considered important deviations and be listed and discussed in the Clinical Study Report (CSR) as appropriate for the study.

- Patients who did not receive either MEDI4736 or tremelimumab (Deviation 1).
- Patients who deviate from key entry criteria (Deviation 2). These are inclusion criteria 3, 4, 6, 8 and exclusion criteria 1, 8, 10 as per clinical study protocol D4193C00003, version 4.
- Baseline RECIST scan > 40 days before first dose of MEDI4736 (Deviation 3). Note that although the screening period for baseline RECIST assessment was 28

days, an additional 12 day window should be applied thus only baseline RECIST assessments of greater than 40 days will be deemed as constituting an important deviation.

- No baseline RECIST 1.1 assessment on or before date of first dose (Deviation 4).
- Received prohibited systemic anti-cancer agents (Deviation 5). Please refer to the CSP section 7.7 for the systemic anti-cancer agents that are detailed as being 'excluded' from permitted use during the study. This will be used as a guiding principle for the physician review prior to database lock.

CRA will be responsible for entering all deviations in CTMS during the course of the study. Any deviations identified by other project team members must be communicated to the CRA for entry after confirming that deviation has not previously been recorded.

CRA will source data verification (SDV) protocol deviations at monitoring visits and update CTMS if discrepancies identified between CTMS and source notes. The Medical Monitoring Representative reviews protocol deviation data and applies categorization codes, indicating any 'important' deviations.

On a monthly basis after MMA/MD review and coding the CTM communications protocol deviations to the project team for further discussion and escalation and to identify trends.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Derivation of RECIST Visit Responses

For all patients, the RECIST version 1.1 (see further Appendix F of the CSP) tumor response data will be used to determine each patient's visit response. It will also be used to determine if and when a patient has progressed and also their best objective response. RECIST 1.1 assessments will be performed using CT/MRI assessments of the neck (from base of skull) though the chest and abdomen (including liver). Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up.

The baseline assessment should be performed no more than 28 days before start of study treatment, and ideally as close as possible to the start of study treatment (Table 2 of CSP). Efficacy for all patients will be assessed by objective tumor assessments every 8 weeks for the first 48 weeks (relative to the date of the first MEDI4736 or tremelimumab infusion), and then every 12 weeks after discontinuation of assigned IP in patients who have disease control after 12 months of treatment (Table 3 of CSP) until confirmed objective disease progression as defined by RECIST 1.1 (irrespective of the reason for stopping treatment or subsequent therapy).

If an unscheduled assessment was performed and the patient had not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This

schedule is to be followed in order to minimize any unintentional bias caused by some patients being assessed at a different frequency than other patients.

Patients who have discontinued treatment due to toxicity or symptomatic deterioration, or who have commenced subsequent anticancer therapy, will be followed up until confirmed disease progression or death (whichever occurs first). Patients who discontinue treatment in 1 treatment group may not switch to treatment in a different group.

Disease progression requires confirmation, the confirmatory scan should occur preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Treatment with IP will continue between the initial assessment of progression and confirmation for progression. Additional assessments will be performed post confirmed objective disease progression for patients remaining on study treatment, re-treatment or until subsequent cancer therapy according to the clinical study protocol. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

For all patients who are treated through progression, including patients who achieve disease control (i.e., CR, PR, or SD) and restart study treatment upon evidence of PD (according to RECIST 1.1), with or without confirmation, during follow-up, the Investigator should ensure patients do not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient. The Investigator should also ensure that the patient still meets all of the inclusion criteria and none of the exclusion criteria for this study, including re-consenting to continue or restart treatment. Patients with rapid tumor progression or with symptomatic progression that requires urgent medical intervention (e.g., central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) will not be eligible to continue to receive study drug.

Progression would be considered confirmed if the following criteria are met:

- ≥20% increase in the sum of diameters of target lesions (TL) compared with the nadir at 2 consecutive visits with an absolute increase of 5 mm(1)
- And/or significant progression (worsening) of non-target lesions (NTL) or new lesions at the confirmatory PD timepoint compared with the first timepoint where progression of non-target lesions or new lesions identified
- And/or additional new unequivocal lesions at the confirmatory PD timepoint compared with the first timepoint new lesions were identified.

(1) The assessment of progression requires a ≥20% increase in the sum diameters of target lesions at the first progression timepoint relative to the nadir. The nadir is the smallest sum of diameters, and this may be at baseline or subsequent follow-up assessments. The confirmatory scan confirms the persistence of the ≥20% increase relative to the nadir. The minimum absolute increase in the sum of diameters of target lesions is at least 5 mm at both assessments.

At each visit for the site investigator data, an overall visit response will be determined programmatically - using the information from TLs, NTLs and new lesions. Conversely, overall visit responses will be provided by the BICR (i.e., the reviewers will provide the overall visit response according to RECIST 1.1 and no programmatic derivation of visit response is necessary).

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

3.1.1 Blinded Independent Central Review (BICR) Assessment Using RECIST 1.1

The BICR of all radiological imaging data will be carried out using RECIST 1.1. All radiological scans for all patients (including those at unscheduled visits or outside visit windows) will be provided to the BICR. Details of prior radiotherapy will also be provided to the BICR to allow the selection of appropriate target lesions. The imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1 and will be adjudicated, if required. For each patient, the BICR will define the visit response data (CR, PR, SD, PD, or not evaluable [NE]) and the relevant scan dates for each timepoint (i.e., for visits where response or progression is/is not identified). If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of NE (unless there is evidence of progression, in which case the response will be assigned as PD). Endpoints of ORR, DoR, DCR, and PFS will be derived from the visit response data.

A BICR of all radiological imaging data will be carried out using RECIST 1.1 modified for confirmation of progression and the overall visit response will be provided. RECIST 1.1 will be regarded as primary in terms of the efficacy analyses and RECIST 1.1 modified for confirmation of progression is supportive. Additionally, the BICR will also be performed using Immune-related response criteria (irRECIST 1.1) (Nishino et al. 2013) for exploratory purpose.

Further details of the BICR will be documented in the BICR Charter.

3.1.2 Site Investigator Assessment Using RECIST 1.1

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

At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, or PD depending on the status of their disease compared with baseline and previous assessments. Baseline will be assessed within the 28 days prior to enrollment. If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of NE (unless there is evidence of progression in which case the response will be assigned as PD).

3.1.2.1 Site Investigator Assessment Using RECIST 1.1: Target lesions (TLs)

Measurable disease is defined as having at least one measurable lesion, not previously irradiated, which is ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with CT or MRI and which is suitable for accurate repeated measurements.

A patient can have a maximum of 5 measurable lesions recorded at baseline with a maximum of 2 lesions per organ (representative of all lesions involved suitable for accurate repeated measurement) and these are referred to as target lesions (TLs). If more than one baseline scan is recorded then measurements from the one that is closest to the date of first dose will be used to define the baseline sum of TLs. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits.

Measurable disease (i.e. at least one TL) is one of the entry criteria for the study. However, if a patient with non-measurable disease is enrolled in the study, the evaluation of overall visit responses will be based on the overall NTL assessment and the absence/presence of new lesions (see Section 3.1.2.2 for further details). If a patient does not have measurable disease at baseline then the TL visit response will be not applicable (NA).

Table 6 TL Visit Responses

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

Rounding of TL data

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

Missing TL data

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

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

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

Lymph nodes

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

TL visit responses subsequent to CR

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

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

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

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

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

TL too large to measure

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

TL too small to measure

If a TL becomes too small to measure a value of 5 mm will be entered into the database and used in TL calculations, unless the radiologist has indicated and entered a smaller value that

can be reliably measured. If a TL response of PD results then this will be reviewed by the study team.

Lesion intervention

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

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

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

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

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

Scaling (applicable only for lesion intervention)

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

If ≤ 1/3 of the target lesion measurements are treated as missing (because of intervention) then the results will be scaled up (based on the sizes at the nadir visit to give an estimated sum of diameters and this will be used in calculations; this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the nadir sum of diameters excluding the lesions with missing measurements).

Example of scaling

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

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

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

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

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

Lesions that split in two or more parts

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

Lesions that merge

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

Change in method of assessment of TLs

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

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

3.1.2.2 Non-target lesions (NTLs) and New lesions.

At each visit an overall assessment of the NTL response should be recorded by the investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

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

Table 7 NTL Visit Responses

Visit Responses	Description
Complete Response (CR)	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10 mm short axis).
Progressive Disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Non CR/Non PD	Persistence of one or more NTLs-with no evidence of progression.
Not Evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
Not Applicable (NA)	Only relevant if there are no NTLs at baseline

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

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor.

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.

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

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

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

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

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

3.1.2.3 Site Investigator Assessment Using RECIST 1.1: Overall visit response

Table 8 defines how the previously defined TL and NTL visit responses will be combined with new lesion information to give an overall visit response.

Table 8 Overall Visit Responses

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

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

3.1.3 Independent Central Review Assessment Using RECIST 1.1 Modified for Confirmation of Progression and irRECIST 1.1

The BICR of all scans used in the assessment of tumors will be assessed using RECIST 1.1 modified for confirmation of progression as detailed in Sections 3.1 and 3.1.1. This means that the visit response of PD must be confirmed by another visit response of PD at the next scheduled visit and no earlier than 4 weeks after the initial assessment of PD in the absence of clinical deterioration and if clinically feasible. Confirmation of progression needs to be programmatically derived based on the rules given in the BICR charter.

Additionally for exploratory analysis, the visit responses according to irRECIST 1.1 will also be provided. The definitions of irCR, irPR, irSD, irPD, and irNED (i.e. responses according to irRECIST 1.1), as outlined by Nishino et al 2013, will be outlined clearly in the BICR charter, but a brief description of the methodology is here given. In this project irRECIST 1.1 using a RECIST base will be implemented where the target lesions will be measured unidimensionally.

In irRECIST 1.1 the presence of new lesions will not automatically trigger a declaration of Progressive Disease, but instead the new lesions will be measured and these measurements will be added to the sum of diameters of the target lesions. Based on the sum of these measurements and % calculations thereof, the target lesion response assessment will be derived. The overall response assessment (irCR, irPR, irSD, irPD, irNE or irND) will be obtained at the BICR and confirmation of irPD is required. The imaging scans will be reviewed by 2 independent radiologists and will be adjudicated, if required.

Some endpoints in Section 3.2 below will also be derived using these assessment methods for supportive purposes.

3.2 Outcome Variables

All RECIST assessments, whether scheduled or unscheduled, will be included in the calculations. This is also regardless of whether a patient discontinues investigational product or receives another anti-cancer therapy.

RECIST outcomes will be derived using the overall visit responses and relevant dates from the BICR. This will be repeated using the programmatically derived overall visit response from investigator RECIST assessments.

3.2.1 Primary endpoint (objective response rate)

The primary endpoint is ORR. ORR (per RECIST 1.1 as assessed by the BICR) is defined as the number (%) of patients with a confirmed overall response of CR or PR and will be based on all treated patients who have measurable disease at baseline per BICR (evaluable analysis set).

A confirmed response of CR/PR means that a response of CR/PR is recorded at one visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. Therefore, data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Any patient who discontinues treatment without progression, receives a subsequent therapy, and then responds will not be included as responders in the ORR.

Patients who continue IP through progression and respond during the re-challenge period (up to a maximum of an additional 12 months) would not be included as responders in ORR assessment.

Additionally, ORR will also be assessed using irRECIST 1.1 data obtained from BICR for exploratory purposes. Responses of CR/PR need confirmation under this approach.

For sensitivity analysis, ORR will be assessed using tumor data recorded by the Investigator according to RECIST 1.1, and the denominator will be all randomized patients. ORR (per RECIST 1.1 as assessed by the BICR) will also be analyzed using FAS population (all randomized patients).

3.2.2 Duration of response

DoR (per RECIST 1.1 as assessed by the BICR) will be defined as the time from the date of first documented response until the first date of documented progression or death in the absence of disease progression (i.e., date of PFS event or censoring – date of first response + 1). The end of response should coincide with the date of progression or death from any cause used for the RECIST 1.1 PFS endpoint. The denominator for DoR will be defined as described for ORR (see Section 3.2.1).

The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of CR or PR. If a patient does not progress following a response, then their DoR will be censored at the PFS censoring time. DoR will not be defined for those patients who do not have documented response.

For sensitivity analysis, DoR will be assessed using tumor data recorded by the Investigator according to RECIST 1.1.

3.2.3 Disease control rate

DCR at 4, 6 or 12 months is defined as the percentage of patients who have a best objective response (BoR) of CR or PR in the first 4, 6 or 12 months, respectively, or who have demonstrated SD for a minimum interval of 16, 24 or 48 weeks, respectively (-7 days, i.e., 105, 161 or 329 days, respectively), following randomization.

As additional analysis, DCR at 6 months will also be assessed as percentage of patients who have a best objective response (BoR) of CR or PR in the first 6 months or who have demonstrated SD for a minimum interval of 16 weeks (-7 days, i.e., 105 days) following randomization.

DCR will be determined programmatically based on RECIST 1.1 using BICR data using all data up until the first progression event. For sensitivity analysis, DCR will be determined programmatically based on RECIST 1.1 using site Investigator tumor data using all data up until first progression event.

3.2.4 Time to response

Time to response (per RECIST 1.1 as assessed by the BICR) is defined as the time from the date of first dose until the date of first documented response (which is subsequently confirmed). The date of first documented response should coincide with that used for the RECIST 1.1 DoR endpoint.

Time to response will not be defined for those patients who do not have documented confirmed response. Time to response will also be derived for the RECIST 1.1 site investigator data.

3.2.5 Change in tumor size

For supportive purposes percentage change from baseline in tumor size will be derived at each scheduled tumor assessment visit (i.e., week 8, week 16, etc. hereafter referred to as week X for convenience). Best percentage change from baseline in tumor size will also be derived as the biggest decrease or, if no decrease, as the smallest increase in tumor size from baseline.

This is based on RECIST target lesion measurements taken at baseline and at the timepoint of interest. Tumor size is defined as the sum of the longest diameters of the target lesions for the BICR data based upon RECIST assessments. Target lesions are measurable tumor lesions. Baseline for RECIST is defined to be the last evaluable assessment prior to starting treatment. The change in target lesion tumor size at week X will be obtained for each patient by taking the difference between the sum of the target lesions at week X and the sum of the target lesions at baseline. To obtain the percentage change in target lesion tumor size at week X the change in target lesion tumor size is divided by the sum of the target lesions at baseline and multiplied by 100 (i.e. (week X - baseline) / baseline * 100). More details on target lesions and measurements can be found in Section 3.1.

Apply a window around the week X visit: Whenever tumor size data for the week X visit (Note: or visit at which progression was documented if before week X) is available then this should be used in the analysis. A windowing rule will be applied and will follow the protocol allowed visit window; therefore any RECIST scan performed within ± 1 week of the protocol scheduled visit will be used for that visit.

The above derivations will be programmed for the BICR data based upon RECIST 1.1 assessments.

Measurements from the reviewer selected by the adjudicator will be used when adjudication for overall visit response has occurred, but in the case where no adjudication was required the measurements from the reviewer who reviewed the baseline scan first will be used for this analysis.

3.2.6 Progression free survival

PFS (per RECIST 1.1 as assessed by the BICR) will be defined as the time from the date of randomization 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 anti-cancer therapy prior to progression (i.e., date of event or censoring – date of randomization + 1). Patients who have not progressed or died at the time of analysis will be

censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the two missed visits. If the patient has no evaluable visits or does not have baseline data they will be censored at Day 1 unless they die within 2 visits of baseline, then they will be treated as an event with date of death as the event date.

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

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

- Date of progression will be determined based on the earliest of the dates of the component that triggered the progression on the first set of scans that indicates progression for the adjudicated reviewer selecting PD or of either reviewer where both select PD as a time point response and there is no adjudication for central review (ICR) data.

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

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

For sensitivity analysis, PFS will be assessed using tumor data recorded by the Investigator according to RECIST 1.1 (Ascertainment bias).

Also for sensitivity analysis, PFS will be assessed using the RECIST 1.1 ICR tumor data following a modification where any objective progression must be confirmed by the next scheduled scan. The confirmatory scan must be no sooner than 4 weeks after the initial suspected progression. If disease progression is confirmed (or disease progression occurs and no further scans are recorded) then the date of progression will be when it was originally observed. Patients with a single disease progression and no further tumor assessment scans will be treated as PD in the analysis.

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

3.2.7 Overall survival

OS is defined as the time from the date of randomization until death due to any cause (i.e., date of death or censoring – date of randomization + 1). Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive (SUR_DAT, recorded within the SURVIVE module of the eCRF).

Note: Survival calls will be made in the week following the date of data cut-off for the analysis, and if patients are confirmed to be alive or if the death date is post the data cut-off date, these patients will be censored at the date of data cut-off. Death dates may be found by checking publicly available death registries (as applicable under local laws).

3.2.8 Best objective response

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

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

CR or PR must be confirmed (see Section 3.2.1). For determination of a best response of SD, the earliest of the dates contributing towards a particular overall visit assessment will be used. SD should be recorded at least 49 days (to allow for the assessment window), after date of first dose. For CR/PR, the initial overall visit assessment which showed a response will use the latest of the dates contributing towards a particular overall visit assessment.

BoR will be determined programmatically based on RECIST 1.1 using BICR data using all data up until the first progression event.

For sensitivity analysis, it will be determined programmatically based on RECIST 1.1 using site Investigator data using all data up until the first progression event.

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

For patients who die with no evaluable RECIST assessments, if the death occurs ≤17 weeks (i.e., 16 weeks ±7 days) after randomization, then BoR will be assigned to the progression (PD) category. For patients who die with no evaluable RECIST assessments, if the death occurs >17 weeks (i.e., 16 weeks ±7 days) after the date of randomization then BoR will be assigned to the NE category.

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

3.3 Safety

Safety and tolerability will be assessed in terms of adverse events (AEs) (including serious adverse events [SAEs]), deaths, laboratory data, vital signs, electrocardiograms (ECGs) and exposure. These will be collected for all patients. Data from all cycles of treatment will be combined in the presentation of safety data. ‘On treatment’ will be defined as assessments between date of start dose and 90 days following discontinuation of IP (i.e., the last dose of

MEDI4736 in combination with tremelimumab or only MEDI4736). For AEs, on treatment (or treatment emergent AEs) will be defined as any AEs that started after dosing or prior to dosing and which worsens following exposure to the treatment (see section 4.2.8.1 Adverse events for a more detailed definition).

The safety analysis set will be used for reporting of safety data.

3.3.1 Adverse events (AEs)

AEs and SAEs will be collected throughout the study. Any AE occurring before treatment with IP will be included in the data listings but will not be included in the summary tables of AEs. Any AE occurring within 90 days of discontinuation of IP (i.e., the last dose of MEDI4736 in combination with tremelimumab or only tremelimumab or only MEDI4736) may be included in the AE summaries, but the majority of those summaries will omit those AEs observed after a patient has received further therapy for cancer. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of IP) will be flagged in the data listings.

A separate data listing of AEs occurring more than 90 days after discontinuation of MEDI4736 in combination with tremelimumab, only tremelimumab or only MEDI4736 will be produced. These events will not be included in AE summaries.

The Medical Dictionary for Regulatory Activities (MedDRA) dictionary (using the latest or current MedDRA version) will be used to code the AEs. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for AEs (CTCAE Version 4.03 or higher).

AEs of special interest

Adverse events of special interest (AESIs) are events of scientific and medical interest specific to the further understanding of the MEDI4736 and tremelimumab safety profile and require close monitoring and rapid communication by the Investigator to the Sponsor. MEDI4736 and tremelimumab AESIs may be serious or non-serious. The rapid reporting of these AESIs allows ongoing analysis of these events in order to characterize and understand them in association with the use of these IPs.

Currently, these AESI's have been identified in the CSP as:

- Colitis
- Pneumonitis
- ALT/AST increases/hepatitis/hepatotoxicity
- Neuropathy/neuromuscular toxicity (ie, events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)

- Endocrinopathy (ie, events of hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism)
- Dermatitis
- Nephritis
- Pancreatitis (or labs suggestive of pancreatitis, including increased serum lipase or increased serum amylase)

An AstraZeneca medically qualified expert, after consultation with the Global Patient Safety Physician, has reviewed the AEs of interest and identified which preferred terms contribute to each AESI. A further review will take place prior to database lock to ensure new terms not already included in the older MedDRA version are captured within the categories for the new higher MedDRA version. The list will be provided by AZ prior to database lock.

3.3.2 Treatment exposure

Total (or intended) exposure of MEDI4736 (monotherapy)

- Total (or intended) exposure is defined as the total treatment period from first dose date of study drug to the earliest of "last dose date of study drug + 13 days" or death date or DCO.

Total (or intended) exposure of tremelimumab (monotherapy)

- Total (or intended) exposure is defined as the total treatment period from first dose date of study drug to the earliest of "last dose date of study drug + (13 days or 83 days)" or death date or DCO. Thirteen days will be added in the above formulae if the subject stopped dosing before week 24 and 83 days will be added if the subject stopped dosing at week 24 or later.

Total (or intended) exposure of MEDI4736 (combination)

- Total (or intended) exposure is defined as the total treatment period from first dose date of study drug to the earliest of "last dose date of study drug + (13 days or 27 days)" or death date or DCO or start of re-treatment (applies to initial treatment period only). Twenty-seven days will be added in the above formulae if the subject stopped dosing before week 16 and 13 days will be added if the subject stopped dosing at week 16 or later.

Total (or intended) exposure of tremelimumab (combination)

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

Actual exposure of MEDI4736/tremelimumab

- Actual exposure is defined as above, but excluding total duration of dose delays

The total (or intended) exposure for each SOC treatment will be calculated using the same principle as above, according to the dose schedule required for each SOC. The total (or intended) exposure will also be summarized by combining the SOC treatments together. Actual exposure will not be calculated for SOC.

Dose reductions are not permitted per the CSP for the immunotherapy agents (MEDI4736, tremelimumab or MEDI4736+tremelimumab). The actual exposure calculation makes no adjustment for any dose reductions that may have occurred.

Exposure will also be measured by the number of cycles received. For SOC, the number of days in a cycle will be study specific, but generally a cycle corresponds to a period of 28 days. If a cycle is prolonged due to toxicity, this should still be counted as one cycle. A cycle will be counted if treatment is started even if the full dose is not delivered. Each immunotherapy agent will be measured in terms of number of doses given.

Patients who permanently discontinue during a dose interruption

If a decision is made to permanently discontinue study treatment in-between cycles or during a cycle delay then the date of last administration of study medication recorded will be used in the programming.

Calculation of duration of dose delays (for actual exposure):

- MEDI4736 (monotherapy)

  Since patients in the MEDI4736 monotherapy treatment group will receive 10 mg/kg MEDI4736 via IV infusion q2w for up to 12 months (up to 26 doses), the duration of dose delays will be calculated as:

  Total duration of dose delays= Sum of (Date of the dose - Date of previous dose – 14 days)

  Thus, if no delays were encountered, the duration would sum up to 0, since infusions were done every two weeks.

- MEDI4736 (given in combination)

  Since Patients in the MEDI4736 + Treme treatment group will receive 20 mg/kg MEDI4736 via IV infusion q4w for 4 months and tremelimumab 1 mg/kg q4w for 4 doses followed by MEDI4736 monotherapy at a dose of 10 mg/kg q2w initiated 4 weeks after the last combination dose is administered for up to 18 additional doses, the duration of dose delays will be calculated as follow:

For Cycle 1 to Cycle 4 (for Week 0 to Week 12) doses:
Duration1 = Sum of (Date of the dose - Date of previous dose – 28 days)

For Cycle 5 to Cycle 13 (for Week 16 to Week 50) doses:
Duration2 = Sum of (Date of the dose - Date of previous dose – 14 days)

Total duration of dose delays = Duration1 + Duration2

- Tremelimumab (monotherapy)

  Since Patients in the Treme treatment group will receive 10 mg/kg tremelimumab via IV infusion q4w for 7 doses then q12w for 2 additional doses for up to 12 months (up to 9 doses in total), the duration of dose delays will be calculated as follow:

  For Cycle 1 to Cycle 7 (for Week 0 to Week 24) doses:
  Duration1 = Sum of (Date of the dose - Date of previous dose – 28 days)

  For Cycle 8 to Cycle 9 (for Week 36 to Week 48) doses:
  Duration2 = Sum of (Date of the dose - Date of previous dose – 84 days)

  Total duration of dose delays = Duration1 + Duration2

- Tremelimumab (given in combination):

  Since Patients in the MEDI4736 + Treme treatment group will receive tremelimumab 1 mg/kg q4w for 4 doses only, the duration of dose delays will be calculated as follows:

  For Cycle 1 to Cycle 4 (for Week 0 to Week 12) doses:
  Total duration of dose delays = Sum of (Date of the dose - Date of previous dose – 28 days

3.3.3 Dose intensity

Dose intensity will be derived for the initial treatment period. Relative dose intensity (RDI) is the percentage of the actual dose delivered relative to the intended dose intensity through to treatment discontinuation.

Relative dose intensity (RDI) will be defined as follows for MEDI4736, tremelimumab and the combination:

- RDI = 100% * d/D, where d is the actual cumulative dose delivered up to the actual last day of dosing and D is the intended cumulative dose up to the actual last day of dosing. D is the total dose that would be delivered, if there were no modification to dose or schedule.

When deriving actual dose administered the volume before and after infusion will also be considered.

3.3.4 Laboratory data

Laboratory data will be collected throughout the study, from screening to the follow-up visits as described in Table 2, 3 and 4 of the CSP. Blood and urine samples for determination of hematology, clinical chemistry, and urinalysis will be collected as described in Section 5.2.1 of the CSP. For derivation of baseline and post baseline visit values considering visit window and how to handle multiple records, derivation rules as described in Section 3.3.6 below will be used.

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

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

Corrected calcium (mmol/L) = Total calcium (mmol/L) + ([40 – Albumin (G/L)] x 0.02)

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

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

Local reference ranges will be used for the primary interpretation of laboratory data. The denominator used in laboratory summaries of CTCAE grades will only include evaluable patients, in other words those who had sufficient data to have the possibility of an abnormality.

For example:

- If a CTCAE criterion involves a change from baseline, evaluable patients would have both a pre-dose and at least 1 post-dose value recorded.
- If a CTCAE criterion does not consider changes from baseline, to be evaluable the patient needs only to have 1 post dose-value recorded.

3.3.5 ECGs

ECG data obtained up until the 30 days from date of last dose of study treatment will be used for reporting. For derivation of post baseline visit values considering visit window and to

handle multiple records present in any visit window, derivation rules as described in Section 3.3.6 below will be used.

At each time point the Investigator's assessment of the ECG will be collected locally. Heart rate, duration of QRS complex, RR, pulse rate and QT intervals will be collected centrally via a digital read. QTcF (Fridericia) and QTcB (Bazzetts) will also be collected by the central vendor.

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

3.3.6 Vital signs

Vital signs data obtained up until the 30 days from date of last dose of study treatment will be used for reporting. Change from baseline in vital signs variables will be calculated for each post-dose visit on treatment. For derivation of post baseline visit values considering visit window and to handle multiple records, derivation rules as described in Section 3.3.6 below will be used.

For the change from baseline summaries for vital signs, the baseline value will be the latest result obtained prior to the start of study treatment.

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

3.3.7 General considerations for safety assessments

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

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

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

- The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls half way between the two visits (the lower limit of the first post-baseline visit will be Day 1). If an even number of days exists between two consecutive visits then the upper limit will be taken as the midpoint value minus 1 day. Note that in protocol Table 5, Day 0 is mentioned as the first day after screening (Day -28 to -1). Day 0 should be considered the same as reporting Day 1. The Statistical windows only referred to reporting Day 1 to avoid confusion.

For example, the visit windows for vital signs data for MEDI4736 monotherapy treatment arm are shown in the example below.

Visit	**Week**	**Day**	**Statistical Window**
Screening	NA	-28 to -1	D-28 – D-1
Baseline	NA	D0[1]	Low – D1[1]
V0	W0	D0	D1[2] – D7
V1	W2	D14	D8 – D21
V2	W4	D28	D22 – D35
V3	W6	D42	D36 – D49
V4	W8	D56	D50 – D63
V4a	W10	D 70	D64 – D77
V5	W12	D84	D78 – D91
V5a	W14	D 98	D92 – D105
V6	W16	D112	D106 – D119
V6a	W18	D 126	D120 – D133
V7	W20	D140	D134 – D147
V7a	W22	D 154	D148 – D161
V8	W24	D168	D162 – D175
V8a	W26	D182	D176 – D189
V9	W28	D196	D190 – D203
V9a	W30	D210	D204 – D217
V10	W32	D224	D218 – D231

Visit	Week	Day	Statistical Window
V10a	W34	D238	D232 – D245
V11	W36	D252	D246 – D259
V11a	W38	D266	D260 – D273
V12	W40	D280	D274 – D287
V12a	W42	D294	D288 – D301
V13	W44	D308	D2302 – D315
V13a	W46	D322	D316 – D329
V14	W48	D336	D330 – D343
V15	W50	D350	D344 – High[3]

[1]Latest pre-dose value available
[2]post-dose values only
[3] Note that visits up to 13 days after the last dosing date will be considered as being on treatment for the purposes of visit windowing and may be assigned to an on-treatment visit. Visits after this will be considered as follow-up and may be assigned accordingly

- For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used (regardless of where it falls in an interval).
- Listings should display all values contributing to a time point for a patient.
- For visit based summaries:
  - If there is more than one value per patient within a time window then the closest value to the scheduled visit date should be summarized, or the earlier in the event the values are equidistant from the nominal visit date. The listings should highlight the value for that patient that went into the summary table, wherever feasible. Note: in summaries of extreme values all post baseline values collected are used including those collected at unscheduled visits regardless of whether or not the value is closest to the scheduled visit date.
  - To prevent very large tables or plots being produced that contain many cells with meaningless data, for each treatment group visit data should only be summarized if the number of observations is greater than the minimum of 20 and > 1/3 of patients dosed.

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

- Baseline will be defined as the last non-missing measurement prior to dosing with study treatment. For the re-treatment period then baseline is similarly defined as the last non-missing measurement prior to the first dose on the re-treatment period. For laboratory data, any assessments made on day 1 will be considered pre-dose. Alternatively, if two visits are equally eligible to assess patient status at baseline (e.g., screening and baseline assessments both on the same date prior to first dose with no washout or other intervention in the screening period), the average can be taken as a baseline value. For non-numeric laboratory tests (i.e., some of the urinalysis parameters) where taking an average is not possible then the best value would be taken as baseline as this is the most conservative. In the scenario where there are two assessments on day 1, one with time recorded and the other without time recorded, the one with time recorded would be selected as baseline. Where safety data are summarized over time, study day will be calculated in relation to date of first study treatment

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

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

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

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

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

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

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

3.4 Patient reported outcome

PRO questionnaires will be assessed using the EORTC QLQ-C30 and EORTC QLQ-H&N35. All items/questionnaires will be scored according to published scoring guidelines. All PRO analyses will be based on the full analysis set (FAS).

3.4.1 EORTC QLQ-C30

The EORTC QLQ-C30 consists of 30 questions that can be combined to produce 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), and a global measure of health status. The EORTC QLQ-C30 will be scored according to the EORTC QLQ-C30 scoring manual (Fayers et al 1999). An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales, each of the functional scales, and the global health status scale in the EORTC QLQ-C30 according to the EORTC QLQ-C30 Scoring Manual. Higher scores on the global health status and functioning scales indicate better health status/function, but higher scores on symptom scales represent greater symptom severity.

The change from baseline in health-related QoL will be assessed using the EORTC QLQ-C30 global QoL scale, which includes 2 items from the EORTC QLQ-C30: "How would you rate your overall health during the past week? (Item 29) and "How would you rate your overall QoL during the past week? (Item 30)."

Definition of clinically meaningful changes

Changes in score compared with baseline will be evaluated. A minimum clinically meaningful change is defined as an absolute change in the score from baseline of ≥10 for scales from the EORTC QLQ-C30 (Osoba et al 1998). For example, a clinically meaningful improvement in physical function (as assessed by EORTC QLQ-C30) is defined as an increase in the score from baseline of ≥10, whereas a clinically meaningful deterioration is defined as a decrease in the score from baseline of ≥10. At each post-baseline assessment, the change in symptoms/functioning from baseline will be categorized as improvement, no change or deterioration as shown in Table 9.

Table 9 Mean change and visit response in health related quality of life

Score	Change from baseline	Visit response
EORTC QLQ-C30 Global quality of life score	≥+10	Improvement
	≤-10	Deterioration
	Otherwise	No change
EORTC QLQ-C30 symptom scales/items	≥+10	Deterioration
	≤-10	Improvement
	Otherwise	No change
EORTC QLQ-C30 functional scales	≥+10	Improvement
	≤-10	Deterioration
	Otherwise	No change

EORTC European Organisation for Research and Treatment of Cancer; QLQ-C30 30-item core quality of life questionnaire.

For each subscale, if <50% of the subscale items are missing, then the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscales (Fayers et al 1999). If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded. If there is evidence that the missing data are systematic, missing values will be handled to ensure that any possible bias is minimized.

Time to symptom deterioration

For each of the symptoms scales in the EORTC QLQ-C30, time to symptom deterioration will be defined as the time from randomization until the date of the first clinically meaningful symptom deterioration (an increase in the score from baseline of ≥10) or death (by any cause) in the absence of a clinically meaningful symptom deterioration, regardless of whether the patient withdraws from study treatment or receives another anticancer therapy prior to symptom deterioration. Death will be included as an event only if the death occurs within two visits of the last PRO assessment where the symptom change could be evaluated.

Patients whose symptoms (as measured by EORTC QLQ-C30) have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the symptom could be evaluated. Also, if symptoms deteriorate after two or more missed PRO assessment visits or the patient dies after two or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where the symptom could be evaluated (prior to the two missed assessment visits). If a patient has no evaluable visits or does not have baseline data they will be censored at 0 days. The population for the analysis of time to symptom deterioration will include a subset of the FAS who have baseline scores of ≤90.

Time to HRQoL/Function deterioration

For HRQoL, time to deterioration will be defined as the time from the date of randomization until the date of the first clinically meaningful deterioration (a decrease in the function scales or the global health status/QoL from baseline of ≥10) or death (by any cause) in the absence of a clinically meaningful deterioration, regardless of whether the patient withdraws from study treatment or receives another anticancer therapy prior to HRQoL/function deterioration. Death will be included as an event only if the death occurs within two visits of the last PRO assessment where the HRQoL/function change could be evaluated.

Patients whose HRQoL (as measured by EORTC QLQ-C30) have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the HRQoL/function could be evaluated. Also, if HRQoL deteriorates after two or more missed PRO assessment visits or the patient dies after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where HRQoL/function could be evaluated. If a patient has no evaluable visits or does not have baseline data they will be censored at 0 days. The population for the analysis of time to HRQoL/function deterioration will include a subset of the FAS who have baseline scores of ≥10.

Symptom improvement rate

The symptom improvement rate will be defined as the number (%) of patients with 2 consecutive assessments at least 14 days apart that show a clinically meaningful improvement (a decrease from baseline score ≥10 for EORTC QLQ-C30 symptom scales) in that symptom from baseline. The denominator will consist of a subset of the FAS who have a baseline symptom score ≥10.

HRQoL/function improvement rate

The HRQoL/function improvement rate will be defined as the number (%) of patients with 2 consecutive assessments at least 14 days apart that show a clinically meaningful improvement (an increase from baseline score ≥10 for EORTC QLQ-C30 functional scales and global health status/QoL) in that scale from baseline. The denominator will consist of a subset of the FAS who have a baseline QoL/function score ≤90.

3.4.2 EORTC QLQ-H&N35

The H&N35 is a head and neck cancer-specific module from the EORTC for head and neck cancer comprising 35 questions to assess head and neck cancer symptoms. The head and neck cancer module includes 11 single items and 7 multi-item scales that assess pain, swallowing, senses (taste and smell), speech, social eating, social contact, and sexuality. For all items and scales, high scores indicate increased symptomatology/more problems.

The scoring approach for the H&N35 is identical in principle to that for the symptom scales/single items of the EORTC QLQ-C30. As the wording is reversed on the H&N35, higher scores represent greater symptom severity.

Definition of clinically meaningful changes

Changes in score compared with baseline will be evaluated. The developers of the H&N35 have suggested that a minimum clinically meaningful change is a change in the score from baseline of ≥10 for scales/items from the H&N35 module (Bjordal et al 2000). For example, a clinically meaningful deterioration or worsening in dry mouth (as assessed by H&N35) is defined as an increase in the score from baseline of ≥10. At each post-baseline assessment, the change in symptoms/functioning from baseline will be categorized as improved, no change, or deterioration, as shown in Table 10. Since there is no well-established minimal clinically important difference for the H&N35 module, an exploratory analysis will be conducted to determine the most appropriate threshold in this patient population.

Table 10 Change from BL and Visit response for EORTC QLQ H&N35

Score	Change from baseline	Visit response
H&N35 symptom scales and items	≥+10	Deterioration
	≤-10	Improved
	Otherwise	No change

HRQoL Health-related quality of life; H&N35 35-item head and neck quality of life questionnaire.

Time to symptom deterioration

For each of the symptom scales/items in the H&N35, time to symptom deterioration will be defined as the time from the date of the first dose until the date of the first clinically meaningful symptom deterioration (an increase in the score from baseline of ≥10) or death (by any cause) in the absence of a clinically meaningful symptom deterioration, regardless of whether the patient withdraws from study treatment or receives another anticancer therapy prior to symptom deterioration. Death will be included as an event only if the death occurs within 2 visits of the last PRO assessment where the symptom change could be evaluated.

Patients whose symptoms (as measured by the H&N35) have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the symptom could be evaluated. Also, if symptoms progress after 2 or more missed PRO assessment visits or the patient dies after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where the symptom could be evaluated. If a patient has no evaluable visits or does not have baseline data, they will be censored at 0 days. The population for analysis of time to symptom deterioration will include a subset of the FAS population who has baseline scores ≤90.

Symptom improvement rate

The symptom improvement rate will be defined as the number (%) of patients with 2 consecutive assessments at least 14 days apart that show a clinically meaningful improvement (a decrease from baseline score ≥10 for H&N35 scales/items) in that symptom from baseline.

3.5 Pharmacokinetics and Immunogenicity Variables

Analyses to evaluate the pharmacokinetics of MEDI4736 monotherapy, tremelimumab monotherapy, and MEDI4736 + tremelimumab combination therapy and to investigate the immunogenicity of MEDI4736 and tremelimumab will be performed by AstraZeneca/ MedImmune Clinical Pharmacology group or designee.

3.5.1 Population of pharmacokinetics and exposure-response/safety analysis

A population PK model will be developed using a non-linear mixed-effects modeling approach. The impact of physiologically-relevant patient characteristics (covariates) and disease on PK will be evaluated. The relationship between PK exposure and the effect on safety and efficacy end points will be evaluated. The results of such an analysis will be reported in a separate report.

3.5.2 Pharmacokinetic analysis

The actual sampling times will be used in the PK calculations. MEDI4736 and tremelimumab concentration data and summary statistics will be tabulated. Individual and mean blood MEDI4736 and tremelimumab concentration-time profiles will be generated. The following PK parameters will be determined after the first and steady-state doses: peak and trough concentration (as data allow).

3.5.3 Immunogenicity analysis

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable anti-MEDI4736 and/or anti-tremelimumab antibodies. The immunogenicity titre will be reported for samples confirmed positive for the presence of anti-MEDI4736 antibodies and/or anti-tremelimumab antibodies. Summaries will be based upon all patients from the safety population. The effect of immunogenicity on PK, PDx, efficacy and safety will be evaluated, but such analyses, if applicable, will be reported in a separate report.

3.6 Biomarker variables

Negative PD-L1 expression status is defined as follows:

- Negative:- < 25% tumor cell membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control.

Ventana PD-L1 SP263 IHC assay will also be re-scored to re-define PD-L1 negative as follows:

- Negative:- < 1% tumor cell membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control.

- Negative:- < 10% tumor cell membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control.

3.7 Pharmacogenetic variables

In the case of genetic data, only the date the patient gave consent to participation in the genetic research and the date the blood sample was taken from the patient will be recorded in the eCRF and database. The genetic data generated from the study will be stored in the AstraZeneca LIMS database or other appropriate system. This database is a secure database, which is separate from the database used for the main study. Some or all of the dataset from the main study may be duplicated within the AstraZeneca LIMS database for exploratory genetic analysis. Data will be reported outside the CSR (please see Appendix D of the CSP).

4. ANALYSIS METHODS

Generally, all analyses and reporting will be presented by treatment group. Patients with tumoral PD-L1 expression below a pre-specified cut-off level, as determined by an immunohistochemistry assay (referred to hereafter as patients with PD-L1-negative tumors), will be enrolled in the study.

The initial data cut-off will take place approximately 6 months after the last patient is first dosed. All study endpoints will be analyzed at this time. However, if the required number of PFS events is not observed, only descriptive analyses of PFS and OS will be presented at this time. A further analysis of efficacy will take place approximately 12 months after the last patient is dosed when the occurrence of 116 PFS events between the MEDI4736 + tremelimumab therapy group and the MEDI4736 monotherapy group will be observed. The formal analysis of OS will be conducted approximately 18 months after the last patient is dosed when the occurrence of 125 death events between the MEDI4736 + tremelimumab therapy group and the MEDI4736 monotherapy group will be observed.

Formal analysis of PFS will only be done when 116 PFS events are observed (approximately 12 months after the last patient is dosed) and formal analysis of OS will only be done when 125 death events are observed (approximately 18 months after the last patient is dosed) for MEDI4736 + tremelimumab combination therapy versus MEDI4736 monotherapy.

4.1 General principles

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

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

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

- For continuous data the mean and median will be rounded to 1 additional decimal place compared to the original data. The standard deviation will be rounded to 2 additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data.

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

- Results of all statistical analysis will be presented using a 95% confidence interval (CI) and 2-sided p-value, unless otherwise stated.

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

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

Efficacy and PRO data will be summarized and analyzed based on either the evaluable analysis set or FAS. PK data will be summarized and analyzed based on the PK analysis set. Safety data will be summarized on the safety analysis set.

Study population and demography summaries will be summarized by full analysis set. Efficacy from the retreatment phase will be listed only. Any derivations relative to baseline (e.g., day, RECIST derivations) in the 12-month retreatment period will be relative to the baseline scan prior to the 12-month retreatment period.

Safety data will be summarized from the 12-month initial treatment period only at the time of analysis of ORR. Safety data from the retreatment phase will be listed only at this time. This approach will be followed also at the time of the OS analysis unless there are sufficient numbers of retreated patients to warrant summaries in which case the following combinations of summaries would also be produced:

- A small set of headline summaries of safety data from the retreatment phase only.

- Summaries of safety data from the initial phase and the re-treatment phase aggregated.

Table 11 details which endpoints are to be subject to formal statistical analysis, together with pre-planned sensitivity analyses making clear which analysis is regarded as primary for that endpoint.

Table 11 Statistical analyses to be conducted and pre-planned sensitivity analyses

Endpoints Analyzed	Notes
Objective Response Rate	Main study objective (assess efficacy of MEDI4736 + tremelimumab combination) • Primary analysis - 95% CI using exact binomial test, BICR data (RECIST 1.1) (EAS) • Sensitivity analyses using 1) site Investigator tumor data (RECIST 1.1) (FAS) 2) Additionally, ORR will also be evaluated based on assessment according to RECIST 1.1 by BICR using FAS • Exploratory analysis using BICR data (irRECIST 1.1) (EAS) Secondary objective (assess efficacy of MEDI4736 + tremelimumab combination therapy compared with a) MEDI4736 monotherapy and b) tremelimumab monotherapy, in terms of ORR) • Primary analysis – Logistic regression using BICR data (RECIST 1.1) (EAS) • Sensitivity analysis using 1) site Investigator tumor data (RECIST 1.1) (FAS) 2) Additionally, ORR will also be evaluated based on assessment according to RECIST 1.1 by BICR using FAS • Exploratory analysis - Logistic regression using BICR data (irRECIST 1.1) (EAS)
Time to treatment Response	Secondary analysis • Kaplan-Meier plots using BICR data (RECIST 1.1) (EAS) • Sensitivity analysis using 1) site Investigator data (RECIST 1.1) (FAS) 2) RECIST 1.1 by BICR using FAS
Duration of Response	Secondary analysis • Kaplan-Meier plots using BICR data (RECIST 1.1) (EAS) • Sensitivity analysis using 1) site Investigator data (RECIST 1.1) (FAS) 2) RECIST 1.1 by BICR using FAS
Disease Control Rate	Secondary analysis • N (%), using BICR data (RECIST 1.1) (EAS) • Sensitivity analysis using 1) site Investigator data (RECIST 1.1) (FAS) 2) RECIST 1.1 by BICR using FAS

Endpoints Analyzed	Notes
Progression-Free Survival	Secondary objective (assess efficacy of MEDI4736 + tremelimumab combination therapy compared with a) MEDI4736 monotherapy and b) tremelimumab monotherapy, in terms of PFS) • Stratified log-rank test using BICR data (RECIST 1.1) (FAS) • Kaplan-Meier plots using BICR data (RECIST 1.1) (FAS) • Sensitivity analyses using o site Investigator tumor data (RECIST 1.1) (FAS) o Censoring data at subsequent therapy (FAS) o Using BICR data (RECIST 1.1, modified for confirmation of progression) (FAS) Exploratory analysis • Stratified log-rank test using BICR data (irRECIST 1.1) (FAS) • Kaplan-Meier plot using BICR data (irRECIST 1.1) (FAS)
Overall Survival	Secondary analysis • Stratified log-rank test (FAS) • Kaplan-Meier plots of OS (FAS)
Best Objective Response	Secondary analysis • N (%), using BICR data (RECIST 1.1) (EAS) • Sensitivity analysis 1) site Investigator tumor data (RECIST 1.1) (FAS) 2) Additionally, BoR will be assessed using RECIST 1.1 data obtained from BICR (FAS)
Symptom improvement rate (EORTC QLQ-C30 and EORTC QLQ-H&N35 endpoints)	Descriptive statistics N (%)
QoL/Function improvement rate (EORTC QLQ-C30 endpoints)	Descriptive statistics N (%)
Time to QoL/Function deterioration (EORTC QLQ-C30 endpoints)	Kaplan-Meier plots

Endpoints Analyzed	Notes
Time to symptom deterioration (EORTC QLQ-C30 and EORTC QLQ-H&N35 endpoints)	Kaplan-Meier plots

CI Confidence interval; BICR Blinded Independent Central Review; irRECIST 1.1 Immune-related response criteria; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1; OS Overall survival.

4.2 Analysis methods

4.2.1 Primary variable – Objective response rate

Main objective (assess the efficacy of MEDI4736 + tremelimumab combination)

The primary endpoint, ORR, will be evaluated by summarizing the number and percentage of patients with a tumor response (CR/PR), along with 2-sided 95% exact Clopper-Pearson CI. The primary analysis will be based on the programmatically derived ORR based on BICR assessments, and using all scans regardless of whether they were scheduled or not. An exploratory analysis will be conducted using irRECIST 1.1 data obtained from the BICR. An analysis of ORR using the results of the programmatically derived RECIST 1.1 using the site Investigator tumor data from all scans will be conducted as a sensitivity analysis to confirm the results of the primary analysis using data derived from the eCRFs. The primary analysis population for ORR will be the evaluable analysis set, but ORR will also be analyzed using FAS population.

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

Overall visit response data will be listed and summarized over time for all patients (i.e., FAS).

Secondary objective (assess the efficacy of MEDI4736 + tremelimumab combination therapy compared with a) MEDI4736 monotherapy and b) tremelimumab, in terms of ORR and PFS)

Objective Response Rates will be compared between the three treatment groups, using logistic regression. The comparisons will include the following:

MEDI4736 + tremelimumab combination therapy versus MEDI4736 monotherapy

MEDI4736 + tremelimumab combination therapy versus tremelimumab monotherapy

Evaluable patients data analysis for the MEDI4736 or tremelimumab monotherapy versus MEDI4736 + tremelimumab combination groups will be based on the programmatically derived ORR using BICR assessments (RECIST 1.1). The logistic regression models adjusting for stratification variables (HPV status and smoking status) will be performed, and

results of the analyses will be presented in terms of odds ratios together with their associated profile likelihood 95% CIs (e.g. using the option 'LRCI' in SAS procedure GENMOD), and p-values (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model). The covariates in the statistical modeling will be based on the values entered into IVRS at randomization, even if it is subsequently discovered that these values were incorrect. Since the analysis is not the main objective of the study, no adjustment for the type 1 error will be done.

All scans for evaluable patients will be used for the analysis, regardless of whether or not they were scheduled. An exploratory analysis will be conducted using irRECIST 1.1 data obtained from the BICR.

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

Overall visit response data will be listed and summarized over time for all patients (i.e., FAS)

ORR using re-scored Ventana PD-L1 SP263 IHC assay

The analysis of ORR based upon BICR RECIST assessments on EAS and FAS will be presented for PD-L1 negative status using the re-scored Ventana PD-L1 SP263 IHC assay (<1%, ≥1% and <10%, ≥10%)

Subgroup analysis

The analysis of ORR based upon BICR RECIST assessments on EAS and FAS will also be presented by subgroup. The subgroups are defined as follows:

- HPV status (positive, negative)
- Smoking Status (>10, ≤10 pack-years)
- Primary tumor site (oral cavity, oropharynx, hypopharynx, and larynx)
- Prior radiation therapy (yes, no)
- Use of chewing tobacco, oral snuff, and sublingual nicotine (yes, no)
- Smoking history (current, former, never)
- Metastatic disease at baseline (stage IVc and other stages)
- Time to recurrence from last dose of platinum in a platinum-containing multimodality therapy (≤6 months, >6 months)
- Sex (male, female)
- Age at randomization (<65, ≥65 – <75, and ≥75 years of age)
- Race (Asian, non-Asian)
- ECOG Performance status (0, ≥1)
- Prior lines of systemic therapy for treatment of SCCHN (1, 2, and ≥3)
- Extent of Disease (recurrent, recurrent and metastatic)
- Prior use of Cetuximab (yes, no)

The comparison of interest will be MEDI4736 + tremelimumab combination therapy versus MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy versus tremelimumab monotherapy. Treatment effect will be estimated by the odds ratio together with its corresponding 95% CI using a logistic model with treatment as the only covariate. A forest plot will be presented for all relevant comparisons and subgroups.

4.2.2 Duration of response

Kaplan-Meier plots of DoR based on the BICR assessment of RECIST 1.1 will be presented per treatment arm. Median DoR and 95% CI will be summarized for only patients who have a response. In addition, a sensitivity analysis using DoR from the site Investigator tumor data will be done.

4.2.3 Progression free survival

If the required target events have not been accumulated for formal statistical analysis of PFS, only descriptive statistics will be presented.

For formal statistical analysis, PFS will be compared between the three treatment groups (MEDI4736 + tremelimumab vs. MEDI4736 monotherapy and MEDI4736 + tremelimumab vs. tremelimumab monotherapy) using stratified log rank test adjusting for HPV status (positive and negative) and smoking status (>10 and ≤10 pack-years). The effect of treatment will be estimated by the HR together with its corresponding 95 % CI and p-value.

The HR and its CI will be estimated from the stratified Cox proportional hazards model with treatment as the only covariate (Cox 1972Cox 1972).

The stratification factors in the statistical modeling will be based on the values entered into IVRS at randomization, even if it is subsequently discovered that these values were incorrect.

Kaplan-Meier plots of PFS will be presented per treatment arm. Summaries of the number and percentage of patients experiencing a PFS event, and the type of event (RECIST 1.1 or death) will be provided along with median PFS.

PFS at 6 months and at 12 months will be summarized (using the Kaplan-Meier curve) and presented by treatment arm.

Effect of covariates on the HR estimate (Cox Proportional Hazards model)

An unstratified Cox proportional hazards modeling will be employed to assess the effect of covariates on the HR estimate. The following covariates will be included in the statistical model: treatment and the stratification factors as main effects (HPV Status, and smoking status).

This model will be done to ensure that any output from the Cox modeling is likely to be consistent with the results of the stratified log-rank test.

Moreover, a sensitive analysis will be performed to evaluate the treatment effect, adjusted for pre-specified baseline prognostic factors. For this analysis, a stratified Cox adjusted for the following covariates will be used. They are:

- HPV Status
- Smoking Status (>10 and ≤10 pack-years)
- Time to recurrence from multimodality therapy (<6 months versus ≥6 months or presentation with metastatic disease
- Sex at randomization
- Age at randomization

The two models described above will include the effect regardless of whether the inclusion of effect significantly improves the fit of the model providing there is enough data to make them meaningful.

Interactions between treatment and the stratification factors will also be tested to rule out any qualitative interaction using the approach of Gail and Simon 1985.

Sensitivity and Exploratory Analyses

A sensitivity analysis of PFS using the site Investigator tumor data will be performed. The stratified log rank test will be repeated on the programmatically derived PFS using the site investigator data based upon RECIST 1.1 as described above. In addition, a sensitivity analysis of PFS using ICR data (RECIST 1.1 modified for confirmation of progression) will be performed to determine the effect of confirmation of progression. Another sensitivity analysis will be performed by repeating the PFS analysis where patients who take subsequent therapy prior to progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy.

An exploratory analysis of PFS using the irRECIST 1.1 data obtained from the BICR will be performed. The stratified log-rank test will be repeated on PFS using the BICR based upon the irRECIST 1.1 data as described above in section 4.2.1. Results of the exploratory analyses will be reported outside of the CSR.

4.2.4 Overall survival

If the required target events have not been accumulated for the formal statistical analysis of OS, only descriptive statistics will be presented.

Formal statistical analysis of OS will be performed as described above for the PFS.

Kaplan-Meier plots of OS will be presented per treatment arm. Summaries of the number and percentage of patients who have died, are still in survival follow-up, are lost to follow-up and have withdrawn consent will be provided along with median OS.

The proportion of patients alive at 12 months and 18 months will be summarized (using the Kaplan-Meier curve) as described for PFS above.

4.2.5 Best objective response (BoR)

BoR will be summarized by n (%) for each category (CR, PR, SD, PD, and NE), per treatment arm. A sensitivity analysis of BoR using the site Investigator tumor data will be performed.

Additionally, BoR will be repeated according to RECIST 1.1 data obtained from BICR data using FAS.

4.2.6 Disease control rate (DCR)

As a secondary endpoint, DCR will be summarised (i.e., number of patients [%]) for the BICR assessment of RECIST 1.1.

A sensitivity analysis of DCR using the site Investigator tumor data will also be performed.

4.2.7 Time to response

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

As a sensitivity analysis, time to response will also be summarised based upon the site investigator tumor assessment data according to RECIST 1.1.

4.2.8 Patient reported outcome

The PRO endpoints that have been identified as secondary are EORTC QLQ-C30 time to HRQoL deterioration for global health status, time to symptom deterioration for fatigue, time to symptom deterioration for functional deterioration for physical domain and QLQ-H&N35 time to symptom deterioration for these 2 symptoms; pain and swallowing.

QLQ-C30

Time to symptom deterioration will be presented using a Kaplan-Meier plot and/or table for each of the 3 symptom scales (fatigue, pain, and nausea/vomiting), 5 functional scales (physical, role, emotional, cognitive, and social), and global health status/QoL per treatment arm.

A summary of the symptom improvement rate (along with a 95% confidence interval using the Newcombe-Wilson method) for each of the 3 symptom scales (fatigue, pain, and

nausea/vomiting) will be produced. Similarly, a summary of HRQoL/function improvement rate for each of the 5 function scales (physical, role, emotional, cognitive, and social) and global health status/QoL will be produced.

Summaries of absolute and change from baseline values for each of the 3 symptom scales (fatigue, pain, and nausea/vomiting), 5 individual symptom items (dyspnea, insomnia, appetite loss, constipation, and diarrhea), 5 functional scales (physical, role, emotional, cognitive, and social), and the global health status\QoL score will be reported by visit. Graphical presentations may also be produced as appropriate.

QLQ-H&N35

For each of the symptom scales in the H&N35 (pain, swallowing, senses and speech), time to deterioration in symptoms will be presented using a Kaplan-Meier plot and/or table.

A summary of the symptom improvement rate (along with a 95% confidence interval using the Newcombe-Wilson method) for each of the 4 symptom scales above will be produced.

Summaries of absolute and change from baseline values for each of the 7 symptom scales (pain, swallowing, senses, speech, social eating, social contact and sexuality) and11 single-item measures (teeth, problems with mouth opening, dry mouth, sticky saliva, coughing, feeling ill, use of analgesics, use of nutritional supplements, use of a feeding tube, weight gain, and weight loss) will be reported by visit. Graphical presentations may also be produced as appropriate.

4.2.9 Change in tumor size

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

Tumor size will also be presented graphically using waterfall plots, to present each subject's best percentage change in tumor size as a separate bar, with the bars ordered from the largest increase to the largest decrease. Reference lines at the +20% and –30% change in tumor size levels will be added to the plots, which correspond with the definitions of progression and 'partial' response respectively. Additionally, 'spider' plots will be produced. This depicts each patient's percentage change in tumor size as a line over time. Additional waterfall plots showing percentage change in tumor size at specific timepoints may be produced if it is felt that these are warranted to provide greater clarity.

The above outputs will be programmed for the BICR data based upon RECIST assessments. They will be repeated for the irRECIST 1.1 data obtained from BICR where tumor size is defined as the sum of the target lesions and the new measured lesions.

4.2.10 Safety

Safety data will be summarized and listed only. No formal statistical analyses are planned for safety data. All safety and tolerability data will be using the safety population.

The following sections describe the planned safety summaries for AEs, vital signs, laboratory parameters, and ECG and WHO performance status. However, additional safety tables (not specified in this SAP) may need to be produced to aid interpretation of the safety data.

4.2.10.1 Adverse Events

All AEs, both in terms of current Medical Dictionary for Regulatory Activities (MedDRA) preferred term and Common Toxicity Criteria for Adverse Events (CTCAE) grade, will be listed and summarized descriptively by count (n) and percentage (%). The current MedDRA dictionary will be used for coding. Any AE occurring before treatment with IP and which did not worsen during the course of the study will be included in the AE listings, but will not be included in the summary tables (unless otherwise stated). These will be referred to as 'pre-treatment'. However, any AE occurring before the administration of the first infusion on Study Day 1 that increases in severity after the first dose will be regarded as treatment emergent and thus will be included in the majority of summary tables.

AEs observed up until 90 days following discontinuation of IP or until the initiation of the first subsequent therapy following discontinuation of IP (whichever occurs first) will be used for reporting of all of the AE summary tables. This will more accurately depict AEs attributable to IP only as opposed to presenting all AEs reported up to 90 days following discontinuation of IP. This is due to the fact that a number of AEs up to 90 days following discontinuation are likely to be attributable to subsequent therapy. However, to assess the longer term toxicity profile, a small selection of the AE summaries may be repeated containing AEs observed up until 90 days following discontinuation of IP (i.e. without taking subsequent therapy into account). A summary will also be produced containing all AEs (by system organ class and preferred term) observed from the initiation of the first subsequent therapy following discontinuation of IP until 90 days following discontinuation of IP treatment (i.e. summarizing those AEs experienced by patients taking subsequent therapy during the 90 day AE collection follow-up window post discontinuation of IP). Any data post 90 days last dose will be listed only apart from a separate summary that presents any events that occur prior to dosing or starting more than 90 days after discontinuing IP.

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

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

- All AEs
- All AEs causally related to study medication
- AEs with CTCAE grade 3 or 4
- AEs with CTCAE grade 3 or 4, causally related to study medication
- AEs with outcome of death
- AEs with outcome of death causally related to study medication
- All SAEs
- All SAEs causally related to study medication
- AEs leading to discontinuation of study medication
- AEs leading to discontinuation of study medication, causally related to study medication
- Immune mediated AEs based on pre-defined criteria presented in the immune mediated AE charter and/or per eCRF (representing physician's evaluation). Footnotes will be added in the summary tables to specify how the immune mediated AEs were identified (i.e. by immune mediated AE charter definition or by eCRF/physician's evaluation).
- Infusion reaction AEs

An overall summary of the number and percentage of patients in each category will be presented, as will an overall summary of the number of episodes in each category. In addition, a truncated AE table of most common AEs, showing all events that occur in at least 5% of patients overall will be summarized by preferred term, by decreasing frequency. This cut-off may be modified after review of the data. When applying a cut-off (i.e., 5 %), the raw percentage should be compared to the cut-off, no rounding should be applied first (i.e., an AE with frequency of 4.9% will not appear if a cut-off is 5%).

Each AE event rate (per 100 patient years) will also be summarized by preferred term within each system organ class. For each preferred term, the event rate (defined as the number of patients with that AE divided by the total drug exposure of patients and then multiplied by 365.25 x 100 to present in terms of 100 patient years) will be presented.

AEs will be assigned CTCAE grades (National Cancer Institute (NCI) CTCAE version 4.03) and summaries of the number and percentage of patients will be provided by maximum reported CTCAE grade, system organ class, preferred term.

Fluctuations observed in CTCAE grades during study will be listed for those AEs which are CTCAE ≥ 3.

In addition, AEs with outcome of death, SAEs, AEs leading to discontinuation of treatment and AEs causally related to IP will be listed.

A summary of deaths will be provided with number and percentage of patients, categorized as:

- Related to disease under investigation,
- AE outcome = death,
- Both related to disease under investigation and with AE outcome=death,
- Patients with unknown reason for death, and
- Other deaths.

A corresponding listing will also be produced.

Adverse events of special interest

Preferred terms used to identify adverse events of special interest (AESIs) will be listed before DBL and documented in the Study Master File. Grouped summary tables of certain MedDRA preferred terms will be produced and may also show the individual preferred terms which constitute each AESI grouping. For each 'grouped' term, the number (%) of patients experiencing any of the specified terms will be presented by maximum CTCAE grade. Additional summaries will include Time to Onset of first CTCAE grade 3 or higher. Time to onset of first AE for each grouped term and preferred term within it will also be produced. Groupings will be based on preferred terms provided by the medical team prior to DBL, and a listing of the preferred terms in each grouping will be provided.

Additional summaries of the above-mentioned grouped AE categories will include number (%) of patients who have:

- At least one adverse event of special interest presented by outcome
- At least one adverse event of special interest causally related to study medication (as determined by the reporting investigator)
- At least one adverse event of special interest leading to discontinuation of IP

A summary of total duration (days) of AESI will be provided for events which have an end date and this will be supported by summaries of ongoing AESIs at death and separately at data cut-off, as well as a summary of time to resolution to grade 1 or less and time to resolution to grade 2 or less.

Haemorrhages adverse events

Key summary tables (e.g. adverse events and event rate by system organ class, preferred term and maximum reported CTCAE grade, time to onset of first adverse event (days), serious adverse events) will also be produced considering selected hemorrhage adverse events.

Summary of long term tolerability

To assess long term tolerability, provided that there are a sufficient number of patients with events to warrant it, prevalence plots, life table plots and cumulative incidence plots will be presented for each of the AESI grouped terms and any other events considered important after review of the safety data, provided there are ≥ 10 events.

A prevalence plot provides information on the extent to which the events may be an ongoing burden to patients. The prevalence at time t after first dose of study treatment is calculated as the number of patients experiencing the event divided by the number of patients receiving study treatment or in safety follow-up at time t; generally, t is categorized by each day after dosing. The prevalence will be plotted over time presented. Multiple occurrences of the same event are considered for each patient but a patient is only counted in the numerator whilst they are experiencing one of the occurrences of the event. These plots will only be produced for AESIs that have ≥10 events.

For each AE, median time to first onset of the AE from the date of first dose will be presented in patients in the safety analysis. Patients who did not experience the AE will be censored at the end of their safety follow-up. Summary tables of time to first onset for each AE will also be produced (e.g. 1-28 days, 29-56 days, 57-84 days, 85-112 days, >112 days). Median duration of the AE will be presented in patients who experienced each AE, as well as the median time to resolution to grade 1 or less and time to resolution to grade 2 or less.

A life table plot can be used to describe the time to onset of the event and specifically when patients are at most risk of first experiencing the event. The hazard, or in other words, the probability of having an AE in a specified time period (e.g. 0-1 months, 1-3 months, 3-6 months, etc.) given that the patient reaches that time period without having an event is plotted for each time period. These plots will only be produced for AESIs that have ≥10 events.

A cumulative incidence plot is a plot of the raw cumulative incidence and cumulative incidence function over time, this will be presented on separate plots. The raw cumulative incidence is the actual probability that a patient will have experienced their first occurrence of the event by a given time point. The cumulative incidence function estimates the cumulative incidence if the data cut-off had not been imposed and all patients had completed safety follow-up (Pintilie M.). These plots will only be produced for AESIs that have ≥10 events.

4.2.10.2 Laboratory assessments

Data obtained up until the 90 days following discontinuation of IP or until the initiation of the first subsequent therapy following discontinuation of IP (whichever occurs first) will be used for reporting. This will more accurately depict laboratory toxicities attributable to IP only as a number of toxicities up to 90 days following discontinuation of IP are likely to be attributable to subsequent therapy. However, to assess the longer term toxicity profile, a small selection of the summaries of laboratory data will be repeated containing data collected up until 90 days following discontinuation of IP (i.e., without taking subsequent therapy into account). A small selection of summaries of laboratory data will also be produced containing data from initiation of the first subsequent therapy following discontinuation of IP until 90 days following discontinuation of IP (i.e., summarizing the laboratory data collected on patients taking subsequent therapy during the 90 day follow-up window post discontinuation of IP). These outputs will only be produced if the number of laboratory toxicities observed warrant the inclusion of such outputs for interpretational purposes. Any data post 90 days last dose will be listed only.

Data summaries and listings will be provided in International System (SI) of units.

All laboratory data will be listed. Flags will be applied to values falling outside - reference ranges (which will be explicitly noted on these listings where applicable), and to values for which CTCAE grading applies.

Scatter plots (shift plots) of baseline to maximum/minimum value (as appropriate) on treatment (i.e. on treatment is defined as data collected between the start of treatment and the relevant follow-up period following the last dose of IP) may be produced for certain parameters if warranted after data review.

Box-plots of absolute values by week, and box-plots of change from baseline by week, may be presented for certain parameters if warranted after data review.

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

- Hematology: Hemoglobin, Leukocytes, Lymphocytes, absolute count, Neutrophils, absolute count, Platelets
- Clinical chemistry: ALT, AST, Alkaline Phosphatase (ALP), Total bilirubin, Albumin, Magnesium – hypo and – hyper, Sodium – hypo and – hyper, Potassium – hypo and – hyper, Corrected calcium – hypo and – hyper, Glucose – hypo and – hyper, GGT, Creatinine

Additional summaries will include a shift table for urinalysis (Bilirubin, Blood, Glucose, Ketones, Protein) comparing baseline value to maximum on treatment value.

Hy's law

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

- Elevated ALT, AST, and Total bilirubin during the study
  - ALT ≥ 3x –< 5x, > 5x- ≤8x, > 8x > 10x and > 20x Upper Limit of Normal (ULN) during the study
  - AST ≥ 3x – <=5x, > 5x ≤8x, > 8x > 10x and > 20x ULN during the study
  - Total bilirubin ≥2x -≤3x, >3x-≤5x, >5x ULN during the study
  - ALT or AST ≥3x - ≤5x, >5x - ≤8x, >8x, >10x and >20x ULN during the study
  - ALT or AST ≥3x ULN and Total bilirubin ≥2x ULN during the study (Potential Hy's law)
- Narratives will be provided in the CSR for patients who have ALT ≥ 3x ULN plus Total bilirubin ≥ 2x ULN or AST ≥ 3x ULN plus Total bilirubin ≥ 2x ULN at any visit.

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

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

Abnormal Thyroid function

Elevated TSH will be summarized per treatment group in terms of number (%) of patients with elevated TSH (higher than the upper normal range), low TSH (lower than lower normal range), elevated TSH post-dose and within normal range at baseline, low TSH post-dose and within normal range at baseline.

4.2.10.3 ECGs

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

Overall evaluation of ECG is collected by visit as normal or abnormal, and the relevance of the abnormality is termed as "clinically significant" or "not clinically significant, but this information will not be summarized as the central ECG read information is deemed as being more clinically interpretable.

Continuous ECG measurements (including QTcF and QTcB) may be summarized through the use of boxplots for each visit for certain ECG parameters if warranted after data review.

QTcF and QTcB changes (values of >450, >480, and >500; increase/decrease of >30, >60, and >90 from baseline to any time; and value >450 and increase of > 30 and value >500 and increase of >60) during treatment will be summarized.

4.2.10.4 Vital signs

Box plots for absolute values and change from baseline by week may be presented for certain vital signs parameters if warranted after data review.

4.2.10.5 Other Safety Data

Data from positive pregnancy tests will be listed and not summarized.

4.2.11 WHO performance status

All WHO performance status will be summarized over time for FAS.

4.2.12 PK Data

MEDI4736/tremelimumab concentration data will be listed for each patient and each dosing day, and a summary provided for all patients in the PK analysis set. These outputs will be produced by AstraZeneca/MedImmune Clinical Pharmacology group or designee.

4.2.13 Immunogenicity analysis

Immunogenicity results will be listed by patient and a summary will be provided by the number and percentage of patients who develop detectable ADA for MEDI4736 or tremelimimab based on the safety population.

The immunogenicity titre will be listed for samples confirmed positive for the presence of ADA. These outputs will be produced by AstraZeneca/MedImmune Clinical Pharmacology group or designee.

The effect of immunogenicity as well as the effect of its neutralizing properties on PK, pharmacodynamics, efficacy, and safety will be evaluated, if the data allow. A detailed plan will be written by the AstraZeneca/MedImmune Clinical Pharmacology group or designee.

4.2.14 Demographic and baseline characteristics data

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

- Patient disposition (including screening failures and reason for screening failure)
- Important protocol deviations specified in this SAP
- Inclusion in analysis populations
- Demographics (age, age group [<65, ≥65 – <75, and ≥75 years], sex, race and ethnicity)
- Patient characteristics at baseline (weight, weight group)
- Patient recruitment by country and centre
- Previous disease-related treatment modalities
- Number of regimens of previous chemotherapy for SCCHN at baseline
- Previous head and neck cancer therapy
- Disease characteristics at baseline (WHO/ECOG performance status, best response to previous therapy)
- Disease characteristics at initial diagnosis (primary tumor location, histology type, tumor grade, time from diagnosis to first dose, overall disease classification, AJCC staging)
- Primary tumor location and TNM classification at initial diagnosis
- Time to recurrence from last dose of platinum in a platinum-containing multimodality therapy (≤6 months, >6 months)
- Extent of disease at baseline
- Disease related medical history

- Time from most recent disease progression to start of IP
- Post-discontinuation anticancer therapy
- Human papillomavirus (HPV) status (positive, negative)
- Smoking status, categorized (>10 versus, <= 10 pack years)
- Stratification factors by IVRS and CRF
- Discrepancy between local and central review

The following will also be listed for all patients in the FAS (unless otherwise specified) per ICH guidlines:

- Important protocol deviations specified in this SAP
- Subject excluded from analysis populations
- Demographics (age, age group [<65, ≥65 – <75, and ≥75 years], sex, race and ethnicity)

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

Patient disposition data will also be summarized and listed at the time of OS analysis.

4.2.15 Treatment exposure

The following summaries related to MEDI4736 and tremelimumab will be produced for the safety analysis set:

- Total exposure.
- Actual exposure.
- Number of dose interruptions.
- RDI (entire intended treatment period).

For patients on study treatment at the time of the ORR and OS analysis, the DCO date will be used to calculate exposure. Summaries of exposure will also be presented for the subgroup of discontinued patients.

All treatment information data will be listed for the safety analysis set.

4.2.16 Subsequent Therapy

Subsequent therapies received after discontinuation of study treatment will have summaries produced, together with number of regimens received. Moreover, a descriptive summary will be produced for time to subsequent therapy from discontinuation of study drug treatment.

5. INTERIM ANALYSES

No interim analysis for futility or superiority is planned for this study. Interim safety assessment will be conducted 3 months after randomization of the first patient in the study or after the randomization of 20 patients in the study, whichever is first, followed by two consecutive 3 monthly safety analysis, and 6 monthly safety review thereafter until primary data analysis. Details of the interim safety assessment will be documented in an IDMC charter.

6. CHANGES OF ANALYSIS FROM PROTOCOL

Table 12 Changes of analysis from protocol

Section of SAP Affected (If applicable)	Change	Rationale
Table 5	Sensitive analyses on DoR, TTR, BoR, DCR, and PFS analyzed by BICR using FAS were added.	To be in line with FDA's request.
Secondary objectives	irRECIST was changed from secondary to exploratory analysis for ORR and PFS.	irRECIST was considered exploratory and will be presented outside the scope of the clinical study report.
Section 4 Analysis method	The wording on the timing of formal analyses for PFS and OS was changed. The option of performing the analyses before the minimum number of events was observed was removed.	In order to have 80% power, the formal analyses for PFS should happen when at least 116 events were observed and the formal analyses for OS should happen when at least 125 events were observed.
Section 4.2.1 Subgroup analysis	Analysis of ORR in subgroup populations.	Additional subgroups were added in order to investigate the impact of additional

Table 12 Changes of analysis from protocol

		prognostic factors on clinical outcome.
Sections 4.2.3 and 4.2.4	CI and HR for PFS and OS to be calculated using Cox models.	To be consistent with updated AZ statistical guidance.
Section 3.5.2 and Table 4	Non-compartmental PK was removed.	The PK sampling scheme of this study is sparse and would not allow meaningful PK parameter estimation.

7. REFERENCES

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8. APPENDIX