Clinical Study Protocol

Drug Substance	MEDI4736 and tremelimumab
Study Code	D4193C00002
Version	07
Date	12 December 2018

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

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

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VERSION HISTORY

Version 7, 12 December 2018

Only changes from CSP v.6 to CSP v.7 are shown in this version history. The sponsor considers changes in this protocol amendment to be non-substantial. Grammatical and editorial changes are not included.

The following sections were updated:

Section 6.3.12 Safety data to be collected following the final data cut-off of the study

- This section has been added to clarify how safety data will be recorded for patients continuing to receive IP treatment after final data cut-off (DCO) and database closure; specifically, that serious adverse events (SAEs), overdoses, and pregnancies must be reported via paper SAE forms.

Section 7.2.1 Treatment regimens

- The text has been amended to clarify that patients currently receiving treatment with MEDI4736 may be transitioned to a roll-over or safety extension study after the analysis is finalized.

Version 6, 23 January 2018

Only changes from CSP v.5 to CSP v.6 are shown in this version history. Grammatical and editorial changes are not included.

Protocol synopsis (MEDI4736 + tremelimumab combination therapy): text was corrected as per Section 7.2.1.

Section 1.3.2.1 (Overall risks): text was added to align with the updated Investigator Brochure (IB) Edition 12.

Section 1.3.2.2 (MEDI4736): text was updated to align with the updated IB (Edition 12).

Section 1.3.2.3 (Tremelimumab): text was updated to align with the updated IB (Edition 12).

Section 1.3.2.4 (MEDI4736 + tremelimumab): text was updated to align with the updated IB (Edition 12).

Section 3.10.2 (Withdrawal of the informed consent): Section 3.10.2.1 (Survival status for withdrawn consent and lost to follow-up patients) was added to clarify follow-up status for withdrawn consent and lost to follow-up patients.

Section 4 (Study plan and timing of procedures): text relating to patients receiving randomized study treatment after the final overall survival analysis was deleted.

Section 6.3.3 (Variables): clarification relating to collection of variables for serious adverse events.

Section 6.7.1 (Adverse events of special interest): text was updated to describe immune-mediated adverse events and to align with the updated IB (Edition 12).

Section 6.7.2 (MEDI4736 and MEDI4736 + tremelimumab): text was added to align with the updated IB (Edition 12). Table 9 (Dosing modification and toxicity management guidelines) was also updated to the 01 November 2017 version.

Section 7.2.1 (Treatment regimens): a new section (Post final data cut-off) was added to describe treatment with MEDI4736 after the final data cut-off (DCO).

Section 7.7 (Concomitant and other treatments): the table was updated to reflect information in the updated IB (Edition 12).

Section 8.4.1.2 (Primary endpoint [Overall survival]): text was updated to allow sites more flexibility in the timing of survival calls following DCO.

Version 5, 07 September 2016

Previous versions of the CSP were developed utilizing the old process with a separate document to describe the changes. Only changes from CSP v.4 to CSP v.5 are shown in this version history.

Throughout the Protocol:

- Treatment in all arms will continue until Progression. Dosing schema for the IMT arms have been modified to continue treatment till objective disease progression has been demonstrated, as a fixed 12 month period of dosing has not shown greater benefit than treatment till progression. Further, this ensures alignment of treatment duration with the SOC arm and permits comparison of the clinical efficacy achieved by each arms of therapy. At the time of this change, no patients have completed the 12 month treatment duration period previously implemented for the IMT arms, and therefore there is no impact as a result of this modification.
    - **Sections updated: Synopsis; 1.2; 1.4; 4; 5.1; 5.3.1; 7.2; 7.8**

- Retreatment sections have been updated to only allow retreatment for patients on the combination arm, provided that progression occurs during the monotherapy portion of dosing. Those patients may benefit from an additional round of combination therapy.
    - **Sections updated: Synopsis; 1.2; 1.4; 4; 5.1; 5.3; 7.2**
- The protocol language has been updated to clarify that patients should have progressed within 6 months of the last dose of platinum given as part of multimodality therapy as curative intent.
    - **Sections updated: Synopsis, 1.1.6, 1.3.3, 1.4, 3.1,**
- The language for confirmed progression has been updated to provide clarity for the requirements and purpose of the scans. All patients should be followed until they have disease progression according to RECIST1.1 criteria, and a second scan obtained at a minimum of 4 weeks later to confirm progression is required, if clinically feasible. The term "Objective disease progression according to RECIST 1.1" has replaced "confirmed disease progression" or "clinical disease progression" throughout the protocol to make it clearer that patients should continue to undergo CT/MRI assessments until objective disease progression according to RECIST 1.1.
    - **Sections updated: Synopsis, 1.4, 3.9.1, 4, 5.1, 7.2, 8.4.1**
- HPV status will be assessed according to local standards. Removed the "or by p16 IHC assay" language.
    - **Section 1.4, 4.1, 5.5.1**
- For re-treatment patients, the following assessments have been removed: HPV, [redacted] (PD-L1 testing at time of retreatment is optional).
    - **Section 1.4, 7.2**

Protocol Synopsis:

- This section has been updated to reflect the change from a single primary objective of MEDI4736 +tremelimumab versus SoC in terms of OS to co-primary objectives of MEDI4736 +tremelimumab versus SoC in terms of OS and MEDI4736 monotherapy versus SoC in terms of OS. The primary objective was changed to co-primary objectives based on emerging data from recent studies that increased confidence that MEDI4736 monotherapy will show survival benefit regardless of the PD-L1 status.
- The hypothesis testing is expected to be performed after approximately 11 months of follow up instead of 10 months, and after approximately 375 death events have occurred instead of 392. The number of events that triggers the interim analysis has been reduced from 314 to 300 as a result of change to the co-primary endpoints.

This section has been further updated to reflect the alpha split between the co-primary objectives, and one interim analysis, such that an alpha level of 2.2% will be used with 90% power for each co-primary objective. Follow-up periods and study duration have been adjusted to reflect updated enrolment timelines due to removal of the requirement for a pre-specified number of PD-L1-positive patients.

- The requirement for a minimum number of 300 patients with PD-L1-positive disease has been removed because the co-primary objectives are being tested regardless of PD-L1 status and the comparison of MEDI4736 monotherapy vs SOC in PD-L1 positive patients is now a secondary objective. Enrolment will now be based on the natural prevalence of PD-L1 positive and negative patients. Therefore, fewer patients will need to be screened in order to identify 720 eligible patients regardless of PD-L1 status, and so the number of patients screened has been reduced from 1800 to 1200.
- The section was updated to clarify that the assignment of patients with ≥25% of tumor cells with membrane staining as PD-L1-positive is being used for stratification purposes.

Section 1.2.3:

- This section has been updated to include the following reference "Ferris et al 2016".

Section 1.2.4:

- This section has been updated to reflect emerging data demonstrating that PD-L1 inhibitors show survival benefit regardless of the PD-L1 status. This data supports the new co-primary endpoints of OS in all patients regardless of PD-L1 status.

Section 1.2.5:

- This section has been updated to reflect the co-primary OS objectives and the secondary objectives.

Section 1.3.2.1:

- This section has been updated based on recent data reviews to reflect the identified and potential risks associated with MEDI4736; this section is now consistent with available data.

Section 1.3.2.2:

- This section has been updated based on recent data reviews to reflect the identified and potential risks associated with tremelimumab monotherapy; this section is now consistent with available data.

Section 1.4:

- This section has been updated to clarify that the specified PD-L1 expression cut-off level will be used for the purpose of stratification, however the cut-off level to be used for the subgroup analyses by PD-L1 status and for determining the PD-L1-negative subgroup in the MTP may be different and will be determined from emerging data outside of this trial. The requirement for a minimum number of patients with PD-L1-positive disease has been removed. The number of patients that is estimated to be screened in order to identify 720 patients has been changed from

1800 to 1200. Figure 1 has been updated to reflect that a minimum number of PD-L1 positive patients is no longer required, and that patients will be stratified based on PD-L1 status, tumor location/HPV status, and smoking history. Figures 2 and 3 have been updated to reflect the tumor assessments should be performed relative to the date of randomization. The footnotes have been updated to provide clarification on the requirements for a confirmatory scan.

Section 2:

- The co-primary objectives and secondary objectives have been updated.

Section 3.3:

- This section has been modified to clarify that patients with a single target lesion that is subsequently used for a screening PD-L1 biopsy, should allow approximately 2 weeks before imaging scans are obtained for baseline disease assessment.

Section 3.11:

- This section has been updated to include language to allow the study to stop for superiority based on interim OS analysis.

Section 4:

- This section has been modified to clarify when dosing may resume after a delay for either treatment-related toxicity or reasons other than treatment-related toxicity to ensure that patients have the opportunity to receive maximal treatment. The timing of tumor efficacy (RECIST) assessments have been clarified in the text, consistent with the timings provided in Tables 2 and 3. In addition, this section has been updated to include an explanation of how patients who are on treatment following the final OS analysis will be managed. Table 2 has been updated to remove a typo to clarify that urinalysis should be conducted as clinically indicated for V0 consistent with footnotes. References to visit 15 week 50 have been removed from Table 2. Table 2 reflects the change from 12 months of treatment to treatment until PD. Tables 2 and 3 have been updated to reflect that Patient Reported outcomes will be collected through week 48.

Section 5.3.1.3:

- The following reference has been added Larkin, et al 2015.

Section 5.5.1:

- The criteria for biopsy of a single target lesion have been updated to clarify the type of biopsy allowed and the timing between the biopsy and the baseline image acquisition. Clarification that the Ventana PD-L1 SP263 IHC analysis will be performed at a laboratory that is approved, trained and monitored by Ventana and meets appropriate regulatory requirements have been added.

Section 6.7.2:

- Table 9 has been updated to reflect the most current toxicity management guidelines for MEDI4736 +/- tremelimumab. Specifically, references to “next scheduled treatment date” and “next scheduled dose”, and “once 5-7 days have passed” in

regard to steroid completion, have been removed and instead the corresponding language has been updated to reflect that study drug/study regimen may be resumed if toxicity improves to Grade ≤1 (or baseline in some cases) after completion of steroid taper. Importantly, the guidelines continue to be based on the maximum grade of each distinct toxicity observed. In addition, it has been clarified in Table 9 that prednisone can be given orally (PO).

Section 7.1:

- Table 10 was updated to correct the typo in the dosage form and strength of MEDI4736 from 500 to 50 mg/mL.
- The language has been updated to allow saline or dextrose for administration with tremelimumab. The final tremelimumab concentration range was changed from 0.15 -10 mg/mL to 0.10 – 10mg/mL. Recent experiments demonstrate no stability change using expanded concentration range.

Section 8.1:

- The section has been updated to reflect the update from a primary objective to the co-primary objectives.

Section 8.2:

- The section has been updated to be consistent with the changes made in the study design (outlined in the protocol synopsis).
- Estimates for the natural prevalence of PD-L1 negative and PD-L1 positive patients have been included under the secondary objective section. The target hazard ratios, critical values, number of events, maturity, and power for co-primary and secondary endpoints have been updated in Table 11 to reflect the changes from primary objective to co-primary objectives and the changes in the secondary objectives.

Section 8.3:

- Table 12 was updated to include OS24 for consistency.

Section 8.3.2

- The definition of the PD-L1-negative analysis set has been updated to clarify that the cut-off level for PD-L1 status may be different from that used for stratification purposes, and that it will be determined from emerging data outside of this trial and included in the SAP prior to database lock.

Section 8.3.3:

- The definition of the PD-L1-positive analysis set has been updated to clarify that the cut-off level for PD-L1 status may be different from that used for stratification purposes, and that it will be determined from emerging data outside of this trial and included in the SAP prior to database lock.

[redacted]

[redacted]

Section 8.4.1:

- Since confirmation of progression with a second scan has been modified to be obtained only when clinically feasible, formal statistical analysis based on confirmation of progression will no longer be performed for PFS, ORR, DOR, and DCR. The relevant paragraphs have been removed.
- A paragraph has been added to describe the time from randomization to the first subsequent therapy or death analysis as this was not included in previous amendments, but is listed as an objective in section 8.5.7.

Section 8.5:

- The section has been updated to be consistent with the changes made in the study design (outlined in the protocol synopsis).
- Table 15 has been updated based on the new primary (now co-primary), objectives, secondary objectives, and PRO objectives. Table 15 has also been updated to reflect the changes in the statistical procedures for analyzing PROs. The symptom improvement rate and QoL/Function improvement rate will be summarized and formal statistical analysis with logistic regression is no longer required and the Time to QoL/Function deterioration (EORTC QLQ-C30 endpoints) has been removed to reduce redundancy since "Time to QoL/Function deterioration" is also covered in "Time to symptom deterioration (EORTC QLQ-C30 and EORTC QLQ-H&N35 endpoints". The duration of response will be analyzed by descriptive statistical and Kaplan Meier plots instead of methods described by Ellis et al 2008. The number of responders is expected to be small making a formal analysis less relevant. The Time from randomization to first subsequent therapy to assess the impact of subsequent use of immunotherapy. The Multiple Testing Procedure has been updated to reflect the co-primary objectives with the focus on all patients regardless of PD-L1 status. It has also been clarified that the multiple testing strategy will use an alpha recycling strategy. Figure 6 has been updated to reflect the changes in the multiple testing procedure.

Section 8.5.1 :

- The title of this section has been updated to clarify that the analysis in the section are related to the Overall Survival analysis.

Section 8.5.1.1:

- The title of this section has been updated for clarity. The results to be presented have been updated to give the CI as 1-α% rather than 95.5% (note: the CI was intended to be 95% in amendment 4) to account for one interim analysis. The section has also been updated to reflect the strata label in IVRS and to clarify that the "HPV status in patients with oropharyngeal cancer only" factor is "Tumor location/HPV status" and is categorized into oropharyngeal cancer with HPV positive status, oropharyngeal

cancer with HPV negative status, and non-oropharyngeal cancer regardless of HPV status.
- The methods for analysis have been updated to reflect that a stratified unadjusted Cox regression will be used to estimate the HR, along with a (1-α) % confidence interval, with the stratified log rank test being used to create the p-value only. This approach is consistent with how such endpoints are normally analyzed.

Section 8.5.1.2:

- The title of this section has been updated for clarity and to correspond to the secondary objectives. The CI has been updated to 1-α% and a statement added to explain that the HR and CI will be estimated from the Cox proportional hazards model. The Kaplan Meier plots by PD-L1 tumor status subgroup have been removed.

Section 8.5.1.3:

- The analysis of OS subgroup populations has been moved up from section 8.5.14. Primary tumor status, prior radiation therapy, use of chewing tobacco, oral snuff, and sublingual nicotine, smoking history, ECOG performance status, prior lines of systemic therapy for treatment of SCCHN, and extent of disease have been added as subgroups for analysis. Additional clarifications have been added to detail the levels used for subgroups of tumor location/HPV status, time to recurrence from platinum containing multimodality therapy, age at randomization, and Standard of Care.
- The section has been updated to describe the comparison of MEDI4736 + tremelimumab combination therapy versus SoC in all patients and in PD-L1 negative patients and MEDI4736 monotherapy versus SoC in all patients. The section has been updated to reflect the purpose of the subgroup analyses to assess the consistency of treatment effects across expected prognostic and/or predictive factors. Analysis will only be conducted if at least 20 events have occurred in all of the subgroups. The section outlines the use of a forest plot to present the subgroup results from OS for MEDI4736 +tremelimumab combination therapy vs. SoC (in all patients and in PD-L1 negative patients) and MEDI4736 monotherapy vs. SoC (in all patients).
- The following sub-section headers were added for clarity: analysis of OS12, OS18, OS24; assumption of proportionality; sensitivity analysis for OS; time from randomization to second progression; time from randomization to first subsequent therapy or death.
- The Weber et al 2012 reference has been updated to Whitehead and Whitehead 1991.
- Additional description has been added to explain the impact of changing to other immunotherapies on overall survival analysis. The analyses are intended to support reimbursement appraisals.

Section 8.5.2:

- The section has been updated to remove the weighted estimate of the overall HR as this analysis is no longer required since study has changed from an enrichment study

to a natural prevalence study. The sensitivity analyses and information on the ascertainment bias, subgroup analysis and its display on forest plot, and adjustment of significance level of testing have been removed since PFS is no longer a co-primary endpoint. Also, the additional analysis based on the confirmation of progression has been removed from the PFS assessment since the study no longer utilizes a central review for imaging and PFS is no longer a primary endpoint.

Section 8.5.4:

- The section has been updated to reflect that Duration of response will be analyzed using descriptive statistics.

Section 8.5.5:

- The Weber et al 2012 reference has been updated to Whitehead and Whitehead 1991.

Section 8.5.8.1:

- The methods of analysis, and number of scales being analyzed for both time to symptom deterioration and time to HRQoL/function deterioration from the EORTC QLQ-C30, have been updated. These revisions have been made to reduce the number of analyses and ensure the protocol is consistent with the statistical analysis plan.

Section 8.5.8.2:

- The methods of analysis, and the number of scales being analyzed for both time to symptom deterioration and symptom improvement from the EORTC QLQ-H&N35 have been updated. These revisions have been made to reduce the number of analyses and ensure the protocol is consistent with the statistical analysis plan.

Section 8.5.14:

- The subgroup analysis section has been moved up to section 8.5.1.3.

8.5.14:

- The section has been updated to be consistent with the changes made in the study design (outlined in the protocol synopsis).

List of References:

- The list of references has been updated to include Ferris et al 2016, and Larkin et al 2015.
- The list of references has been updated to remove Garon et al 2013.

Appendix E (Guidelines for Evaluation of Objective Tumor Response Using RECIST1.1 Criteria):

- The following items have been added for clarity; definition of the short axis, clarification on the requirements for a CT if it is part of a PET/CT; Date of randomization not date of treatment; Months to cycles; statement that lymph nodes are collectively considered as a single organ, A bilateral organ is considered a single

organ for purposes of target lesions, criteria for confirmation of progression have been updated to be consistent with main body of protocol, [redacted]

Version 4, 18 February 2016
Version 4 of the CSP was developed under a previous process where the changes were documented in a separate change memo and are not listed here.

Version 3, 1 June 2015
Version 3 of the CSP was developed under a previous process where the changes were documented in a separate change memo and are not listed here.

Version 2, 3 April 2015
Version 2 of the CSP was developed under a previous process where the changes were documented in a separate change memo and are not listed here.

Version 1, 14 January 2015
Version 1 of the CSP was developed under a previous process where the changes were documented in a separate change memo and are not listed here. The original CSP document was dated 24 October 2014.

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.

AstraZeneca

PROTOCOL SYNOPSIS

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

International Coordinating Investigators

[redacted]

Study site(s) and number of patients planned

The study will screen approximately 1200 patients to identify 720 patients who will be identify in a 1:1:1 fashion (240:240:240 patients) to receive MEDI4736 monotherapy, MEDI4736 + tremelimumab combination therapy, or Standard of Care (SoC) therapy.

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

Study design

This is a randomized, open-label, multi-center, global, Phase III study to determine the efficacy and safety of MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy versus SoC therapy in the target patient population.

The co-primary objectives of the study are:

- To assess the efficacy of **MEDI4736 + tremelimumab combination therapy versus SoC** in patients with squamous cell carcinoma of the head and neck (SCCHN), regardless of programmed cell death ligand 1 (PD-L1) status, in terms of overall survival (OS)

- To assess the efficacy of **MEDI4736 monotherapy versus SoC** in patients with SCCHN, regardless of PD-L1 status, in terms of overall survival (OS)

Patients will undergo a screening assessment on their tumor tissue sample to determine PD-L1 expression per a pre-specified cut-off level. For purposes of stratification, patients with ≥25% of tumor cells with membrane staining will be considered PD-L1-positive while those with 0% to 24% of tumor cells with membrane staining will be considered PD-L1-negative. Based on the underlying PD-L1 status, patients will be randomized in a 1:1:1 ratio to receive treatment with MEDI4736 monotherapy, MEDI4736 + tremelimumab combination therapy, or SoC therapy. Patients who discontinue treatment in 1 treatment group may not switch to treatment in a different group.

Stratification factors include PD-L1 status, tumor location/HPV (human papillomavirus) status, and smoking status. Tumor assessments will be performed every 8 weeks for the first 48 weeks and then every 12 weeks as indicated in the schedule of procedures, with categorization of objective tumor response by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

Objectives

Co-primary Objectives:	**Outcome Measures:**
• To assess the efficacy of MEDI4736 + tremelimumab combination therapy versus SoC in terms of OS	OS in all patients, regardless of PD-L1 status
• To assess the efficacy of MEDI4736 monotherapy versus SoC in terms of OS	OS in all patients, regardless of PD-L1 status

OS Overall survival; PD-L1 programmed cell death ligand 1; SoC Standard of Care.

Secondary Objectives:	**Outcome Measures:**
To further assess the efficacy of MEDI4736 + tremelimumab combination therapy versus SoC in terms of OS	OS in PD-L1-negative patients
To assess the efficacy of MEDI4736 monotherapy versus SoC in terms of OS	OS in PD-L1-positive patients
To further assess the efficacy of MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy versus SoC in terms of PFS, ORR, DoR, DCR, APF6, APF12, OS12, OS18, and OS24	PFS, ORR, DoR, DCR, APF6, and APF12 using the site Investigator's assessments **according to RECIST 1.1** OS12, OS18, and OS24

To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to MEDI4736 monotherapy in terms of PFS, ORR, and OS	PFS and ORR in PD-L1–negative patients using the site Investigator's assessments according to RECIST 1.1 OS in PD-L1–negative patients
To explore symptoms and HRQoL in patients treated with MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy versus SoC using the EORTC QLQ-C30 v3 and the H&N35 module	EORTC QLQ-C30: global health QoL, functioning (physical), and symptoms (fatigue) EORTC QLQ-H&N35: symptoms (pain, swallowing) Changes in World Health Organization/Eastern Cooperative Oncology Group performance status

APF6 Proportion of patients alive and progression free at 6 months from randomization; APF12 Proportion of patients alive and progression free at 12 months from randomization; DCR Disease control rate; DoR Duration of response; EORTC European Organisation for Research and Treatment of Cancer; QLQ-C30 v3 30-item core quality of life questionnaire, version 3; H&N35 35-item head and neck quality of life questionnaire; HRQoL Health-related quality of life; OS12 Overall survival at 12 months; OS18 Overall survival at 18 months; OS24 Overall survival at 24 months; PD-L1 programmed cell death ligand 1; PFS Progression-free survival; QoL Quality of life; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version; SoC Standard of Care.

Safety Objective:	**Outcome Measures:**
To assess the safety and tolerability profile of MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy compared to SoC	AEs, physical examinations, laboratory findings, and vital signs

AE adverse event; ECG electrocardiogram; SoC Standard of Care

Target patient population

Adult patients (age ≥18 years) with histologically or cytologically confirmed, PD-L1–positive or -negative, recurrent or metastatic SCCHN with measurable disease (per RECIST 1.1) who have progressed during or after only one palliative systemic treatment regimen for recurrent or metastatic disease that must have contained a platinum agent or who have progressed within 6 months of the last dose of platinum given as part of multimodality therapy of curative intent.

Duration of treatment

Patients in all treatment arms will continue therapy until objective disease progression according to RECIST 1.1 (PD) (unless there is continued clinical benefit), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, etc.

Patients who the Sponsor and Investigator determine may not continue IMT treatment or who have discontinued IMT or SoC treatment will enter long-term follow up.

Patients in the MEDI4736 + tremelimumab combination therapy arm may be eligible to receive retreatment with MEDI4736 + tremelimumab combination therapy if they meet certain criteria as stated in Section 3.1.

Investigational product, dosage, and mode of administration

MEDI4736 monotherapy

- 10 mg/kg via intravenous (IV) infusion every 2 weeks (q2w) until PD

MEDI4736 + tremelimumab combination therapy

MEDI4736: 20 mg/kg via IV infusion every 4 weeks (q4w) for 4 doses then 10 mg/kg via IV infusion q2w beginning 4 weeks after the last combination dose is administered until PD, AND

- Tremelimumab: 1 mg/kg via IV infusion q4w for 4 doses (4 doses total)

Standard of Care therapy

One of the following:

- Cetuximab: 400 mg/m^2 via IV infusion on Day 0, then 250 mg/m^2 via IV infusion weekly thereafter
- A taxane: docetaxel (40 mg/m^2; **Guardiola et al 2004**) or paclitaxel (80 mg/m^2; **Grau et al 2009**) via IV infusion weekly
- Methotrexate: 40 mg/m^2 via IV infusion weekly per the institution's SoC
- A fluoropyrimidine: (5-fluorouracil [5-FU], TS-1, or capecitabine) as follows:

  5-FU: 2400 mg/m^2 via IV infusion over 46 hours every 2 weeks

  TS-1: 80 mg/m^2 orally once daily for 28 days followed by a 14-day rest

  Capecitabine: 1000 mg/m^2 orally twice daily for 7 days followed by a 7-day rest

Statistical methods

This study is sized for hypotheses testing of improved OS for both 1) MEDI4736 + tremelimumab combination therapy versus SoC in all patients, regardless of PD-L1 status, and 2) MEDI4736 monotherapy versus SoC and in all patients, regardless of PD-L1 status.

Hypothesis testing is expected to be performed after approximately 11 months of follow-up when:

- Approximately 375 death events have occurred in 480 patients (78% maturity) across the MEDI4736 + tremelimumab combination therapy and SoC arms, regardless of PD-L1 status AND when
- Approximately 375 death events have occurred in 480 patients (78% maturity) across the MEDI4736 monotherapy and SoC arms, regardless of PD-L1 status

Interim analysis for OS will be performed when approximately 300 death events (80% of required events) have been accumulated across the MEDI4736 + tremelimumab combination therapy and SoC arms. It is expected that approximately 300 death events have accumulated across the MEDI4736 monotherapy and SoC arms at this time.

Sizing for either MEDI4736 + tremelimumab combination therapy or MEDI4736 monotherapy, in all patients, regardless of PD-L1 status (co-primary objectives)

If OS at 18 months is 25% with MEDI4736 + tremelimumab combination therapy or MEDI4736 monotherapy and 10% with SoC (with a 5.5-month median OS), and assuming the true average OS hazard ratio (HR) is 0. 69, the study will have 90% power to demonstrate statistical significance at the 2.2% level (using a 2-sided test) for the comparison of either MEDI4736 + tremelimumab combination therapy or MEDI4736 monotherapy versus SoC, allowing for 1 interim analysis conducted at approximately 80% of the target events with the smallest treatment difference that could be statistically significant being an average HR of 0. 79. With an assumed 15-month recruitment period and a minimum follow-up period of 11 months from "last patient in", it is anticipated that the final analysis will be performed 26 months after the first patient has been recruited.

OS will be analyzed using a log-rank test, stratified by PD-L1 status, tumor location/HPV status, and smoking status. The effect of treatment will be estimated by the HR together with a 95% confidence interval and p-value using a stratified Cox regression model.

Safety data will be summarized descriptively.

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LIST OF TABLES

LIST OF FIGURES

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
[redacted]	[redacted]
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
APF6	Proportion of patients alive and progression free at 6 months from randomization
APF12	Proportion of patients alive and progression free at 12 months from randomization
AST	Aspartate aminotransferase
AUC	Area under the serum drug concentration-time curve
[redacted]	[redacted]
BoR	Best objective response
BP	Blood pressure
CD	Cluster of differentiation
CI	Confidence interval
CR	Complete response
CSA	Clinical study agreement
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4
DCO	Data cut-off
DCR	Disease control rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviation or special term	Explanation
eCRF	Electronic case report form
EDoR	Expected Duration of Response
EGFR TKI	Epidermal growth factor receptor tyrosine kinase inhibitor
EORTC	European Organisation for Research and Treatment of Cancer
[redacted]	[redacted]
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FU	Fluorouracil
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
H&N35	35-item head and neck quality of life questionnaire
HCC	Hepatocellular carcinoma
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HR	Hazard ratio
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin
ILD	Interstitial lung disease
[redacted]	[redacted]
IMT	Immunomodulatory therapy
IP	Investigational product
ITT	Intent-to-Treat
IV	Intravenous

Abbreviation or special term	Explanation
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Minister of Health, Labor, and Welfare
[redacted]	[redacted]
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non–small-cell lung cancer
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
OS12	Proportion of patients alive at 12 months from randomization
OS18	Proportion of patients alive at 18 months from randomization
OS24	Proportion of patients alive at 24 months from randomization
[redacted]	[redacted]
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L1 –ve	Patients with PD-L1–negative tumor expression status
PD-L1 +ve	Patients with PD-L1–positive tumor expression status
PFS	Progression-free survival
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PR	Partial response
PRO	Patient-reported outcome
q12w	Every 12 weeks
q2w	Every 2 weeks
q4w	Every 4 weeks
QLQ-C30 v3	30-item core quality of life questionnaire, version 3

Abbreviation or special term	Explanation
QoL	Quality of life
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
[redacted]	[redacted]
RR	Response rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable disease
SoC	Standard of Care
sPD-L1	Soluble programmed cell death ligand 1
T_3	Triiodothyronine
T_4	Thyroxine
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
WBDC	Web Based Data Capture
WHO	World Health Organization
w/v	Weight/volume

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 (FU), 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 monotherapy 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**). Note that cetuximab, while approved by the Food and Drug Administration (FDA), is not approved by European Medicines Agency for the second-line treatment. However, its use is accepted in patients that have not received cetuximab as a first-line treatment.

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 (**Vermorken et al 2008**, **Shin and Khuri 2013**). 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**).

[redacted]

1.2.5 Rationale for endpoints

The co-primary objectives of this study are to determine the efficacy of MEDI4736 + tremelimumab combination therapy versus SoC and the efficacy of MEDI4736 monotherapy versus SoC in terms of OS. Testing for improvements in OS provides a non-biased assessment of direct clinical benefit to a patient (**FDA Guidance 2011**). Therefore, OS will be used to meet the co-primary objectives.

A secondary endpoint of OS will be used to assess the efficacy of the MEDI4736+tremelimumab vs SoC in the PD-L1 negative subgroup. Additional secondary efficacy endpoints of PFS, ORR, DoR, disease control rate (DCR), proportion of patients alive and progression free at 6 and 12 months from randomization (APF6 and APF12, respectively), and proportion of patients alive at 12, 18, and 24 months from randomization (OS12, OS18, and OS24, respectively) are being examined to further evaluate the antitumor effect of MEDI4736 + tremelimumab combination therapy versus SoC as well as MEDI4736 monotherapy versus SoC. PFS, ORR, DoR, DCR, APF6, and APF12 will be assessed using the site Investigator's assessments according to RECIST 1.1.

The secondary health-related quality of life (HRQoL) 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 [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.

[redacted]

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 which indicate that of 46 patients with available disease assessments, 4 PRs by RECIST 1.1 were achieved with 2 additional patients showing possible PR using immune-related response criteria. Further, this activity appears despite HPV status, with the majority of response in patients with PD-L1-positive tumors. Of the patients with PD-L1–negative tumors enrolled who have disease response data available at this time, 1 responder was present, but several had achieved some level of disease control.

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 also been 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 who 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).

Based on activity noted in lung cancer and melanoma, however, further exploration in SCCHN is warranted; tremelimumab monotherapy in the treatment of SCCHN will be

evaluated for the first time in Study D4193C00003. Additional data are provided in the tremelimumab IB. Tremelimumab is also being investigated in a Phase I trial in combination with cetuximab in previously untreated patients with SCCHN and is being studied as a single agent in a Phase I/II study in another HPV-driven disease, cervical cancer.

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 version 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 administered once every 3 weeks for 4 and 8 doses, respectively, followed by nivolumab or ipilimumab alone 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 Overall risks

Monoclonal antibodies directed against immune checkpoint proteins, such as PD-L1 as well as those directed against PD-1 or CTLA-4, aim to boost endogenous immune responses directed against tumor cells. By stimulating the immune system however, there is the potential for adverse effects on other tissues.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. These immune-mediated effects can occur in nearly any organ system and are most commonly seen as gastrointestinal (GI) AEs such as colitis and diarrhea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis and endocrinopathies including hypothyroidism and hyperthyroidism.

1.3.2.2 MEDI4736

Risks with MEDI4736 include, but are not limited to, diarrhea/colitis and intestinal perforation, pneumonitis/ILD, endocrinopathies (hypothyroidism and hyperthyroidism, type I diabetes mellitus, hypophysitis and adrenal insufficiency) hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/pruritus/dermatitis, myocarditis, myositis/polymyositis, other rare or less frequent

inflammatory events including neurotoxicities, infusion-related reactions, hypersensitivity reactions and infections/serious infections.

For information on all identified and potential risks with MEDI4736 please always refer to the current version of the MEDI4736 IB.

In monotherapy clinical studies AEs (all grades) reported very commonly (≥10% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, asthenia, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 9% of patients experienced an AE that resulted in permanent discontinuation of MEDI4736 and approximately 6% of patients experienced an SAE that was considered to be related to MEDI4736 by the study investigator.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (please see Section 6.7.2 and Table 9).

A detailed summary of MEDI4736 monotherapy AE data can be found in the current version of the MEDI4736 IB.

1.3.2.3 Tremelimumab

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

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

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

A detailed summary of tremelimumab monotherapy AE data can be found in the current version of the tremelimumab IB.

1.3.2.4 MEDI4736 + tremelimumab

The safety of MEDI4736 + tremelimumab combination therapy was initially evaluated in the ongoing dose escalation and dose expansion Study 006, in patients with NSCLC, and is being studied in a number of other ongoing clinical trials, in a number of different indications, and has to date shown a manageable safety and tolerability profile.

The types of risks with the combination of MEDI4736 + tremelimumab (based on an equivalent MEDI4736 dose of 20 mg/kg and a tremelimumab dose of 1 mg/kg) are similar to those for MEDI4736 and tremelimumab monotherapy. Emerging data from Study 006, other studies evaluating the combination, and from combinations of other agents in the same class indicate an increased frequency and/or severity of some of these immune-mediated toxicities.

For information on all identified and potential risks with the MEDI4736 + tremelimumab combination please always refer to the current version of the MEDI4736 IB.

In MEDI4736 + tremelimumab combination studies at the dose of MEDI4736 20 mg/kg and tremelimumab 1 mg/kg AEs (all grades) reported very commonly (≥10% of patients) are fatigue, diarrhea, nausea, dyspnea, decreased appetite, pruritus, vomiting, anemia, constipation, cough, abdominal pain, pyrexia, back pain, arthralgia, hypothyroidism, asthenia, edema peripheral, weight decreased, hyponatremia and rash.

Approximately 15% of patients experienced an AE that resulted in permanent discontinuation of study drug and approximately 15% of patients experienced an SAE that was considered to be related to MEDI4736 and tremelimumab by the study investigator.

A detailed summary of MEDI4736 + tremelimumab combination AE data can be found in the current version of the MEDI4736 IB.

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 only one palliative systemic treatment regimen for recurrent or metastatic disease that must have contained a platinum agent or who have progressed within 6 months of the last dose of platinum given as part of multimodality therapy of curative intent. 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 early signs of clinical activity, and data from competitors indicate that the combination may act synergistically (**Wolchok et al 2013**). 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, ie, MEDI4736, MEDI4736 + tremelimumab, and SoC).

The toxicity profile of the combination MEDI4736 + tremelimumab includes the frequently reported AEs, regardless of causality, of fatigue, colitis, diarrhea, AST or ALT increases, amylase and lipase increases, rash, 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 AEs assessed by the Investigator as treatment related 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 events assessed by the Investigator as treatment related in 53%. The most frequent of these Grade 3 or 4 events assessed by the Investigator as treatment related include increased lipase (in 13% of patients), AST (in 13%), and ALT levels (in 11%). SAEs assessed by the Investigator as treatment related were noted in 49% of patients. Frequent Grade 3 or 4 selected AEs assessed by the Investigator as treatment related for 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, the activity seen with MEDI4736 in this tumor type, and the strength of the scientific hypotheses under evaluation, the MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy 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 quality of life (QoL) and potentially extending survival. Further, preclinical and clinical evidence indicate that monotherapy anti-PD-L1 agents and the combination of PD-1/PD-L1 and CTLA-4 targeting agents may provide antitumor activity, regardless of PD-L1 expression levels, with additional synergy from the combination (**Wolchok et al 2013**). Therefore, the investigation of the potential therapeutic efficacy of MEDI4736 alone and in combination with tremelimumab in patients with recurrent/metastatic disease with PD-L1-positive and -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 III study to determine the efficacy and safety of MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy versus SoC therapy in the treatment of patients with recurrent or metastatic SCCHN who have progressed during or after only one palliative systemic treatment regimen for recurrent or metastatic disease that must have contained a platinum agent or who have progressed within 6 months of the last dose of platinum given as part of multimodality therapy of curative intent (ie, those who are refractory to prior platinum therapy). A schematic diagram of the overall study design is shown in Figure 1, a flow chart for the IMT treatment groups (MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy) is presented in and a flow chart for the SoC group is presented in Figure 2 and a flow chart for the SoC group is presented in Figure 3.

Patients will undergo a screening assessment on their tumor tissue sample to determine PD-L1 and HPV status (for patients with oropharyngeal cancer only). PD-L1 status will be defined by an IHC assay being developed by Ventana in which 25% or greater PD-L1-expression in tumoral tissue is considered positive and anything less than 25% is considered negative for PD-L1 expression (referred to hereafter as patients with PD-L1-positive or -negative tumors, respectively). If the patient's PD-L1 status has already been assessed using the Ventana PD-L1 SP263 IHC assay as a part of the screening process for another AstraZeneca/MedImmune study, this test result can be used for the determination of eligibility. The specified expression cut-off level will be used for the purpose of stratification and therefore included in the stratified log rank tests for OS. However, the actual cut-off level for the subgroup analyses of OS by PD-L1 status and the cut-off used as the basis for determining the PD-L1-negative subgroup in the MTP may be different and will be determined from emerging data outside this trial. Such a cut-off will be detailed in the statistical analysis plan prior to database lock.

HPV status will be assessed according to local standards.

Patients will be randomized in a stratified manner according to prognostic factors: PD-L1 status, tumor location/HPV status, and smoking status. HPV status and smoking status are known prognostic markers for patients with head and neck cancer; patients who have HPV-positive tumors fare better than those with HPV-negative tumors, and patients who don't smoke fare better than those who continue to smoke after their cancer diagnosis (**Gritz et al 1993**, **Rischin et al 2010**). Patients will be randomized in a 1:1:1 ratio to receive treatment with MEDI4736 monotherapy, MEDI4736 + tremelimumab combination therapy, or SoC therapy.

Patients in the MEDI4736 monotherapy treatment group will receive 10 mg/kg MEDI4736 via intravenous (IV) infusion q2w until PD.

Patients in the MEDI4736 + tremelimumab treatment group will receive 20 mg/kg MEDI4736 via IV infusion q4w for up to 4 months and tremelimumab 1 mg/kg via IV infusion q4w for 4 months. Upon completion of 4 months of combination therapy, patients in the MEDI4736 +

tremelimumab arm will then continue dosing with MEDI4736 monotherapy at 10 mg/kg q2w beginning 4 weeks after the last dose is administered until PD.

Patients in the SoC treatment group will receive monotherapy with 1 of the following therapies at the Investigator's discretion until PD: cetuximab, a taxane (ie, docetaxel or paclitaxel), methotrexate, or a fluoropyrimidine (ie, 5-FU, TS-1, or capecitabine).

Patients randomized to 1 of the IMT treatment groups will receive treatment with either MEDI4736 or MEDI4736 + tremelimumab beginning on Day 0 until objective disease progression according to RECIST 1.1 (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). Patients with PD who, in the Investigator's opinion, continue to receive benefit from their assigned IMT treatment and who meet the criteria for treatment in the setting of PD may continue to receive their assigned IMT treatment with the Sponsor and at the Investigator's discretion. All patients randomized to 1 of the IMT treatment groups require documentation of objective disease progression according to RECIST 1.1. A second scan obtained at a minimum of 4 weeks later to confirm progression is required for treatment management decisions only and only where it is clinically feasible. Disease response assessment should be solely based on RECIST 1.1 with response of PD entered for the first scan that meets progression criteria as outlined by RECIST 1.1. Patients with confirmed progression in the monotherapy arm or in the combination portion of therapy in the MEDI4736 + tremelimumab arm cannot continue therapy if the progression occurred during dosing after objective 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 who the Investigator determines may not continue IMT treatment after PD, will enter follow-up and will be followed up until death (see Table 5). Patients who have discontinued IMT treatment due to toxicity or symptomatic deterioration, those who have no objective disease progression according to RECIST 1.1, or who have commenced subsequent anticancer therapy, will be followed up until death (see Table 4).

Patients randomized to the SoC arm will receive the Investigator-chosen SoC treatment beginning on Day 0 until PD, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. All patients randomized to the SoC treatment group require documentation of objective disease progression according to RECIST 1.1. A second scan obtained at a minimum of 4 weeks later to confirm progression is required in patients where it is clinically feasible and only for treatment management decisions. Disease response assessment should be solely based on RECIST 1.1 with response of PD entered for the first scan that meets progression criteria as outlined by RECIST 1.1. Patients who the Investigator determine may not continue SoC will enter follow-up (see Table 5). Patients who have discontinued SoC treatment due to toxicity or symptomatic deterioration, who have no objective disease progression or who have commenced subsequent

anticancer therapy, will be followed up for study endpoints (objective disease progression according to RECIST 1.1 and death; see Table 4).

Tumor assessments will be performed using computed tomography (CT) or magnetic resonance imaging (MRI) at the times specified in Table 2 and Table 3. RECIST 1.1 measurements as given by the site Investigator's assessments will be used to derive the secondary variables of PFS, ORR, DoR, DCR, APF6, and APF12.

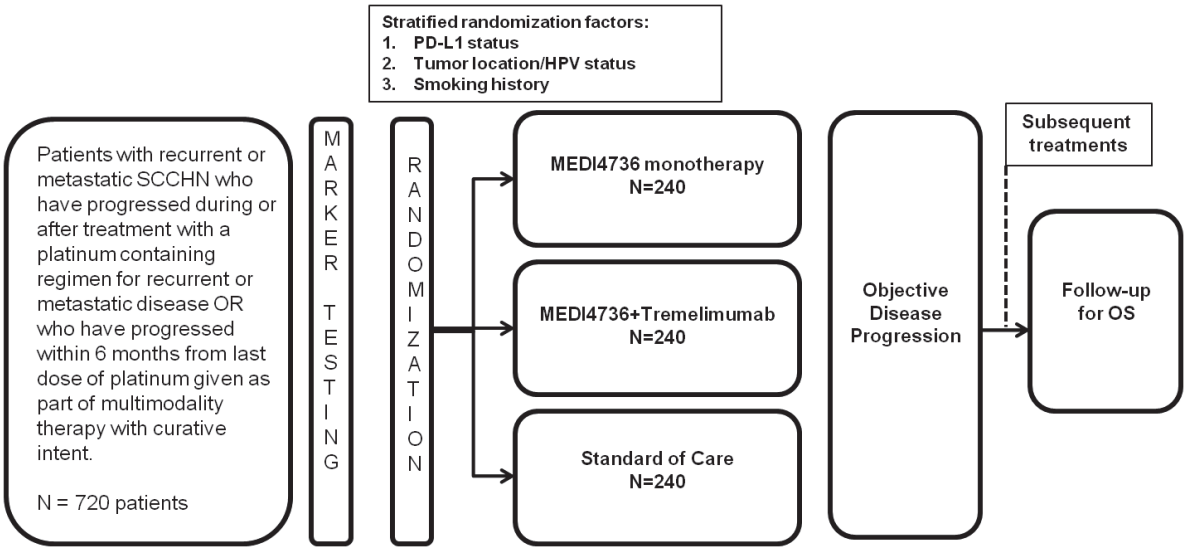
See Section 5.1 and Appendix E for further information regarding RECIST 1.1 tumor assessments in this study.

Patients in the MEDI4736 + tremelimumab combination therapy group who complete the 4 dosing cycles of the MEDI4736 + tremelimumab combination therapy portion of the regimen (with clinical benefit per Investigator's judgement) but subsequently have evidence of PD during the MEDI4736 monotherapy portion of the combination regimen will be given the option to restart treatment with the entire combination regimen. During the retreatment period, the patients 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 in the combination arm would then resume at 10 mg/kg q2w starting 4 weeks after the last combination dose is administered until PD. Patients should have a baseline tumor assessment and complete PRO assessments within 28 days of restarting treatment with their assigned IP; all further scans and PRO assessments should occur every 8 weeks (q8w) (relative to the date of restarting treatment) until study treatment is stopped. 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 the combination therapy regimen. For retreatment patients, all assessments, including screening procedures, will be required using the original schedule of procedures unless otherwise indicated in Section 4, (PD-L1 re-testing is optional).

Imaging and procedures performed before signing the informed consent form (ICF) may be used for screening purposes if the patient consents. Patients with objective disease progression according to RECIST 1.1 in the monotherapy arms or in the combination portion of therapy in the MEDI4736 + tremelimumab arm cannot obtain retreatment if the progression occurred during dosing after objective 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).

This study will screen approximately 1200 patients to identify 720 patients suitable for enrollment (ie, who fulfill the eligibility criteria) and randomization.

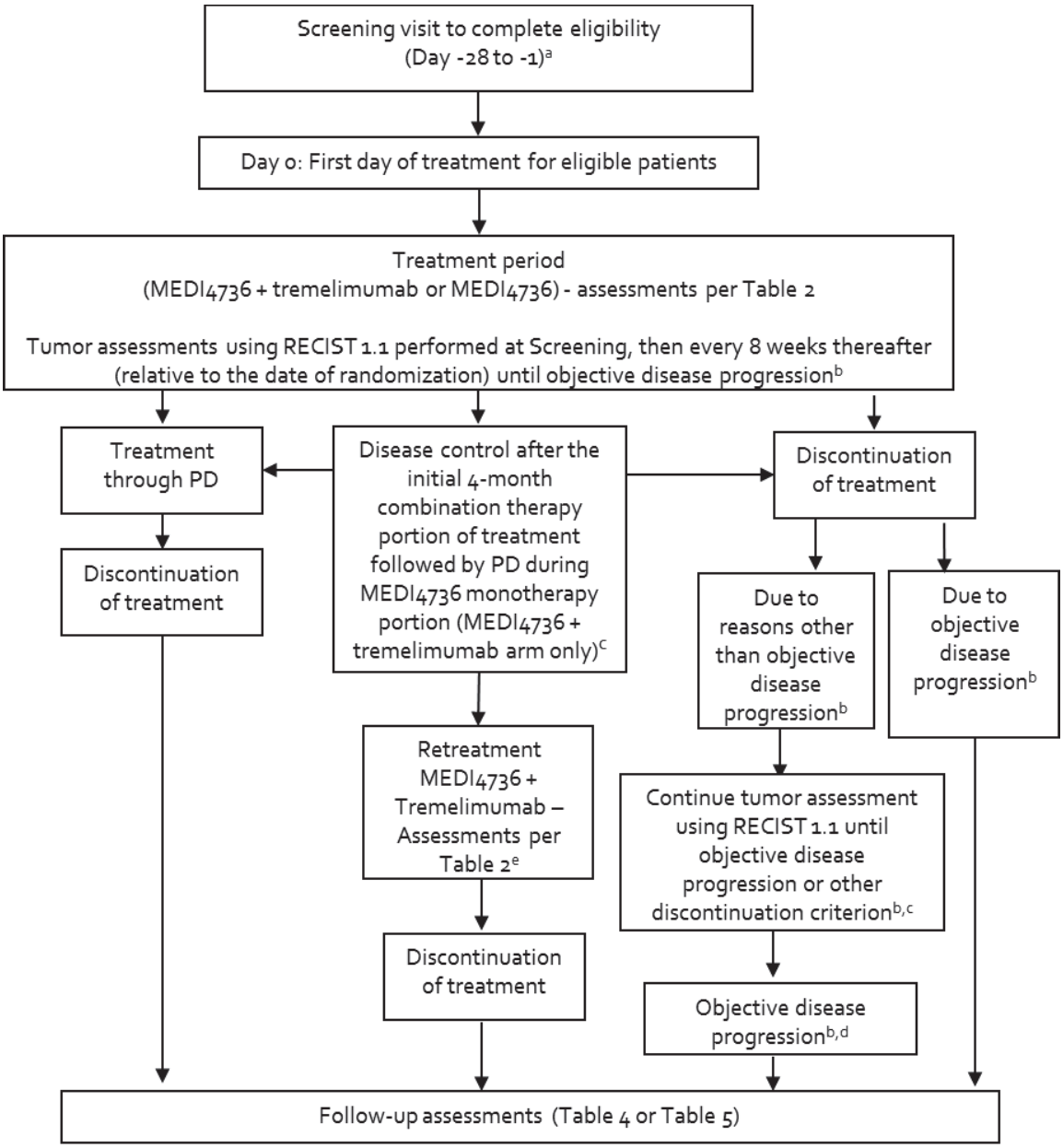
Figure 1 Overall study design



Note: For all Standard of Care therapies, a particular treatment (cetuximab, taxane, methotrexate, or fluoropyrimidine-based regimen) will not be used in patients who have previously received that treatment for recurrent/metastatic disease or who have experienced recurrence or progression of disease within 6 months of prior multimodal therapy using that particular treatment.

HPV human papillomavirus; PD-L1 programmed cell death ligand 1; OS overall survival; SCCHN Squamous Cell Carcinoma of the Head and Neck.

Figure 2 Study flow chart for MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy groups



[a] Screening assessments may be performed over multiple visits. Imaging and procedures performed before signing the ICF may be used for screening purposes if the patient consents to their use. However, randomization must occur within 28 days of all procedures (with the exception of tumor biopsy [if required] and PD-L1 testing) used for screening purposes. If the patient's PD-L1 status has already been assessed using the Ventana PD-L1 SP263 IHC assay as a part of the screening process for another AstraZeneca/MedImmune study, this test result can be used for the determination of eligibility.

[b] A confirmatory scan is required following the initial demonstration of PD, if clinically feasible. A second scan obtained at a minimum of 4 weeks later to confirm progression is required for treatment management decisions only and only where it is clinically feasible. Disease response assessment should be solely based on RECIST 1.1 with

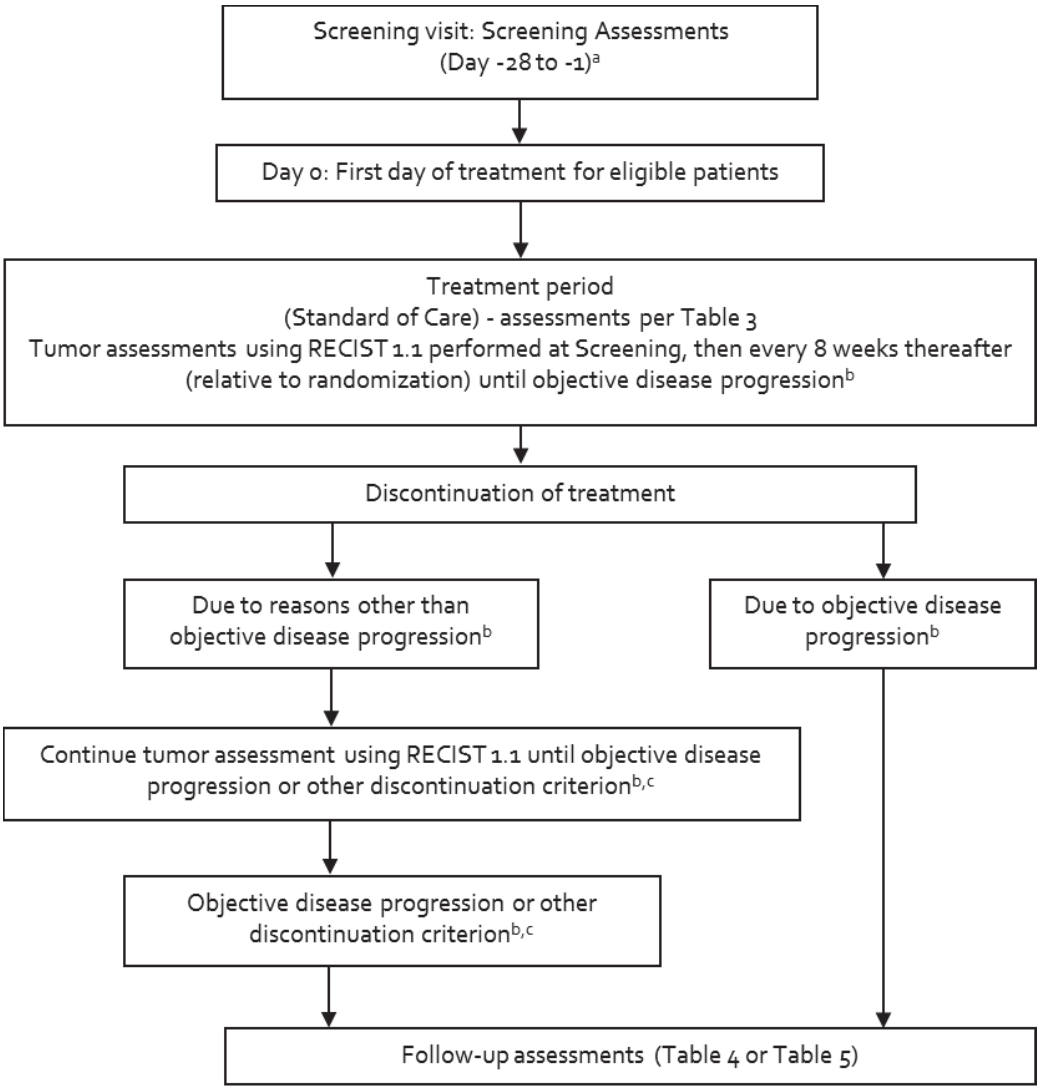
response of PD entered for the first scan that meets progression criteria as outlined by RECIST 1.1. Administration of IMT treatment will continue between the initial assessment of progression and confirmation for progression. Patients in the IMT treatment groups with confirmed PD who continue to receive study treatment at the discretion of the Investigator (following consultation with the Sponsor) will continue to follow the assessments in Table 2 until treatment is discontinued. This will not be considered retreatment but will be considered a part of the initial 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 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 assigned to the MEDI4736 + tremelimumab combination therapy arm who complete the 4 cycles of the combination therapy portion of the treatment regimen that achieve and maintain disease control (ie, CR, PR, or SD) and subsequently progress on monotherapy MEDI4736 may restart their assigned treatment once Before restarting MEDI4736 + tremelimumab combination 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). Patients cannot obtain retreatment if the progression occurred during dosing with the combination portion of therapy after objective 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 of dosing.

[d] Patients with objective disease progression according to RECIST 1.1 who discontinue IP should have scans conducted according to local practice until the patient commences a new treatment (these scans are optional).

[e] Patients who progress on the MEDI4736 + tremelimumab arm may be eligible for retreatment if they progress during the monotherapy portion of dosing.CR Complete response; 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.

Figure 3 Study flow chart for Standard of Care group



[a] Screening assessments may be performed over multiple visits. Imaging and procedures performed before signing the ICF may be used for screening purposes if the patient consents to their use. However, randomization must occur within 28 days of all procedures (with the exception of tumor biopsy [if required] and PD-L1 testing) used for screening purposes. If the patient's PD-L1 status has already been assessed using the Ventana PD-L1 SP263 IHC assay as a part of the screening process for another AstraZeneca/MedImmune study, this test result can be used for the determination of eligibility.

[b] A confirmatory scan is required if clinically feasible following the initial demonstration of PD. A second scan obtained at a minimum of 4 weeks later to confirm progression is required for treatment management decisions only and only where it is clinically feasible. This 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 if clinically feasible. For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may

continue until the next scheduled assessment. Disease response assessment should be solely based on RECIST 1.1 with response of PD entered for the first scan that meets progression criteria as outlined by RECIST 1.1.
In the SoC group, it is at the Investigator's discretion whether or not a patient with uncertain PD continues treatment until PD is confirmed; however, a scan with objective disease progression according to RECIST 1.1 is required for all patients in the SoC group, even if a subsequent treatment is started.

[c] Patients with objective disease progression according to RECIST 1.1 who discontinue SoC treatment should have scans conducted according to local practice until the patient commences a new treatment (these scans are optional).

2. STUDY OBJECTIVES

2.1 Primary objective

Co-primary Objectives:	Outcome Measures:
• To assess the efficacy of MEDI4736 + tremelimumab combination therapy versus SoC in terms of OS	OS in all patients, regardless of PD-L1 status
• To assess the efficacy of MEDI4736 monotherapy versus SoC in terms of OS	OS in all patients, regardless of PD-L1 status

OS Overall survival; PD-L1 programmed cell death ligand 1; SoC Standard of Care.

2.2 Secondary objectives

Secondary Objectives:	Outcome Measures:
To further assess the efficacy of MEDI4736 + tremelimumab combination therapy versus SoC in terms of OS	OS in PD-L1-negative patients
To assess the efficacy of MEDI4736 monotherapy versus SoC in terms of OS	OS in PD-L1-positive patients
To further assess the efficacy of MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy versus SoC in terms of PFS, ORR, DoR, DCR, APF6, APF12, OS12, OS18, and OS24	PFS, ORR, DoR, DCR, APF6, and APF12 using the site Investigator's assessments according to RECIST 1.1 OS12, OS18, and OS24
To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to MEDI4736 monotherapy in terms of PFS, ORR, and OS	PFS and ORR in PD-L1–negative patients using the site Investigator's assessments according to RECIST 1.1 OS in PD-L1–negative patients
To explore symptoms and HRQoL in patients treated with MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy versus SoC using the EORTC QLQ-C30 v3 and the H&N35 module	EORTC QLQ-C30: global health QoL, functioning (physical), and symptoms (fatigue) EORTC QLQ-H&N35: symptoms (pain, swallowing) Changes in World Health Organization/Eastern Cooperative Oncology Group performance status

APF6 Proportion of patients alive and progression free at 6 months from randomization; APF12 Proportion of patients alive and progression free at 12 months from randomization; DCR Disease control rate; DoR Duration of response; EORTC European Organisation for Research and Treatment of Cancer; QLQ-C30 v3 30-item core quality of life questionnaire, version 3; H&N35 35-item head and neck quality of life questionnaire; HRQoL Health-related quality of life; OS12 Overall survival at 12 months; OS18 Overall survival at 18 months; OS24 Overall survival at 24 months;

PD-L1 programmed cell death ligand 1; PFS Progression-free survival; QoL Quality of life; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version; SoC Standard of Care.

2.3 Safety objective

Safety Objective:	Outcome Measures:
To assess the safety and tolerability profile of MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy compared to SoC	AEs, physical examinations, laboratory findings, and vital signs

AE adverse event; SoC Standard of Care

[redacted]

[redacted]

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. (For patients aged <20 years and enrolling in Japan, a written informed consent should be obtained from the patient and his or her legally acceptable representative.)

3. Histologically or cytologically 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 only one palliative systemic treatment regimen for recurrent or metastatic disease that must have contained a platinum agent **OR** progression within 6 months of the last dose of platinum given as part of multimodality therapy with curative intent.

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 fresh 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-positive or -negative SCCHN by the Ventana PD-L1 SP263 IHC 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 Ventana PD-L1 SP263 IHC assay as a part of the screening process for another AstraZeneca/MedImmune study, this test result can be used for the determination of eligibility, provided the PD-L1 status was obtained on tissue within the last 3 years.

   - Note: A positive PD-L1 sample is measured using a defined cut-off based on ≥25% of tumor cells with membrane staining of any intensity for PD-L1. A negative PD-L1 sample is defined as <25% of tumor cells with membrane staining for PD-L1.

7. WHO/Eastern Cooperative Oncology Group (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 a 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 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 below. Patients requiring routine transfusions should be discussed with the Sponsor.

    – Hemoglobin ≥9 g/dL

    – Absolute neutrophil count ≥1500/mm^3

    – Platelet count ≥100000/mm^3

- Serum bilirubin ≤1.5 × the 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 or 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 and have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution, had radiation-induced oophorectomy with last menses >1 year ago, or 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 progressive disease

For all patients who are treated through progression (including patients with confirmed PD who continue their assigned IMT [MEDI4736 or MEDI4736 + tremelimumab] at the Investigator's discretion and patients receiving IMT who achieve disease control [ie, CR, PR, or SD] and restart treatment upon evidence of PD during follow-up), 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 IMT treatment upon evidence of PD during follow-up, the patient also must not have received an intervening cancer therapy after IMT treatment discontinuation. Patients who discontinue treatment in 1 treatment group may not switch to treatment in a different group.

IP should be discontinued if there is confirmed PD while receiving IMT following a previous response (CR or PR) to IP 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).

Additional details pertaining to retreatment are presented in Section **7.2.**

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 or cytologically confirmed squamous cell carcinoma of any other primary anatomic location in the head and neck not specified in the inclusion criteria, patients with SCCHN of unknown primary, and non-squamous histologies (eg, nasopharynx or salivary gland)

2. Received more than 1 palliative systemic 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. Receipt of any investigational anticancer therapy within 28 days or 5 half-lives, whichever is longer, prior to the first dose of study treatment. 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.

5. 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.

6. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, lymphopenia, 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 a 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.

7. 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)

8. History of allogeneic organ transplantation

9. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel 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 any skin condition not requiring systemic treatment

10. 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 IP, or compromise the ability of the patient to give written informed consent

11. 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

12. Patients with a 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.

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

14. History of active primary immunodeficiency

15. Active 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 IP.

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 after the last dose of IP for those randomized to the monotherapy MEDI4736 arm and 180 days after the last dose of IP for those randomized to the MEDI4736 + tremelimumab arm

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

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

21. For patients randomized to the SoC arm, any contraindication to a specific standard of care agent as specified by the accompanying package insert or Summary of Product Characteristics will require patients to receive an alternative SoC agent specified in the protocol.

22. Prior randomization or treatment in a previous MEDI4736 and/or tremelimumab clinical study, regardless of treatment arm assignment

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

[redacted]

3.3 Patient enrolment and randomization

Investigators should keep a record (ie, the patient screening log) of patients who entered screening (including assessment of PD-L1).

At Screening (Days -28 to -1), the Investigators or suitably trained delegate will:

1. Obtain signed informed consent before any study-specific procedures are performed. Procedures required for screening that were performed prior to signing informed consent can be used for screening if the patient consents. All screening procedures (with the exception of tumor biopsy [if required] and PD-L1 testing) must be performed within 28 days prior to randomization. For patients with a single target lesion that is subsequently used for a screening PD-L1 biopsy, allow approximately 2 weeks before imaging scans are obtained for baseline disease assessment.

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

3. 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 600 in each center and go up sequentially (eg, at Center 01, patients will be assigned enrollment numbers E0101600, E0101601, etc). This number is the patient's unique identifier and is used to identify the patient on the electronic case report forms (eCRFs).

4. For any patient who does not have obvious exclusion parameters, obtain tumor sample and send for PD-L1 expression and HPV status (if needed, for patients with oropharyngeal cancer only) evaluation. The PD-L1 result must be available prior to randomization. All other screening activities must be completed within the 28-day screening window prior to randomization.

5. Determine patient eligibility (see Sections **3.1** And **3.2**).

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

5. Define the SoC treatment (based on the most appropriate option for the patient) that the patient would receive if randomized to the SoC group (this group will be defined prior to randomization of the patient).

6. Call the IVRS/IWRS to assign the eligible patient a unique patient identification number. Patient identification numbers will start at 600 and will be assigned strictly sequentially by IVRS/IWRS as patients are eligible for entry into the study. The system will randomize the eligible patient to 1 of the 3 treatment groups.

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, which should be within 72 hours of randomization. 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.

3.4 Procedures for handling incorrectly enrolled or randomized 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.

When 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 at least 1 highly effective method of contraception (Table 1) from the time of screening and must agree to continue using such precautions for 90 days after the last dose of IP for those randomized to the monotherapy MEDI4736 arm and 180 days after the last dose of IP for those randomized to the MEDI4736 +

tremelimumab arm); 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. Male partners of a female patient must use a male condom plus spermicide throughout this period. Female patients should refrain from breastfeeding throughout this period.

- 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).

- Highly effective methods of contraception are described in Table 1. A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette (desogestrel) which is considered highly effective]; and triphasic combined oral contraceptive pills).

2. Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from screening through 90 days after receipt of the final dose of IP for those randomized to the MEDI4736 arm or 180 days for those randomized to the MEDI4736 + tremelimumab arm. Male patients should refrain from sperm donation throughout this period. Female partners of a male patient must use a highly effective method of contraception throughout this period.

3. **SoC therapy:** Follow the local prescribing information relating to contraception, the time limits for such precautions, and any additional restrictions for agents in the SoC group.

4. **All patients:** 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 1 Highly effective methods of contraception (<1% failure rate)

Barrier/Intrauterine methods	Hormonal Methods
Copper T intrauterine device	Etonogestrel implants: eg, Implanon® or Norplant®
Levonorgesterel-releasing intrauterine system (eg, Mirena®)[a]	Intravaginal device: eg, ethinylestradiol and etonogestrel
	Medroxyprogesterone injection: eg, Depo-Provera
	Normal and low-dose combined oral contraceptive pill
	Norelgestromin/ethinylestradiol transdermal system
	Cerazette (desogestrel)

[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, MEDI4736 + tremelimumab combination, or SoC) 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 or clinical disease progression, 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). All study drugs should be returned by the patient. 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 4). Patients permanently discontinued due to objective disease progression according to RECIST 1.1will 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 2 months as an alternative.

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 randomized. These patients should have the reason for study withdrawal recorded as “Incorrect Enrollment” (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (ie, not randomized patients). Patients can be rescreened a single time, but they cannot 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 participation in the study drug administration will not receive any further IP, but will continue with post-withdrawal study assessments and follow-up for survival until patient death, withdrawal of consent for ongoing follow-up, or end of the study, whichever comes first. If the patient has expressly withdrawn their consent for study assessments or survival follow-up, this should be clearly noted in the source documentation. Note that the patient may be offered additional tests or tapering of treatment to discontinue the IP 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. The patient will return electronic PRO devices, if applicable.

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.

3.10.2.1 Survival status for withdrawn consent and lost to follow-up patients

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.

In order to support key endpoints of PFS and OS analyses, the survival status of all patients in the full analysis (FAS) and the safety analysis sets (SAS) should be re-checked, this includes those patients who withdrew consent or are classified as "lost to follow-up."

- Lost to follow-up – site personnel should check hospital records, the patient's current physician, and a publicly available death registry (if available) to obtain a current survival status. (The applicable case report form [CRF] modules will be updated.)

- In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status. (The applicable CRF modules will be updated.)

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of the Sponsor, 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 or for superiority based on interim OS analysis conducted by the Independent Data Monitoring Committee (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 the Screening and Treatment periods in this study are presented for the MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy groups in Table 2 and for the SoC therapy group in Table 3. The procedures for the follow-up period are presented in Table 4 and Table 5.

Imaging and procedures performed before signing the ICF may be used for screening purposes if the patient consents. All screening procedures (with the exception of tumor biopsy [if required] and PD-L1 testing) must be performed within 28 days prior to randomization. Dosing must occur within 72 hours of randomization. Screening procedures required for Cycle 1, Day 0 need not be repeated if they were performed within 3 days of Cycle 1, Day 0.

For re-treatment patients, the following assessments do not need to be completed: HPV, [redacted] (PD-L1 testing at time of retreatment is optional).

All visits should be conducted based on the schedules provided in Table 2 through Table 5, below, unless otherwise indicated.

- For patients on the immunotherapy arms, if dosing must be delayed due to a treatment-related toxicity, the Toxicity Management Guidelines should be followed (Table 9). If dosing must be delayed for reasons other than treatment-related toxicity, dosing should occur as soon as clinically feasible.

- For patients on the standard of care arm, dosing may be delayed due to treatment-related toxicity and subsequently resumed per the local standard clinical practice. If dosing must be delayed for reasons other than treatment-related toxicity, dosing should occur as soon as clinically feasible.

Tumor efficacy (RECIST) assessments dates are not affected by dose delays and remain as originally scheduled, as they are based on the date of randomization (not the date of treatment). All other scheduled assessments must be performed relative to the day of dosing (even if dosing is delayed); all laboratory procedures required for dosing should be performed within 3 days prior to dosing.

Table 2 Schedule of assessments for the treatment period for the MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy arms and optional retreatment period for the MEDI4736 + tremelimumab combination therapy arm

	Screening[a]	C1		C2		C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13 until PD
Visit	**Day -28 to -1**	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**
Week		**0[b]**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48, 52, 56, etc**
Informed consent																
Consent: IHC PD-L1 expression[a]	X															
[redacted]	[redacted]															
Informed consent: study procedures[a]	X															
Study procedures																
Physical exam: height	X															
Physical exam and weight (not including height)[c]	X	X	Conduct at each drug infusion or administration and/or visit, and as clinically indicated													
Vital signs: BP, pulse, and oxygen saturation[d]	X	X	Conduct at each drug infusion or administration and/or visit, and as clinically indicated													
Vital signs: body temperature, respiratory rate[e]	X	X	Conduct at each drug infusion or administration and/or visit, and as clinically indicated													
Concomitant medications	X	X	Conduct at each drug infusion or administration and/or visit, and as clinically indicated													
HPV status[a]	X															
Demography, disease status, and time to recurrence from multimodality therapy	X															
Medical/surgical history	X															
Tobacco use and/or smoking	X															
Eligibility criteria	X															
Laboratory assessments																
Clinical chemistry[e]	X	X	Conduct at each drug infusion or administration and/or visit, and as clinically indicated													
Hematology[e]	X	X	Conduct at each drug infusion or administration and/or visit, and as clinically indicated													
TSH (and reflex free T_3 or free T_4)[f]	X	X		X		X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	Conduct as clinically indicated														
Hepatitis B and C and HIV	X															

	Screening[a]	C1		C2		C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13 until PD
Visit	**Day -28 to -1**	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**
Week		**0[b]**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48, 52, 56, etc**
Pregnancy test	X	X		X		X	X	X	X	X	X	X	X	X	X	X
Other laboratory assessments and assays																
[redacted]		[redacted]					[redacted]			[redacted]						
IHC PD-L1 expression (tumor tissue)[h]	X															
[redacted]		[redacted]														
[redacted]		[redacted]														
[redacted]		[redacted]														
Tumor biopsy[a]	X															
Tumor evaluation (CT or MRI) (RECIST 1.1)[i,k,l]	X					X		X		X		X		X		X
[redacted]	[redacted]															
[redacted]																
[redacted]		[redacted]					[redacted]			[redacted]						
[redacted]		[redacted]					[redacted]									
Other safety examinations																
ECG[n]	X	Conduct as clinically indicated														
Monitoring																
WHO/ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE assessment		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
IP administration																
MEDI4736 monotherapy[o]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MEDI4736 (in combination with tremelimumab)[p, k]		X		X		X	X	X	X	X	X	X	X	X	X	X

	Screening[a]	C1		C2		C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13 until PD
Visit	**Day -28 to -1**	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**
Week		**0[b]**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48, 52, 56, etc**
Tremelimumab (in combination with MEDI4736)		X		X		X	X									
PRO assessments																
EORTC QLQ-C30	X	X		X		X		X		X		X		X		X[r]
EORTC QLQ-H&N35	X	X		X		X	X	X	X	X	X	X	X	X	X	X[r]
[redacted]	■	■		■		■	■	■	■	■	■	■	■	■	■	■
[redacted]	■			■		■		■		■		■		■		■
[redacted]				■				■								■
[redacted]																
[redacted]	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■

[a] Imaging and procedures performed before signing informed consent form may be used for screening purposes if the patient consents. HPV status only for patients with oropharyngeal cancer. All screening procedures (except tumor biopsy [if required] and PD-L1 testing) must be performed within the 28-day screening period prior to randomization.

[b] Cycle 1, Day 0 procedures need not be repeated if the same procedures were performed for screening purposes within 3 days prior to Cycle 1, Day 0.

[c] Pre-dose and as clinically indicated before every infusion or administration.

[d] Pre-dose, during treatment, and post-dose as per Section 5.2.4

[e] Pre-dose prior to each infusion. Results for urea and electrolytes, full blood count, and liver function tests must be available before commencing an infusion. Bicarbonate (where available, at baseline only), creatinine clearance, gamma-glutamyltransferase, and magnesium testing are to be performed at Screening, on Day 0 (unless screening laboratory assessments are performed within 3 days prior to Day 0), and if clinically indicated. Activated partial thromboplastin time testing is to be conducted at Screening only, unless clinically indicated. All other clinical chemistry assessments (including serum creatinine) as detailed in Table 6 are conducted at each drug infusion or administration and/or visit, and as clinically indicated.

[f] Free T_3 or free T_4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

[g] In the combination arm, samples do not need to be collected or tested for anti-tremelimumab antibodies after Week 12.

[h] Based on a newly acquired tumor sample (preferred) or archival tissue (≤3 years old) as per Section **3.1**.

[i] These assessments will be conducted for the first 100 patients enrolled in each treatment group only.

[j] 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. Follow-up assessments will be performed q8w (relative to the date of randomization) until objective disease progression according to RECIST 1.1. The confirmatory scans should preferably be performed at the next scheduled visit (relative to the date of randomization) 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 assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits (relative to the date of randomization). All confirmatory scans should be recorded in the database. 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 fulfills 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.

[k] For patients in the MEDI4736 + tremelimumab combination therapy arm who go on to retreatment, the same assessments should be done as in the first treatment period with the exception of the [redacted] HPV assessments, which do not need to be collected for retreatment. 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 + 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.

[l] Patients with objective disease progression according to RECIST 1.1 who continue to receive their assigned IMT treatment at the discretion of the Investigator can continue to receive treatment until a criterion in Section 3.9 is met. Patients will have scans q8w while on treatment (relative to the date of randomization) 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 (CR or PR) to IP.

[m] Week 0 sample will be collected within 10 minutes of end of infusion of each agent; Week 12 samples will be collected up to 60 minutes pre-dose and within 10 minutes of end of infusion of each agent; Week 24 samples collected up to 60 minutes prior to MEDI4736 dose only. In the combination arm, tremelimumab samples do not need to be collected after Week 12.

[n] See Section **5.2.3**.

[o] Administered q2w.

[p] Administered q4w for 4 doses and then q2w beginning 4 weeks after last combination dose. Assessments scheduled at Week 2 and Week 6 (Cycle 1, Visit 1 and Cycle 2, Visit 3) will not be performed in patients assigned to the MEDI4736 + tremelimumab combination therapy arm.

[redacted]

[r] Patient Reported Outcomes will occur at Week 48, but will not occur at subsequent treatment visits. Upon treatment discontinuation, the patient will follow the schedule outlined in Table 4 and Table 5

Note: All assessments on treatment days are to be performed prior to infusion, unless otherwise indicated.

[redacted]; AE Adverse event; BP Blood pressure; C Cycle; CR Complete response; CT Computed tomography; DNA deoxyribonucleic acid; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; [redacted] Exam Examination; HIV Human immunodeficiency virus; HPV Human papillomavirus; IHC Immunohistochemistry; IMT immunomodulatory therapy; IP Investigational product; [redacted] MRI Magnetic resonance imaging: [redacted] PD Progressive disease; [redacted]; PR Partial response; PRO patient reported outcomes; q2w Every 2 weeks; q4w Every 4 weeks; q8w Every 8 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;TSH Thyroid-stimulating hormone; T_4 Thyroxine; T_3 Triiodothyronine; V Visit; WHO World Health Organization

Table 3 Schedule of assessments for Standard of Care therapy

	Screening[a]	C1		C2		C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13 until PD
Visit	Day -28 to -1	V0[b]	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14
Week		0	2	4	6	8	12	16	20	24	28	32	36	40	44	48, 52, 56, etc
Informed consent																
Consent: IHC PD-L1 expression[a]	X															
[redacted]	[redacted]															
Informed consent: study procedures[a]	X															
Study procedures																
Physical exam: height	X															
Physical exam and weight (not including height)[c]	X	X	Conduct at each drug infusion or administration and/or visit, and as clinically indicated													
Vital signs: BP, pulse, and oxygen saturation[c]	X	X	Conduct at each drug infusion or administration and/or visit, and as clinically indicated													
Vital signs: body temperature, respiratory rate[c]	X	X	Conduct at each drug infusion or administration and/or visit, and as clinically indicated													
Concomitant medications	X	X	Conduct at each drug infusion or administration and/or visit, and as clinically indicated													
HPV status[a]	X															
Demography, disease status, and time to recurrence from multimodality therapy	X															
Medical/surgical history	X															
Tobacco use and/or smoking	X															
Eligibility criteria	X															
Laboratory assessments																
Clinical chemistry	X	X[c,d]	Conduct at each drug infusion or administration and/or visit, and as clinically indicated[c]													
Hematology	X	X[c,d]	Conduct at each drug infusion or administration and/or visit, and as clinically indicated[c]													
TSH (and reflex free T_3 or free T_4)[e]	X															

	Screening[a]	C1		C2		C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13 until PD
Visit	Day -28 to -1	**V0[b]**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**
Week		**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48, 52, 56, etc**
Urinalysis	X															
Hepatitis B and C and HIV	X															
Pregnancy test	X															
Other laboratory assessments and assays																
IHC PD-L1 expression (tumor tissue)[g]	X															
[redacted]		[redacted]														
[redacted]		[redacted]														
[redacted]		[redacted]														
Tumor biopsy[a]	X															
Tumor evaluation (CT or MRI) (RECIST 1.1)[h]	X					X		X		X		X		X		X
[redacted]	[redacted]															
Other safety examinations																
ECG[i]	X	As clinically indicated														
Monitoring																
WHO/ECOG performance status	X	X		X		X	X	X	X	X	X	X	X	X	X	X
AE/SAE assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SoC administration[j]																
Cetuximab		X	Administer weekly (4 administrations per 4 week cycle)													
Paclitaxel/docetaxel		X	Administer weekly (4 administrations per 4 week cycle)													
Methotrexate		X	Administer weekly (4 administrations per 4 week cycle)													
5-FU		X	Administer daily for 2 days, then repeat at Day 14 (2 repetitions per 4 week cycle)													
TS-1		X	Administer daily for 28 days, then 14 days off (2 repetitions per 12 weeks)													

	Screening[a]	C1		C2		C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13 until PD
Visit	Day -28 to -1	**V0[b]**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**
Week		**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48, 52, 56, etc**
Capecitabine		X	Administer twice daily for 7 days, then 7 days off (2 repetitions per 4 week cycle)													
PRO assessments																
EORTC QLQ-C30	X	X		X		X		X		X		X		X		X[k]
EORTC QLQ-H&N35	X	X		X		X	X	X	X	X	X	X	X	X	X	X[k]
[redacted]	■	■		■		■	■	■	■	■	■	■	■	■	■	■
[redacted]	■			■		■		■		■		■		■		■
[redacted]				■				■								■

[a] Imaging and procedures performed before signing informed consent form may be used for screening purposes if the patient consents. HPV status only for patients with oropharyngeal cancer. All screening procedures (except tumor biopsy [if required] and PD-L1 testing) must be performed within the 28-day screening period prior to randomization.

[b] Cycle 1, Day 0 procedures need not be repeated if the same procedures were performed for screening purposes within 3 days prior to Cycle 1, Day 0.

[c] Pre-dose and as clinically indicated before every infusion or administration (cetuximab infusions may require more frequent monitoring as per site specific standards).

[d] For paclitaxel/docetaxel, 5-FU, or methotrexate: Results for urea and electrolytes, full blood count, and liver function tests must be available before commencing an infusion. For capecitabine and TS-1/S1: Results for urea and electrolytes, full blood count, and liver function tests must be available at least every 2 weeks, unless the Investigator at a specific site decides it is not clinically indicated. Under these circumstances, the labs may be drawn at a minimum of every 4 weeks. Bicarbonate (where available, at baseline only), creatinine clearance, gamma glutamyltransferase, magnesium, and activated partial thromboplastin time testing are to be performed at Screening, on Day 0 (unless screening laboratory assessments are performed within 3 days prior to Day 0), and if clinically indicated. All other clinical chemistry assessments as detailed in Table 6 are done every 4 weeks unless otherwise clinically indicated. For cetuximab, magnesium monitoring and subsequent supplementation may occur more frequently as clinically indicated per site specific standards.

[e] Free T_3 or free T_4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

[f] These assessments will be conducted for the first 100 patients enrolled in each treatment group only.

[g] Based on a newly acquired tumor sample (preferred) or archival tissue (≤3 years old) as per Section **3.1**.

[h] 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. Follow-up assessments will be performed q8w (relative to the date of randomization) until objective disease progression per RECIST 1.1. The confirmatory scans should preferably be performed at the next scheduled visit (relative to the date of randomization) and no less than 4 weeks after the initial assessment of CR/PR. Confirmatory scans are required for patients with PD no less than 4 weeks after the initial assessment of PD and prior to start of the next therapy if clinically feasible. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits (relative to the date of randomization). All confirmatory scans should be recorded on the database.

[i] See Section **5.2.3**.

[j] As per product label.

[k] Patient Reported Outcomes will occur at Week 48, but will not occur at subsequent treatment visits. Upon treatment discontinuation, the patient will follow the schedule outlined in Table 4 and Table 5.

Note: All assessments on treatment days are to be performed prior to infusion or administration, unless otherwise indicated.

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; [redacted] IHC Immunohistochemistry; IP Investigational product; [redacted] MRI Magnetic resonance imaging: [redacted] PD Progressive disease; [redacted] PR Partial response; q2w Every 2 weeks; q4w Every 4 weeks; q8w Every 8 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; TSH Thyroid-stimulating hormone; T_4 Thyroxine; T_3 Triiodothyronine; V Visit; WHO World Health Organization

Table 4 Schedule of assessments for patients treated with MEDI4736 monotherapy, MEDI4736 + tremelimumab combination therapy or Standard of Care who have discontinued treatment for reasons other than objective disease progression according to RECIST 1.1 (for example - toxicity reasons)

	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[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]
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 2 months)
Hematology	X	X	X					X
Clinical chemistry	X	X	X					
TSH (and reflex free T_3 or free T_4)[b, c]	X							
[redacted]			[redacted]					
[redacted]			[redacted]					

	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**
EORTC QLQ-C30	For patients in any group who **discontinue their assigned IP for reasons other than disease progression (for example, due to toxicity or symptomatic deterioration)**, all questionnaires [redacted] should be completed relative to the date of **randomization** as follows: q8w up to Week48 (per Table 2 or Table 3), then q12w until confirmed PD.						
EORTC QLQ-H&N 35							
[redacted]							
[redacted]							
[redacted]							
Tumor assessment (CT or MRI)[d]	For patients in any group who **discontinue their assigned IP for reasons other than disease progression (for example, due to toxicity or symptomatic deterioration)**, tumor assessments should be performed q8w relative to the date of **randomization** until treatment discontinuation. Please refer to Table 2 or Table 3 for timings of confirmatory scans. Upon objective disease progression according to RECIST 1.1, scans should be conducted according to local standard clinical practice until a new treatment is started (these scans are optional).						

[a] WHO performance status should also be collected at other site visits that the patient attends, if appropriate site staff are available to collect such information. In addition, WHO performance status should be provided when information on subsequent anticancer therapy is provided, where possible.

[redacted]

[c] Free T_3 or free T_4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

[d] 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). Additional anatomy should be imaged based on signs and symptoms of individual patients.

[redacted]; AE Adverse event; CT Computed tomography; ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; Exam Examination; HPV Human papillomavirus; IHC Immunohistochemistry; IMT Immunomodulatory therapy; IP Investigational product; MRI Magnetic resonance imaging: PD Progressive disease; q8w Every 8 weeks; q12w Every 12 weeks; q2w Every 2 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; TSH Thyroid-stimulating hormone; T_4 Thyroxine; T_3 Triiodothyronine; WHO World Health Organization.

Table 5 Schedule of assessments for patients in any group who have discontinued investigational product due to objective disease progression according to RECIST 1.1

	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	X[a]	X[a]					
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 2 months)
Hematology	X	X	X					
Clinical chemistry	X	X	X					
TSH (and reflex free T_3 or free T_4)[b, c]	X							
[redacted]			[redacted]					
[redacted]			[redacted]					

Evaluation	Time since last dose of IP							
	Day (±3)	Months (±1 week)						12 months and every 6 months (±2 weeks)
	30	2	3	4	6	8	10	
EORTC QLQ-C30	X	X	X					
EORTC H&N35	X	X	X					
[redacted]	[redacted]	[redacted]	[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]					
[redacted]	[redacted]							
Tumor assessment (CT or MRI)	For patients who **continue their assigned IP following objective disease progression according to RECIST 1.1** at the Investigator's discretion (following consultation with the Sponsor), tumor assessments should be performed relative to the date of **randomization** (Table 2 or Table 3) until IP is stopped. For patients who **discontinue their assigned IP following objective disease progression according to RECIST 1.1, scans should be conducted according to local clinical practice** until a new treatment is started (these scans are optional).							

[a] WHO performance status should also be collected at other site visits that the patient attends within 3 months since the last dose of IP, if appropriate site staff are available to collect such information. In addition, WHO performance status should be provided when information on subsequent anticancer therapy is provided, where possible and if within 3 months since the last dose of IP.

[redacted]

[c] Free T_3 or free T_4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

[redacted] AE Adverse event; CT Computed tomography; ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; Exam Examination; H&N35 35-Item head and neck quality of life questionnaire; IHC Immunohistochemistry; IP Investigational product; MRI Magnetic resonance imaging: PD Progressive disease; q8w Every 8 weeks; q12w Every 12 weeks; q2w Every 2 weeks; QLQ-C30 30-Item core quality of life questionnaire; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1; SAE Serious adverse event; TSH Thyroid-stimulating hormone; T_4 Thyroxine; T_3 Triiodothyronine; WHO World Health Organization.

4.1 Enrollment/screening period

All screening and enrollment procedures will be performed according to the assessment schedule in Table 2 and Table 3.

Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations unless otherwise specified. Procedures required for screening that were performed prior to the patient signing informed consent can be used for screening if the patient consents; however, all screening procedures (with the exception of tumor biopsy [if required] and PD-L1 testing) must have occurred within 28 days of randomization. Screening procedures required for Cycle 1, Day 0 need not be repeated if they were performed within 3 days prior to Cycle 1, Day 0. All patients will be required to provide consent to supply a sample of their tumor (archival or fresh biopsy) for entry into this study. This consent is included in the main patient ICF.

All screening/baseline procedures must be performed within 28 days before randomization, unless otherwise specified. Screening/baseline evaluations may be performed over more than 1 visit. Informed consents of study procedures and tumor sample acquisition may be obtained prior to the 28-day screening window in order to permit tumor sample acquisition; results of PD-L1 testing must be available prior to randomization.

If the patient's PD-L1 status has already been assessed using the Ventana PD-L1 SP263 IHC assay as a part of the screening process for another AstraZeneca/MedImmune study, this test result can be used for the determination of eligibility.

HPV status will be assessed according to local standards for patients with oropharyngeal cancer only. If HPV result is not available for an oropharyngeal patient, tissue may be submitted for HPV assessment by the sponsor.

4.2 Treatment period

All procedures to be conducted during the treatment period will be performed according to the assessment schedule (see Table 2 and Table 3).

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 [redacted] to occur at the exact nominal time.

4.3 Follow-up period

All procedures to be conducted during the follow-up period will be performed according to the assessment schedule (see Table 4 and 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.

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.

5.1 Efficacy assessments

RECIST 1.1 criteria will be used to assess patient response to treatment by determining PFS, ORR, DoR, DCR, APF6, and APF12. 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. OS12, OS18, and OS24 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). Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients.

The baseline assessment should be performed no more than 28 days before randomization and ideally as close as possible to the start of the assigned IP. Efficacy for all patients will be assessed by objective tumor assessments q8w (relative to the date of randomization; Table 2 and Table 3) until treatment discontinuation. 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.

Confirmation of progression is primarily required for treatment management decisions. Investigators should enter disease response assessment solely based on RECIST 1.1 criteria.

A confirmatory scan is required following the initial demonstration of PD in patients enrolled in the MEDI4736 and MEDI4736 + tremelimumab arms, if clinically feasible. 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 IMT (MEDI4736 or MEDI4736 + tremelimumab) will continue between the initial assessment of progression and confirmation for progression.

In the SoC group, it is at the Investigator's discretion whether or not a patient with uncertain PD continues treatment until objective disease progression; however, a scan showing evidence of objective progression according to RECIST 1.1 is required for all patients in the SoC group, even if subsequent treatment is started. Confirmation of disease progression in patients enrolled in the SOC arm is requested no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration, if clinically feasible.

Radiographic progression would be considered confirmed if the following criteria are met. **(Note: confirmatory scans are solely for purposes of treatment management decisions. All response assessments and documentation of PD are based on RECIST 1.1 criteria with the assessment of PD recorded on the date of the initial scan that meets PD criteria per RECIST 1.1)**

- ≥20% increase in the sum diameters of target lesions compared with the nadir at 2 consecutive scan timepoints with an absolute increase of 5 mm, *and/or*

- Significant progression (worsening) of non-target lesions at the confirmatory scan timepoint compared with the first timepoint where progression of non-target lesions was identified (Note: new lesions identified at the previous scan timepoint are considered non-target lesions at the confirmatory scan timepoint), *and/or*

- Additional new unequivocal lesions at the confirmatory scan timepoint.

Patients in the immunotherapy arms are permitted to be treated through progression at the Investigator's discretion only if the following criteria are met:

- For patients in the MEDI4736 monotherapy arm: confirmed progression has not occurred after objective 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)

- For patients in the MEDI4736 + tremelimumab arm: confirmed progression has not occurred during the combination dosing portion of treatment after objective 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 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.

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.

Following objective disease progression according to RECIST 1.1, patients should continue to be followed up for survival monthly for 90 days after the last dose of study drug and then every 2 months as outlined in the study plan (Table 5).

An exception is patients with objective disease progression according to RECIST 1.1 who continue to receive IMT at the discretion of the Investigator (after consultation with the Sponsor); these patients will continue to have RECIST 1.1 assessments q8w (relative to the date of randomization per Table 2 and Table 3) until the study drug is discontinued.

Patients with objective disease progression according to RECIST 1.1 who discontinue IP should have scans conducted according to local practice until the patient commences a new treatment (these scans are optional; see Table 5).

If a patient discontinues treatment for any reason except due to objective disease progression according to RECIST 1.1, including toxicity, and/or receives a subsequent cancer therapy, the patient should still continue to be followed until objective disease progression q8w (relative to the date of randomization) until objective disease progression

Patients in the MEDI4736 + tremelimumab combination therapy group who complete the 4 dosing cycles of the MEDI4736 + tremelimumab combination therapy portion of the regimen (with clinical benefit per Investigator's judgement) but subsequently have evidence of PD during the MEDI4736 monotherapy portion of the combination regimen will be given the option to restart treatment with the entire combination regimen. To restart treatment, the patient must not have received an intervening systemic anticancer therapy post-IMT discontinuation. Patients who restart IMT must have a baseline tumor assessment within 28 days of restarting treatment with IMT; all further scans should occur every 8 weeks (q8w) (relative to the date of restarting treatment) until study treatment is stopped. Only patients who the Investigator determines do not have any significant, unacceptable, or irreversible toxicities, or would continue to receive benefit from therapy can begin retreatment.

It is important to follow the assessment schedule as closely as possible. Please refer to the study plans (Table 2 and Table 3 [Screening and the treatment period], Table 4 [for follow-up of patients in all 3 treatment groups who are discontinued due to toxicity in the absence of objective disease progression according to RECIST 1.1], and Table 5 [for follow-up of patients discontinuing due to objective disease progression according to RECIST 1.1]) 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.

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 and as clinically indicated (see Table 2 through Table 6).

Clinical laboratory safety tests, including serum pregnancy tests, will be performed in a licensed clinical laboratory according to local standard procedures. 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.

The laboratory variables to be measured are presented in Table 6 (clinical chemistry), Table 7 (hematology), and Table 8 (urinalysis).

Table 6 Clinical chemistry

Albumin	Lipase
Alkaline phosphatase[a]	Magnesium[b,c]
Alanine aminotransferase[a]	Potassium
Amylase	Serum creatinine
Aspartate aminotransferase[a]	Sodium
Bicarbonate[b]	Thyroid-stimulating hormone
Calcium	Free thyroxine (T_4)
Chloride	Total bilirubin[a]
Creatinine clearance[b]	Total protein
Gamma glutamyltransferase[b]	Free triiodothyronine (T_3)
Glucose	Urea or blood urea nitrogen, depending on local practice
Lactate dehydrogenase	

[a] Tests for alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently.

[b] Bicarbonate (where available, at baseline only), creatinine clearance, magnesium, and gamma glutamyltransferase testing are to be performed at Screening and Day 0 (unless screening laboratory assessments are performed within 3 days prior to Day 0), and if clinically indicated. Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an adverse event related to the endocrine system.

[c] For patients receiving cetuximab, magnesium monitoring and subsequent supplementation may occur more frequently as clinically indicated per site specific standards.

Note: Clinical chemistry assessments are to be performed at each visit and when clinically indicated unless otherwise noted.

Table 7 Hematology

Activated partial thromboplastin time[a]	Neutrophils
Hemoglobin	Platelet count
International normalized ratio[a]	Total white cell count
Lymphocytes	

[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 8 Urinalysis

Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

Note: Urinalysis is to be performed at Screening 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 2 and Table 3) 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 and as clinically indicated throughout the study (see Table 2 and Table 3). ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position. All ECGs must be obtained in triplicate at Screening. At Screening, a mean QTc will be calculated using 3 ECGs performed approximately 5 minutes apart. The mean QTcF must be <470 ms for the patient to meet eligibility criteria.

In case of clinically significant ECG abnormalities after screening has been completed, including a QT interval corrected for heart rate using 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**.

5.2.4 Vital signs

Vital signs (blood pressure [BP], pulse, temperature, respiration rate, and oxygen saturation) will be evaluated according to the assessment schedules (see Table 2 and Table 3).

On infusion days, patients in the IMT treatment groups will be monitored during and after infusion of IP as presented in the bulleted list below. Patients in the SoC group will be monitored pre-dose and as clinically indicated before every infusion or administration. (Cetuximab infusions may require more frequent monitoring as per site specific standards.)

Supine BP will be measured after the patient has rested for at least 5 minutes. BP and pulse will be collected from patients in the IMT treatment groups before, during, and after the infusion of each agent at the following times (based on a 60-minute infusion for each agent):

- Prior to the beginning of the infusion (measured once up to 30 minutes prior to the start of the infusion)
- Every 30 minutes during the infusion (±5 minutes) of each agent
- At the end of the infusion (±5 minutes) of each agent
- 30 and 60 minutes after the infusion (±5 minutes) of each agent for the first infusion only

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 2 and Table 3). Tests will be performed by the hospital's local laboratory. If results are positive, the patient is ineligible and must be discontinued from treatment. 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. Thyroid stimulating hormone should be evaluated at Screening and through the treatment period as described in Table 2 and Table 3.

5.3 Other assessments

5.3.1 Patient reported outcomes

"PRO" is an umbrella term referring to all outcomes and symptoms that are directly reported by the patient. PROs have become a significant endpoint when evaluating effectiveness of treatments in clinical trials. The following PROs will be administered in this study: EORTC QLQ-C30 (core questionnaire), H&N35 (head and neck-specific questionnaire), [redacted]

The PRO instruments will be completed by the patients using an electronic PRO (ePRO) device. All questionnaires should be completed according to the assessment schedules (see Table 2 through Table 5). 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. It takes approximately 30 to 45 minutes for patients to complete all 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.

For patients in the MEDI4736 + tremelimumab combination therapy arm who are receiving retreatment, questionnaires a[redacted] should be completed according to the original schedule of procedures during the retreatment period.

5.3.1.1 EORTC QLQ-C30

The EORTC QLQ-C30 v3 questionnaire is included for the purpose of assessing HRQoL and is a well-established measure of HRQoL/health status, and commonly used as an endpoint in cancer clinical trials. It assesses HRQoL/health status through 9 multi-item scales:

5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), and a global health and QoL scale. Six single-item symptom measures are also included: dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties (see Appendix F). For each of the 15 domains, final scores are transformed such that they range from 0 to 100, where higher scores indicate greater functioning, greater HRQoL, or greater level of symptoms (**Aaronson et al 1993**).

5.3.1.2 EORTC QLQ-H&N35

The main purpose of the EORTC H&N35 is to assess symptoms specifically relevant to patients with head and neck cancer. It is a 35-item questionnaire with scales that assess pain in the mouth, problems with swallowing, senses, speech, social eating, social contact, and sexuality (see Appendix F). There are 11 single-item measures, 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. 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**).

[redacted]

5.3.2 Administration of the patient-reported outcome questionnaires

Patients will complete the PRO assessments by using an electronic tablet during clinic visits.

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 2 through Table 5). The EORTC QLQ-C30 should always be completed prior to the 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 progression to avoid biasing the patient's responses to the questions.

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

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

- The research nurse or appointed site staff should stress that the information is confidential. Therefore, if the patient has any medical problems, he/she should discuss them with the doctor or research nurse separately from the ePRO assessment.

- The research nurse or appointed site staff must train the patient on how to use the ePRO device using the materials and training provided in the ePRO device.

- The research nurse or appointed site staff must remind patients that there are no right or wrong answers and avoid introducing bias by not clarifying items.

- 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**. The questions and response options should not be paraphrased or interpreted for the patient. It should be documented that the 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.

- The research nurse or appointed site staff must monitor compliance; minimizing missing data is a key aspect of study success. Compliance must be checked at each study visit and should be checked more frequently to identify problems early.

5.3.3 WHO/ECOG performance status

WHO/ECOG performance status will be assessed at the times specified in the assessment schedules (see Table 2 through Table 5) 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.

[redacted]

5.5 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 5.5.1. [redacted]

5.5.1 Collection of patient selection biomarker samples (for PD-L1 assessment)

At Screening, there is 1 mandatory provision of tissue (to be used for determination of eligibility) and optional provisions of tissue:

- 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. Where multiple samples have been submitted for the same patient, the first sample with an evaluable result will inform patient status for eligibility.

- Samples should be collected via an image-guided core needle (at least 18 gauge) or an excisional archival tumor biopsy sample. Where institutional practice, in this setting involves the use of 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 Laboratory Manual. When a smaller gauge needle is used, the number of cores increases to 3 or 4.

  The sample needed to assess eligibility should be of sufficient quantity to allow for analysis (see the Laboratory 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. In this instance only core needle (not excisional/incisional) biopsy is allowed. For patients with a single target lesion being used for a screening biopsy for PD-L1 testing, allow approximately 2 weeks prior to collecting imaging scans for baseline tumor assessment

- OPTIONAL: If archival tissue (≤3 years old) is submitted for PD-L1 analysis for assessment of eligibility, an optional, additional newly acquired biopsy, which will be used to assess exploratory endpoints, is strongly encouraged. Please consult the Laboratory Manual for further details on how this sample should be processed.

- OPTIONAL: The collection of an 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 Laboratory 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 Laboratory Manual for further details of requirements.

Tumor biopsies will be stored at AstraZeneca Research and Development or an appropriate vendor selected by AstraZeneca. Core biopsies may be used for correlative studies such as IHC, [redacted] proteomic analysis, [redacted] Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

The Ventana PD-L1 SP263 IHC assay will be used to determine PD-L1 IHC expression levels in this study. The Ventana PD-L1 SP263 IHC analysis will be performed at a laboratory that is approved, trained and monitored by Ventana and meets appropriate regulatory requirements. No other assays will be accepted.

HPV status will be assessed according to local standards for patients with oropharyngeal cancer only. If HPV status is not available, additional tissue may be submitted to the sponsor for testing.

To meet the requirement of 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 the test approval.

For patients undergoing retreatment in the MEDI4736 + tremelimumab arm, repeat PD-L1 testing is optional. Repeat HPV is not required.

[redacted]

[redacted]

[redacted]

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

An AE is the development of 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

AEs 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 initiation of another therapy, unless the investigator assesses that the event occurring within 90 days after last dose of study treatment but after the initiation of another therapy, is related to the study treatment. Reporting timelines for such events will follow the guidelines described below in Section 6.4.

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

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)
- Causality assessment in relation to other medication, as explained in Section 6.3.4
- 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 laboratory tests and vital signs measurements will be summarized in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory 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 laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory 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 laboratory 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.

6.3.12 Safety data to be collected following the final data cut-off of the study

For patients continuing to receive IP treatment following the final data cut-off (DCO) and database closure, it is recommended that the patients continue the scheduled site visits and investigators monitor the patient's safety laboratory results prior to and periodically during treatment with IP in order to manage AEs in accordance with the MEDI4736 Toxicity Management Guidelines (Section 6.7 and Table 9). All data after the final DCO and database closure will be recorded in the patient notes but will not otherwise be reported for the purposes of this study, with the exception of SAEs, overdoses, and pregnancies.

All SAEs, overdoses, and pregnancies that occur in patients still receiving IP treatment (or within the 90 days following the last dose of MEDI4736 treatment) after the final DCO and database closure must be reported as detailed in Section 6.4 via paper SAE forms.

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. All SAEs will be recorded in the eCRF.

If any SAE 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 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 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 AstraZeneca.

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 following the last dose of MEDI4736 monotherapy or 180 days after the last dose of MEDI4736 + tremelimumab combination therapy. Please follow the local prescribing information relating to contraception and the time limit for such precautions for SoC agents.

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 after the last dose of MEDI4736 monotherapy or 180 days after the last dose of MEDI4736 + tremelimumab combination therapy 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 Investigational Product 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.All dose modifications should be documented with clear reasoning and documentation of the approach taken.

All toxicities will be graded according to NCI CTCAE version 4.03.

In addition, there are certain circumstances in which MEDI4736 and tremelimumab should be permanently discontinued (see Table 9 and Section 3.9).

Following the first dose of IP, subsequent administration of MEDI4736 and tremelimumab can be modified based on toxicities observed as described in Table 9. All toxicities will be Graded according to CTCAE version 4.03. Dose reductions for MEDI4736 or tremelimumab are not permitted.

Dose delays will not be required for AEs that are clearly not attributable to MEDI4736 or tremelimumab (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant. Dosing may continue despite concurrent vitiligo of any AE Grade.

Acetaminophen and/or an antihistamine (eg, diphenhydramine) or equivalent medications per institutional standard may be administered prior to infusion at the discretion of the Investigator for primary prophylaxis against infusion-related reactions. In the event of Grade ≤2 infusion-related reaction, the infusion rate of IP may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. In patients experiencing Grade ≤2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. If a patient experiences an infusion-related reaction, acetaminophen and/or an antihistamine (eg, diphenhydramine) and/or corticosteroid or equivalent medications per institutional standard may be administered prior to subsequent infusions at the discretion of the Investigator for secondary prophylaxis of infusion-related reactions. If the infusion-related reaction is Grade 3 or higher in severity, treatment with IP will be discontinued.

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 understanding of the Investigational Product 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 investigational products.

AESIs for MEDI4736 ± tremelimumab include, but are not limited to events with a potential inflammatory or immune-mediated mechanism that 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 imAE is defined as an AE associated with drug exposure that is consistent with an immune-mediated mechanism of action when there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

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

AESIs observed with MEDI4736 ± tremelimumab include:

- Diarrhea/colitis and intestinal perforation
- Pneumonitis/ILD
- Hepatitis/transaminase increases
- Endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyperthyroidism and hypothyroidism, and type I diabetes mellitus)
- Rash/dermatitis
- Nephritis/blood creatinine increases
- Pancreatitis/serum lipase and amylase increases
- Myocarditis
- Myositis/polymyositis
- Neuropathy/neuromuscular toxicity (eg, Guillain-Barré, and myasthenia gravis)
- Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to, pericarditis, sarcoidosis,

uveitis and other events involving the eye, skin, hematological and rheumatological events.

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

Further information regarding AESIs (eg, presenting symptoms) can be found in the current version of the MEDI4736 and tremelimumab IBs. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (Table 9). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in the treatment of these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting Investigator.

6.7.2 MEDI4736 and MEDI4736 + tremelimumab

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for MEDI4736 monotherapy and MEDI4736 + tremelimumab are provided in the Dosing Modification and Toxicity Management Guidelines in Table 9. The most current version of the Toxicity Management Guidelines is also available through the following link: https://tmg.azirae.com. In addition, a version of the current Toxicity Management Guidelines is maintained within the Site Master File. Please contact your clinical trial associate for information on how to gain access to this website.

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

In addition, there are certain circumstances in which MEDI4736 and tremelimumab should be permanently discontinued (see Section 3.9 of this protocol and the Dosing Modification and Toxicity Management Guidelines in Table 9).

Following the first dose of IP, subsequent administration of MEDI4736 and tremelimumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines in Table 9. 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 monotherapy and the MEDI4736 + tremelimumab regimen by the reporting investigator.

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

Table 9 Dosing modification and toxicity management guidelines for immune-mediated, infusion-related, and non-immune–mediated reactions (MEDI4736 monotherapy or combination therapy with tremelimumab or tremelimumab monotherapy) 1 November 2017 version

General Considerations	
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.	It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table: – It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. – Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. – 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. – Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., 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 (e.g., infliximab) (also refer to the individual sections of the imAEs for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids.

Table 9 Dosing modification and toxicity management guidelines for immune-mediated, infusion-related, and non-immune–mediated reactions (MEDI4736 monotherapy or combination therapy with tremelimumab or tremelimumab monotherapy) 1 November 2017 version

General Considerations	
Dose Modifications	**Toxicity Management**
Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).	– With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. – Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., 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.

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

Pediatric Considerations	
Dose Modifications	**Toxicity Management**
The criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity is the same for pediatric patients as it is for adult patients, as well as to permanently discontinue study drug/study regimen if unable to reduce corticosteroid ≤ a dose equivalent to that required for corticosteroid replacement therapy **within 12 weeks** after last dose of study drug/study regimen	– All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended. – The recommendations for dosing of steroids (i.e., mg/kg/day) and for IV IG and plasmapheresis that are provided for adult patients should also be used for pediatric patients. – The infliximab 5 mg/kg IV dose recommended for adults is the same as recommended for pediatric patients ≥ 6 years old. For dosing in children younger than 6 years old, consult with a pediatric specialist. – For pediatric dosing of mycophenolate mofetil, consult with a pediatric specialist. – With long-term steroid and other immunosuppressive use, consider need for PJP prophylaxis, gastrointestinal protection, and glucose monitoring.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (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, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1 to 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 methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., 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-PJP 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	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):**

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy or intubation])		– Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious disease consult; consider, as necessary, discussing with study physician. – Hospitalize the patient. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., 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 patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Diarrhea/Colitis	**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 (e.g., 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 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only)	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day) (Colitis: abdominal pain; mucus or blood in stool)	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 (e.g., 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 weeks[a]. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with 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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3 diarrhea: stool frequency of ≥7 over baseline per day; Grade 4 diarrhea: life threatening consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medi-cal intervention indi-cated, peritoneal signs;	**Grade 3** Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. **Grade 4** 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 (e.g., 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.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 4 colitis: life-threatening consequences, urgent intervention indicated)		– Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP 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. **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in HCC patients**	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	Grade 1 (AST or ALT >ULN and ≤3.0×ULN and/or TB > ULN and ≤1.5×ULN)	• No dose modifications. • If it worsens, then treat as Grade 2 event.	**For Grade 1:** – Continue LFT monitoring per protocol.
	Grade 2 (AST or ALT >3.0×ULN and ≤5.0×ULN and/or TB >1.5×ULN and ≤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 (e.g., every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to Grade ≤1 in 1 to 2 days, consider, as necessary, discussing 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 work up 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 (i.e., 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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3: AST or ALT >5.0×ULN and	**For Grade 3:**	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent.

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Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	≤20.0×ULN and/or TB >3.0×ULN and ≤10.0×ULN) (Grade 4: AST or ALT >20×ULN and/or TB >10×ULN)	For elevations in transaminases ≤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 (i.e., elevated alkaline P04) and in the absence of any alternative cause.[b] **For Grade 4:** Permanently discontinue study drug/study regimen.	– 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 (i.e., 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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Hepatitis (elevated LFTs)	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg – For HCV+ patients: evaluate quantitative HCV viral load

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Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Infliximab should not be used for management of immune-related hepatitis. See instructions at **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients** bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**			– Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load >2000 IU/ml – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥2-fold – For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above
	Grade 1 (Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline)	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as Grade 2 event. For all grades, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	
	Grade 2 (Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline) (Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline)	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1 or baseline. • 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 (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to 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 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, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should**

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Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			NOT be used.
	Grade 3 (Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline) (Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)	• 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 Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	**For Grade 3:** – Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider, as necessary, discussing with study physician. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate 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 4 (Isolated AST or ALT >20×ULN, whether normal or elevated at baseline)	Permanently discontinue study drug/study regimen.	**For Grade 4:** **Same as above** **(except would recommend obtaining liver biopsy early)**
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR): **- Manage dosing for Grade 1 transaminase rise as instructed for Grade 2 transaminase rise** **- Manage dosing for Grade 2 transaminase rise as instructed for Grade 3 transaminase rise** **- Grade 3-4: Permanently discontinue study drug/study regimen**			
Nephritis or renal dysfunction	**Any Grade**	**General Guidance**	**For Any Grade:** – Consult with nephrologist.

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Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
(elevated serum creatinine)			– Monitor for signs and symptoms that may be related to changes in renal function (e.g., 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 (e.g., 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 or baseline, then resume study drug/study regimen after completion of steroid taper.	**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. – 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-PJP 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
			– 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. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP 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 (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., 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	**For Grade 2:** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., 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, consider, as

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Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		regimen after completion of steroid taper.	necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – 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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	**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:** – Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – 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, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as

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Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			there are no other signs or symptoms of pancreatic inflammation. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., 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. – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – 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 consultation of an endocrinologist.
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, 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 (e.g., adrenal insufficiency) 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.	**For Grade 2 (including those with symptomatic endocrinopathy):** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with

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Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		3. Doses of prednisone are ≤10 mg/day or equivalent.	guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP 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 and Type 1 diabetes mellitus, 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. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) 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 ≤10 mg/day or equivalent.	**For Grade 3 or 4:** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Neurotoxicity (to include but not be limited to limbic encephalitis and	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v4.03	**General Guidance**	**For Any Grade:** – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications).

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Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	for defining the CTC grade/severity)		– Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., 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 steroid taper.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Obtain neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., 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 (e.g., IV IG).
	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 imAE does not resolve to Grade ≤1 within 30 days. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consider, as necessary, discussing 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 (e.g., 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

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Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			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 (e.g., 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 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 (e.g., 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:** – Consider, as necessary, discussing 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.
	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:** – Consider, as necessary, discussing 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 – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that

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Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			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.
	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 imAE 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):** − Consider, as necessary, discussing 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:*

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Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			○ It is important to consider here 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.
Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider, as necessary, discussing with the study physician. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)
	Grade 1 (asymptomatic with laboratory (e.g., BNP) or cardiac imaging abnormalities)	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 (no definitive findings):** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. - Consider using steroids if clinical suspicion is high.

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Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 2, 3 or 4 (Grade 2: Symptoms with mild to moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support))	- If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study drug/study regimen.	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., 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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Myositis/Polymyositis ("Poly/myositis")	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
	Grade 1 (mild pain)	- No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
	Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	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.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., 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.

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, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (pain associated with severe weakness; limiting self-care ADLs)	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** - Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., 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. – Consider whether patient may require IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

[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; imAE immune-mediated 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; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); 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 (e.g., 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 (e.g., 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 (e.g., 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 (i.e., 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.

6.7.3 Specific toxicity management and dose modification information - Standard of Care

Investigators should follow local standard clinical practice regarding dose modifications for agents used in the SoC arm. For specific information regarding the individual agents used in this study, please refer to the local prescribing information for the relevant agent.

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 established comprised of independent experts. The committee will meet approximately 3 months after enrollment of the first patient in the MEDI4736 + tremelimumab group or after the enrollment of 20 patients in that group, whichever is first, then approximately 3 months after the first meeting and every 6 months thereafter 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, processes, and interim analyses 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, while the SoC treatments (cetuximab, a taxane, methotrexate, or a fluoropyrimidine) will be supplied locally (Table 10).

Table 10 List of investigational products for this study

Investigational product	Dosage form and strength	Manufacturer
MEDI4736	50 mg/mL, solution, IV	MedImmune
Tremelimumab	20 mg/mL, solution, IV	MedImmune
Standards of Care[a]		
Cetuximab	IV (as sourced locally)	Sourced locally
Taxanes (ie, docetaxel or paclitaxel)	IV (as sourced locally)	Sourced locally
Methotrexate	IV (as sourced locally)	Sourced locally
Fluoropyrimidine (ie, 5-FU, TS-1, or capecitabine)	IV (5-FU) or oral (TS-1 or capecitabine) (as sourced locally)	Sourced locally

[a] Under certain circumstances when local sourcing isn't feasible, a Standard of Care treatment will be supplied centrally through AstraZeneca.

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 (w/v) 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 investigational product 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 20 mg/kg or 10 mg/kg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) 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.

The calculated volume of MEDI4736 is added to the appropriately-sized IV bag such that final concentration is within 1 to 20 mg/mL. Mix the bag 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 time should not exceed 8 hours at room temperature.

In the event that either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials. MEDI4736 does not contain preservatives, and any unused portion must be discarded.

All the details regarding the preparation of MEDI4736 doses for administration 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:

(20 mg/kg or 10 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 such that the final MEDI4736 concentration is within 1 to 20 mg. 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 by AstraZeneca as a 400 mg vial solution for infusion after dilution. The solution contains 20 mg/mL tremelimumab, 20 mM histidine/histidine-hydrochloride, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dihydrate, and 0.02% (w/v) polysorbate 80; pH 5.5. The nominal fill volume is 20 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen.

Preparation of tremelimumab doses for administration with an IV bag

The dose of tremelimumab for administration must be prepared by the Investigator's or site's designated investigational product manager using aseptic technique. Total time from needle puncture of the tremelimumab 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 1 mg/kg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final tremelimumab concentration ranging from 0.10 to 10 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. The calculated volume of tremelimumab is added to the

appropriately-sized IV bag such that final concentration is within 0.10 to 10 mg/mL. Mix the bag by gentle inversions to ensure homogeneity of the dose in the bag.

Standard infusion time is 1 hour, however if there are interruptions during infusion, the total time should not exceed 8 hours at room temperature.

In the event that either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials. Tremelimumab does not contain preservatives, and any unused portion must be discarded. All the details regarding the preparation of tremelimumab doses for administration can be found in the Drug Handling Instructions.

Dose calculation

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)

Example: For a patient weighing 80 kg, dosed at 1 mg/kg, 4 mL [1 mg/kg × 80 kg divided by 20 mg/mL] of tremelimumab is to be diluted in an IV bag such that the final tremelimumab concentration is within 0.10 to 10 mg/mL. The bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag and the diluted tremelimumab is administered as described above.

7.1.3 Standard of Care treatment

Each SoC agent will be sourced as commercially available material/locally sourced, prescribed according to local regulations, and will be administered according to prescribing information or treatment guidance in general use by the Investigating site. Dosage of SoC agent may be modified based on clinical practice of the investigating site; however, dosing schedule must comply with the protocol stated schedules. Under certain circumstances when local sourcing isn't feasible, a SoC treatment will be supplied centrally through AstraZeneca and this will be labelled with local language translated text in accordance with local regulatory guidelines.

7.2 Dose and treatment regimens

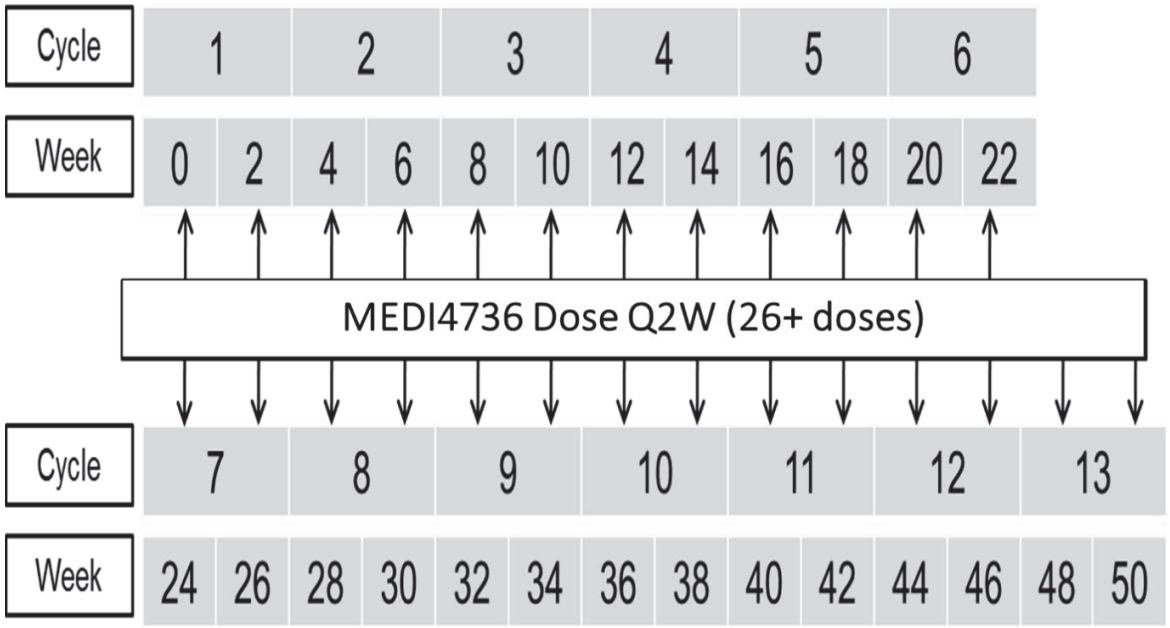
Patients will be randomized in a 1:1:1 ratio to receive treatment with MEDI4736 monotherapy, MEDI4736 + tremelimumab combination therapy, or SoC.

7.2.1 Treatment regimens

MEDI4736 monotherapy

Patients in the MEDI4736 monotherapy treatment group will receive 10 mg/kg MEDI4736 via IV infusion q2w until objective disease progression according to RECIST 1.1 (see Figure 4).

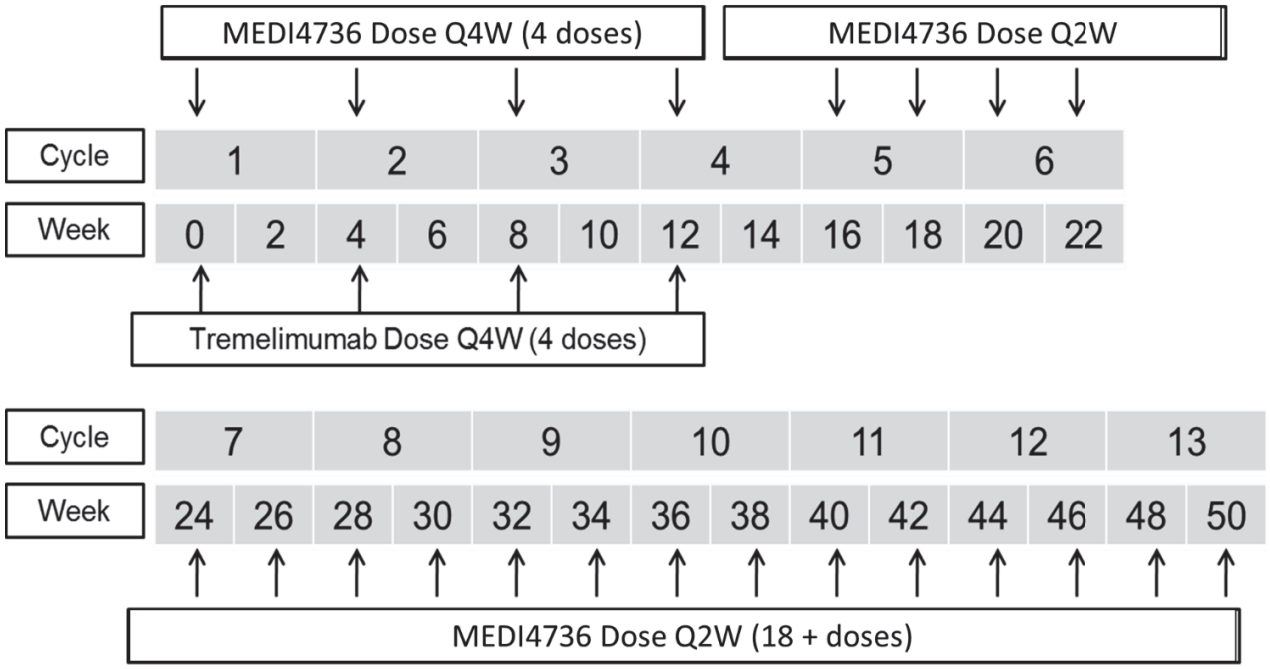
Figure 4 Dosing scheme for MEDI4736 monotherapy



MEDI4736 + tremelimumab combination therapy

Patients in the MEDI4736 + tremelimumab combination therapy treatment group will receive 20 mg/kg MEDI4736 via IV infusion q4w for 4 doses 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, until objective disease progression according to RECIST 1.1 (see Figure 5). 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 MEDI4736 + tremelimumab combination therapy dosing scheme



Q2W Every 2 weeks; Q4W Every 4 weeks.

Standard of Care treatment

Patients in the SoC group will receive 1 of the following treatments until objective disease progression according to RECIST 1.1, unacceptable toxicity, or, if in the opinion of the Investigator, the patient is no longer deriving benefit:

- Cetuximab 400 mg/m^2 will be administered via IV infusion on Day 0, then 250 mg/m^2 will be administered via IV infusion weekly thereafter.
- A taxane (ie, either docetaxel [40 mg/m^2; Guardiola et al 2004] or paclitaxel [80 mg/m^2; Grau et al 2009] will be administered via IV infusion weekly.
- Methotrexate (40 mg/m^2) will be administered via IV infusion weekly.
- A fluoropyrimidine (ie, 5-FU, TS-1, or capecitabine) will be administered as follows:
  - 5-FU (2400 mg/m^2) will be administered over 46 hours via IV infusion q2w.
  - TS-1 (80 mg/m^2) will be administered orally once daily for 28 days followed by a 14-day rest.

- Capecitabine (1000 mg/m^2) will be administered orally twice daily for 7 days followed by a 7-day rest.

For all SoC therapies, a particular treatment (cetuximab, taxane, methotrexate, or fluoropyrimidine-based regimen) will not be used in patients who have previously received that treatment for recurrent/metastatic disease or who have experienced recurrence or progression of disease within 6 months of prior multimodal therapy using that particular treatment.

Duration of treatment

IMT treatment (MEDI4736 or MEDI4736 + tremelimumab)

Patients in the IMT groups will be treated with their assigned IMT or until objective disease progression according to RECIST 1.1, whichever comes first (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).

Disease progression requires confirmation if clinically feasible. A second scan obtained at a minimum of 4 weeks later to confirm progression is required for treatment management decisions only and only where clinically feasible. Disease response assessment should be solely based on RECIST 1.1 with response of PD entered for the first scan that meets progression criteria as outlined by RECIST 1.1. Treatment with IMT will continue between the initial assessment of progression and its confirmation. If progression is not confirmed, then the patient should continue receiving study treatment and participating in study assessments if clinically appropriate.

Patients with objective disease progression according to RECIST 1.1 who, in the Investigator's opinion, continue to receive benefit from IP treatment and who meet the criteria for treatment in the setting of PD (see Section 3.1) may continue to receive treatment under the original schedule after consultation with the Sponsor and at the Investigator's discretion. Patients with confirmed progression in the MEDI4736 monotherapy arm or in the combination dosing portion of therapy in the MEDI4736 + tremelimumab arm cannot continue therapy if progression occurred after objective response (CR or PR) to IMT treatment 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 who the Investigator determine may not continue treatment after objective disease progression according to RECIST 1.1 will enter follow-up as per (Table 5. Patients who have discontinued treatment due to toxicity or symptomatic deterioration, or who have no objective disease progression according to RECIST 1.1, will be followed up for study endpoints (objective disease progression according to RECIST 1.1 and death; Table 4). All patients will be followed until death.

Patients who have a dose interruption due to treatment related or non-treatment toxicity at any point during treatment may resume treatment if they meet criteria as specified in the Toxicity Management Guidelines and provided they are clinically stable to continue therapy. Treatment gaps of 12 weeks due to treatment related toxicity will require discontinuation of therapy for patients randomized to the IMT arms.

Patients who meet the criteria for retreatment may only receive retreatment once. Crossover within the study will not be permitted. Patients meeting the retreatment criteria below will follow the same treatment guidelines followed during the initial treatment period (see Table 2 and Table 3). All assessments, including screening procedures must be repeated except those outlined in Section 4 (PD-L1 testing is optional).

Patients randomized to MEDI4736 monotherapy may not undergo retreatment.

Patients randomized to MEDI4736 + Tremelimumab combination therapy may undergo retreatment in the clinical scenario described below:

- Patients who complete the 4 doses of MEDI4736 + tremelimumab combination therapy portion of the regimen arm (with clinical benefit per Investigator's judgement) but subsequently have evidence of PD during the MEDI4736 monotherapy portion of the combination regimen, with or without confirmation according to RECIST 1.1, may restart treatment with the entire combination regimen (including monotherapy maintenance).

<u>Standard of Care treatment</u>

In the SoC group, it is at the Investigator's discretion whether or not a patient with uncertain PD continues treatment until there is objective disease progression according to RECIST 1.1; however, a scan showing objective disease progression is required for all patients in the SoC group, even if a subsequent treatment is started. Progression per RECIST criteria available in Appendix E.

A confirmatory scan is required following the initial demonstration of PD if clinically feasible. This scan, obtained at a minimum of 4 weeks later to confirm progression is required for treatment management decisions only and only where it is clinically feasible. Disease response assessment should be solely based on RECIST 1.1 with response of PD entered for the first scan that meets progression criteria as outlined by RECIST 1.1. For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes, or necrosis in existing lesions), treatment may continue until the next scheduled assessment (see Table 5).

For patients progressing on treatment with SoC who cannot continue to receive SoC treatment, crossover to MEDI4736 monotherapy or MEDI4736 + tremelimumab will not be permitted.

Post final data cut-off

Patients who continue to receive benefit from their assigned treatment at the final data cut-off (DCO) and database closure may continue to receive their assigned treatment for as long as they and their physician feel they are gaining clinical benefit. For patients continuing to receive MEDI4736 treatment following the final DCO and database closure, it is recommended that the patients continue the scheduled site visits and investigators monitor the patient's safety laboratory results prior to and periodically during treatment with MEDI4736 in order to manage AEs in accordance with the MEDI4736 Toxicity Management Guidelines (Section 6.7 and Table 9).

In the event that a roll-over or safety extension study is available after final analysis patients currently receiving treatment with MEDI4736 may be transitioned to such a study. 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 study would be given a new ICF.

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 labelling. Label text will be translated into the local language.

Labels will be provided as either a 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 IB.

7.5 Compliance

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

Patients should return all unused medication and empty containers to the Investigator.

Treatment compliance will be assured by site reconciliation of 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:**
For all treatment arms	
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 its 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.)**
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
For the MEDI4736 ± tremelimumab treatment arms only	
Sunitinib	Should not be given concomitantly or through 90 days after the last dose of tremelimumab (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib)
EGFR TKIs	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of MEDI4736. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with first generation EGFR TKIs) have been reported when MEDI4736 has been given concomitantly.

AE Adverse event; CT Computed tomography; EGFR TKI Epidermal growth factor receptor tyrosine kinase inhibitor; 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, growth factor 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 MEDI4736 monotherapy or MEDI4736 + tremelimumab as long as, in the Investigator's opinion, the patient is gaining clinical benefit from active treatment.

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 and finalized within 3 months of the first randomized patient and any subsequent amendments will be documented, with final amendments completed prior to reporting of the data. The co-primary objectives of the study are to compare the overall survival of MEDI4736 + tremelimumab combination therapy to SoC and MEDI4736 monotherapy to SoC.

8.2 Sample size estimate

The sample size for this study was selected to be consistent with the research hypotheses as described below in Section 8.5.

The study will enroll approximately 1200 patients in order to identify 720 eligible patients with recurrent or metastatic SCCHN who have progressed during or after only one palliative systemic treatment regimen for recurrent or metastatic disease that must have contained a platinum agent or who have progressed within 6 months of the last dose of platinum given as part of multimodality therapy with curative intent. Patients will be randomized in a 1:1:1 fashion to MEDI4736 monotherapy, MEDI4736 + tremelimumab combination therapy, or SoC (240 patients in each treatment group). An approximate 40% attrition rate due to screen failures and a <2% attrition rate due to withdrawals during treatment are expected.

The study is sized to characterize the OS benefit of MEDI4736 + tremelimumab combination therapy versus SoC in all patients, regardless of PD-L1 status; and to characterize the OS benefit of MEDI4736 monotherapy versus SoC in all patients, regardless of PD-L1 status. The sizing assumes a 3-month delay in separation of the survival curves between each arm, hence the use of average hazard ratios (HRs). The study will be considered positive if either one of these objectives are statistically significant.

The analysis of OS is expected to be performed after approximately 11 months of follow-up when:

- Approximately 375 death events have occurred in 480 patients (78% maturity) across the MEDI4736 + tremelimumab combination therapy and SoC arms, regardless of PD-L1 status AND when

- Approximately 375 death events have occurred in 480 patients (78% maturity) across the MEDI4736 monotherapy and SoC arms, regardless of PD-L1 status.

Interim analysis for OS will be performed when a total of 300 death events (80% of required events) have been accumulated across the MEDI4736 + tremelimumab combination therapy and SoC arms. It is expected that approximately 300 death events would have accumulated across the MEDI4736 monotherapy and SoC arms at this time.

MEDI4736 + tremelimumab combination therapy or MEDI4736 monotherapy in all patients, regardless of PD-L1 status (co-primary objectives)

If OS at 18 months was 25% with either the MEDI4736 + tremelimumab combination therapy or MEDI4736 monotherapy and 10% with SoC (with 5.5 month median OS), and assuming the true average OS HR is0.69, the study will have 90% power to demonstrate statistical significance at the 2.2% level (using a 2-sided test) for the comparison of either MEDI4736 + tremelimumab combination therapy or MEDI4736 monotherapy versus SoC, allowing for 1 interim analysis conducted at approximately 80% of the target events with the smallest treatment difference that could be statistically significant being an average HR of0.79. With an assumed 15-month recruitment period and a minimum follow-up period of 11 months from “last patient in”, it is anticipated that the final analysis will be performed 26 months after the first patient has been recruited.

MEDI4736 + tremelimumab combination therapy in PD-L1-negative patients (secondary objective)

Assuming 70% of randomized patients are PD-L1-negative patients (ie., 504 PD-L1-negative patients with 168 in each treatment arm), and if OS at 18 months was 28% with the MEDI4736 + tremelimumab combination therapy and 10% with SoC (with 5.5 month median OS), and assuming the true average OS HR is 0.64, the study will have 90% power to demonstrate statistical significance at the 2.2% level (using a 2-sided test) for the comparison of MEDI4736 + tremelimumab combination therapy versus SoC in the PD-L1-negative patients, with the smallest treatment difference that could be statistically significant being an average HR of 0.75. The significance level of 2.2% assumes an interim analysis occurs at exactly 80% of the total events in PD-L1 negative patients. With a 15-month recruitment period and a minimum follow-up period of 11 months assumed for PD-L1-negative patients, it is anticipated that this analysis will be performed 26 months after the first patient has been recruited.

MEDI4736 monotherapy in PD-L1-positive patients (secondary objective)

Assuming 30% of randomized patients are PD-L1-positive patients (ie., 216 PD-L1-positive patients with 72 in each treatment arm), and if OS at 18 months was 41% with either MEDI4736 monotherapy and 10% with SoC (with 5.5 month median OS), and assuming the true average OS HR is0.49, the trial will have 90% power to demonstrate statistical significance at the 2.5% level (using a 2-sided test) for the comparison of either MEDI4736 monotherapy versus SoC in PD-L1 positive patients, with the smallest treatment difference that could be statistically significant being an average HR of 0.63. With a 15-month recruitment period and a minimum follow-up period of 11 months assumed, it is anticipated that this analysis will be performed 26 months after the first patient has been recruited.

A summary of the statistical assumptions is provided in Table 11.

Table 11 Summary of statistical assumptions

	N	Overall HR	Landmarks[1]	Events (maturity)	Power	Critical values HR (Landmarks)
MEDI4736 + tremelimumab combination therapy versus SoC						
All patients, regardless of PD-L1 status	480	0.69	10 vs. 25%	375 (78%)	90%	0.79 (10 vs. 19%)
PD-L1–negative	336	0.64	10 vs. 28%	258 (77%)	90%	0.76 (10 vs. 21%)
MEDI4736 monotherapy versus SoC						
All patients, regardless of PD-L1 status	480	0.69	10 vs. 25%	375 (78%)	90%	0.79 (10 vs. 19%)
PD-L1–positive	144	0.49	10 vs. 41%	102 (71%)	90%	0.63 (10 vs. 28%)

[1] OS landmark is 18 months; the assumed recruitment and minimum follow-up periods for all patients, regardless of PD-L1 status, are 15 and 11 months, respectively (ie, 26-month study duration);; Sample size estimate in the PD-L1 negative comparison assume that 70% of the patients enrolled have PD-L1 negative disease. Sample size estimate in the PD-L1 positive comparison assume that 30% of the patients enrolled have PD-L1 positive disease.

HR hazard rate; PD-L1 programmed cell death ligand 1; SoC Standard of Care

8.3 Definitions of analysis sets

Definitions of the analysis sets for each outcome variable are provided in Table 12.

Table 12 Summary of outcome variables and analysis populations

Outcome variable	Population
Efficacy data	
OS	Full Analysis Set (ITT population)
PFS, ORR, DoR, DCR, AFP6, APF12, OS12, OS18, OS24, PROs, and symptom endpoints	Full Analysis Set (ITT population)
OS, PFS, ORR, DoR, DCR	PD-L1-negative analysis set
OS, PFS, ORR, DoR, DCR	PD-L1-positive analysis set
Demography	Full Analysis Set (ITT population)
[redacted]	[redacted]
Safety Data	
Exposure	Safety Analysis Set
AEs	Safety Analysis Set
Laboratory measurements	Safety Analysis Set
WHO performance status	Safety Analysis Set
Vital signs	Safety Analysis Set

8.3.1 Full Analysis Set

The full analysis set (FAS) will include all randomized patients. The FAS will be used for all efficacy analyses (including PROs). 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 PD-L1-negative analysis set

The PD-L1-negative analysis set will include the subset of patients in the FAS whose PD-L1 status is PD-L1-negative as defined by the Ventana PD-L1 SP263 IHC assay. The cut-off level to determine the PD-L1-negative analysis set may be different from the cut-off level used for stratification purposes (<25% PD‑L1–membrane expression in tumor tissue), and will be determined from emerging data outside of this trial. Such a cut-off will be detailed in the statistical analysis plan prior to database lock.

8.3.3 PD-L1-positive analysis set

The PD-L1-positive analysis set will include the subset of patients in the FAS whose PD-L1 status is PD-L1-positive as defined by the Ventana PD-L1 SP263 IHC assay. The cut-off level to determine the PD-L1-positive analysis set may be different from the cut-off level used for stratification purposes (≥25% PD‑L1–membrane expression in tumor tissue), and will be determined from emerging data outside of this trial. Such a cut-off will be detailed in the statistical analysis plan prior to database lock.

8.3.4 Safety Analysis Set

The Safety Analysis Set (SAS) 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.

[redacted]

8.4 Outcome measures for analyses

8.4.1 Calculation or derivation of efficacy variables

The analysis of the secondary endpoints, PFS, ORR, DoR, DCR, APF6, and APF12, will be based on the site Investigator's assessments using RECIST 1.1.

8.4.1.1 RECIST 1.1-based endpoints

Investigator RECIST 1.1-based assessments

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 randomization. If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE, unless there is objective disease progression according to RECIST 1.1 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

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 following the date of DCO for the analysis (these contacts should generally occur within 7 days of the DCO). 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.

8.4.1.3 Secondary endpoints

Progression-free survival

PFS (per RECIST 1.1 as assessed by the site Investigator) 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 (ie, 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 2 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:

- For Investigator assessments, the date of progression will be determined based on the earliest of the RECIST 1.1 assessment/scan dates of the component that indicates objective disease progression according to RECIST 1.1.

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

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

In the absence of significant clinical deterioration, the investigational site is advised to continue the patient on their randomized MEDI4736 + tremelimumab combination therapy or MEDI4736 monotherapy until objective disease progression according to RECIST 1.1. If

progression is not confirmed, the patient should continue their randomized MEDI4736 + tremelimumab combination therapy or MEDI4736 monotherapy treatment and on-treatment assessments. Treatment through PD in the SoC group is at the Investigator's discretion; however, a second scan to confirm PD is required for all patients in the SoC group, if clinically feasible.

Objective response rate

ORR (per RECIST 1.1 as assessed by the site Investigator) is defined as the number (%) of patients with at least 1 visit response of CR or PR and will be based on all randomized patients. Therefore, data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who go off treatment without progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR.

ORR will be obtained using the algorithm described above for the RECIST 1.1 site Investigator tumor data. The denominator for ORR will be all randomized patients with measurable disease at baseline per the site Investigator (ie, a subset of the ITT population).

Duration of response

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

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.

Disease control rate

DCR at 6 months is defined as the percentage of patients who have a best objective response (BoR) of CR or PR in the first 6 months or who have demonstrated SD for a minimum interval of 24 weeks (-7 days, ie, 161 days) following the start of treatment with IP. DCR at 12 months is defined as the percentage of patients who have a BoR of CR or PR in the first 12 months or who have demonstrated SD for a minimum interval of 48 weeks (-7 days, ie, 329 days) following the start of treatment with IP.

DCR will be determined programmatically based on RECIST 1.1 using site Investigator's tumor data using all data up until first progression event.

Proportion of patients alive and progression free at 6 months

The APF6 will be defined as the Kaplan-Meier estimate of PFS (per RECIST 1.1 as assessed by the site Investigator) at 6 months.

Proportion of patients alive and progression free at 12 months

The APF12 will be defined as the Kaplan-Meier estimate of PFS (per RECIST 1.1 as assessed by the site Investigator) at 12 months.

Proportion of patients alive at 12 months

The OS12 will be defined as the Kaplan-Meier estimate of OS at 12 months.

Proportion of patients alive at 18 months

The OS18 will be defined as the Kaplan-Meier estimate of OS at 18 months.

Proportion of patients alive at 24 months

The OS24 will be defined as the Kaplan-Meier estimate of OS at 24 months.

Time from randomization to the first subsequent therapy or death

Time to the first subsequent therapy (TFST) or death will be defined as the time from the date of randomization to the earlier of either the start date of the first subsequent anticancer therapy after discontinuation of randomized treatment or the date of death (ie, the date of first subsequent cancer therapy, death, or censoring defined as the date of randomization + 1 day). Any patient not known to have received a first subsequent anticancer therapy will be censored at the last date that the patient was known not to have received a first subsequent anticancer therapy. If a patient terminated the study before the first subsequent therapy for a reason other than death, the patient will be censored at the earliest of either the patient's last known date to be alive or the study termination date.

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 objective disease progression according to RECIST 1.1 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.

BoR will be determined programmatically based on RECIST 1.1 using site Investigator data using all data up until objective disease progression according to RECIST 1.1. 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 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 monotherapy, MEDI4736 + tremelimumab combination therapy, or SoC) 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 IP 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.

The 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

PROs will be assessed using the EORTC QLQ-C30, EORTC QLQ-H&N35, and PRO CTCAE. 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).

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 2001). 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 HRQoL 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 13.

Table 13 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

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 2001). 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.

Time to quality of life/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.

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 ITT population who has 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.

8.4.3.2 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 14. 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 14 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

Time to symptom deterioration

For each of the symptoms 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.

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.

[redacted]

[redacted]

[redacted]

8.5 Methods for statistical analyses

Formal statistical analysis will be performed to test the main hypotheses:

- H_0: No difference in OS between either MEDI4736 + tremelimumab combination therapy or MEDI4736 monotherapy and SoC in all patients, regardless of PD-L1 status

- H_1: Difference in OS between either MEDI4736 + tremelimumab combination therapy or MEDI4736 monotherapy and SoC in all patients, regardless of PD-L1 status

The study will be considered positive if OS for either co-primary objective (MEDI4736 + tremelimumab versus SoC **or** MEDI4736 monotherapy versus SoC) is statistically significant.

The analysis of OS will be performed when:

- Approximately 375 death events have occurred in 480 patients (78% maturity) across the MEDI4736 + tremelimumab combination therapy and SoC arms regardless of PD-L1 status AND when

- Approximately 375 death events have occurred in 480 patients (78% maturity) across the MEDI4736 monotherapy and SoC arms, regardless of PD-L1 status

Interim analysis for OS will be performed when 300 death events (80% of required events) have been accumulated across the MEDI4736 + tremelimumab combination therapy and SoC arms. It is expected that approximately 300 death events would have accumulated across the MEDI4736 monotherapy and SoC arms at this time.

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.

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 randomization.

All data collected will be listed. Efficacy and PRO data will be summarized and analyzed based on the FAS. [redacted]
Safety data will be summarized on the Safety Analysis Set.

Results of all statistical analysis will be presented using a 95% confidence interval (CI) and 2-sided p-value, unless otherwise stated.

Table 15 provides an overview of all pre-planned statistical and sensitivity analyses.

Table 15 Pre-planned statistical and sensitivity analyses to be conducted

Endpoints analyzed	Notes
Overall survival	Stratified log-rank test and Cox proportional model for: Co-primary objectives – MEDI4736 + tremelimumab combination therapy versus SoC for all patients, regardless of PD-L1 status (stratified for PD-L1 status, tumor location/HPV status, and smoking status) – MEDI4736 monotherapy versus SoC for all patients, regardless of PD-L1 status (stratified for PD-L1 status, tumor location/HPV status, and smoking status) Secondary objectives: – MEDI4736 + tremelimumab combination therapy versus SoC in PD-L1 negative patients (stratified for tumor location/HPV status, and smoking status) – MEDI4736 monotherapy versus SoC in PD-L1 positive patients (stratified for tumor location/HPV status, and smoking status) – MEDI4736 + tremelimumab combination therapy compared to MEDI4736 monotherapy in PD-L1 negative patients (stratified for tumor location/HPV status, and smoking status) Sensitivity analysis using Kaplan Meier plot of time to censoring where the censoring indicator of the primary analysis is reversed – attrition bias .
Progression free survival	A similar analysis will be conducted as described above for overall survival. .
Proportion of patients alive at 12 months, 18 months, and 24 months	HR using the Kaplan-Meier estimates of survival at 12 months 18 months, and 24 months (following the method described by Klein et al 2007)
Objective response rate	Logistic regression using site Investigator assessment (RECIST 1.1)
Duration of response	Descriptive statistical and Kaplan Meier plots
Proportion of patients alive and progression free at 6 and 12 months	HR using the Kaplan Meier estimates of progression free survival at 6 and 12 months (following method described by Klein et al 2007).
Time from randomization to first subsequent therapy	Stratified log-rank test
Disease control rate	Logistic regression using site Investigator data (RECIST 1.1)
Best objective response	N (%) using site Investigator data (RECIST 1.1)
Time to symptom deterioration (EORTC QLQ-C30 and EORTC QLQ-H&N35 endpoints)	Stratified log-rank test
[redacted]	[redacted]

Multiple testing strategy

In order to strongly control the type I error at 5% (2-sided), a Multiple Testing Procedure (MTP) will be used across the co-primary objectives (OS in MEDI4736 + tremelimumab combination therapy versus SoC and OS in MEDI4736 monotherapy versus SoC), and across the analysis populations (all patients regardless of PD-L1 status and PD L1-negative population). If the highest level hypothesis in the MTP is rejected for superiority, the remaining hypothesis will then be tested as shown in Figure 6 below.

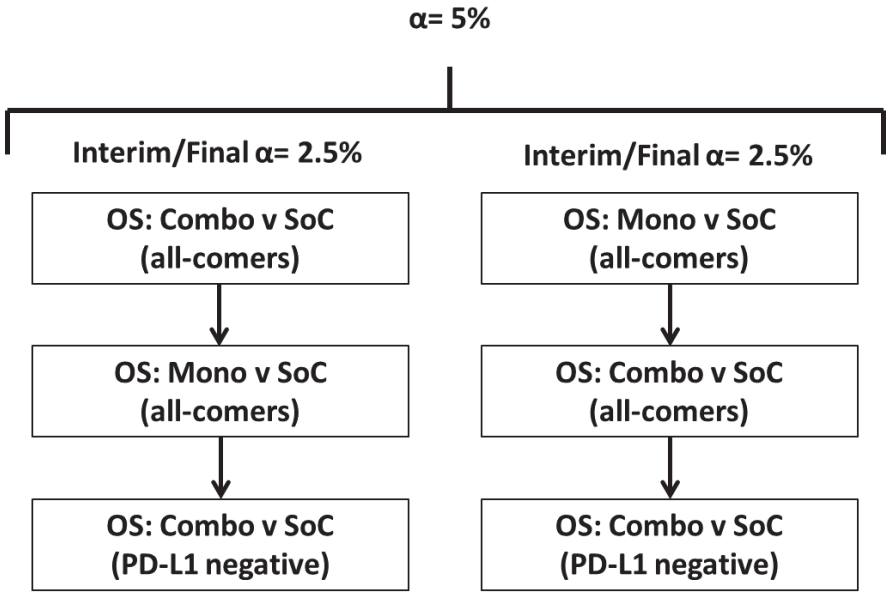
Hypotheses will be tested using an MTP with an alpha recycling strategy (Burman et al 2009). The initial levels of the MTP are shown in Figure 6

, and a full description of the detailed MTP, including the monotherapy versus SoC comparisons, is provided and documented in the statistical analysis plan. Of note, the comparisons of MEDI4736 + tremelimumab combination therapy versus MEDI4736 monotherapy will not be included in the MTP, and therefore will not be conducted under strict alpha control.

According to alpha (test mass) splitting and alpha recycling, the test mass that becomes available after each rejected hypothesis is recycled to the next hypotheses not yet rejected. Since OS is tested at multiple timepoints (ie, 1 interim analysis and final analysis) the OS tests for the same comparison/population (ie, shown in box 2 in the MTP) will be considered as 1 test family. As long as 1 test in the family can be rejected, the family is rejected, thus, the assigned total alpha to the family can be recycled to next MTP level.

The testing procedure stops when the entire test mass is allocated to a non-rejected hypothesis in the multiple testing procedure. Implementation of this pre-defined ordered testing procedure, including recycling, will strongly control type I error at 5% (2-sided), among all key hypotheses. Figure 6 shows the multiple testing procedure.
There will be one interim analysis of OS, conducted after approximately 80% of the target death events have been observed across MEDI4736 + tremelimumab combination therapy and SoC arms, and across MEDI4736 monotherapy and SoC arms, regardless of PD-L1 status. The alpha level allocated to OS for MEDI4736 + tremelimumab combination therapy versus SoC and MEDI4736 monotherapy versus SoC (all patients, regardless of PD-L1 status), will be controlled at the interim and final analysis time points by using the Lan-DeMets spending function (Lan and DeMets 1983) that approximates an O'Brien Fleming approach, where the alpha level applied at the interim depends upon the proportion of information available. If statistically significant, then testing for OS will continue in the PD-L1-negative population. A separate spending function will be used to adjust the alpha levels at the interim and final analyses in the PD-L1-negative population (See Section 8.5.13).

Figure 6 Initial Levels of the Multiple Testing Strategy



Combo: MEDI4736 + tremelimumab.
Mono: MEDI4736 monotherapy.
OS Overall survival; PD-L1 negative Patients with PD-L1–negative tumors; SoC Standard of Care; v Versus.

8.5.1 Overall Survival

8.5.1.1 Analysis of the co-primary variable (s)

The primary analysis of OS in MEDI4736 + tremelimumab and MEDI4736 monotherapy, in all patients, regardless of PD-L1 status will be done using a stratified log-rank test stratified by PD-L1 status (positive and negative), tumor location/HPV status (oropharyngeal cancer with HPV positive status, oropharyngeal cancer with HPV negative status, and non-oropharyngeal cancer regardless of HPV status), and smoking status (>10 and ≤10 pack-years). The effect of treatment will be estimated by the HR together with its corresponding (1-α) % CI and p-value, as described in the multiple strategy (Figure 6). The HR and its CI will be estimated using the stratified Cox proportional hazards model with treatment as the only covariate (Cox 1972).

The stratification factors 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.

8.5.1.2 Secondary Variables

OS will be analyzed in PD-L1-negative patients using a stratified log-rank test, adjusting for tumor location/HPV status, and smoking status.

For the comparisons of, MEDI4736+ tremelimumab combination therapy versus SoC in PD-L1-negative patients , treatment effects will be estimated by the HR together with their

corresponding (1-α)% CIs and p-values using the appropriate alpha, as described in the multiple strategy above (Figure 6). The HR and its CI will be estimated from the stratified Cox proportional hazards model (Cox 1972).

Kaplan-Meier plots of OS will be presented by treatment arm. Summaries of the number and percentage of patients who have died, those still in survival follow-up, those lost to follow-up, and those who have withdrawn consent will be provided along with the median OS for each treatment.

A similar analysis will be conducted to compare MEDI4736 monotherapy versus SoC in the PD-L1 positive patients as described above.

In addition, a secondary analysis of OS will be performed to compare MEDI4736 + tremelimumab combination therapy versus MEDI4736 monotherapy in the PD-L1-negative population as described above.

8.5.1.3 Analysis of OS in subgroup populations

For each one of the following subpopulations:

- PD-L1 status (positive, negative)
- Tumor location/HPV Status (oropharyngeal cancer with HPV positive status, oropharyngeal cancer with HPV negative status, and non-oropharyngeal cancer regardless of HPV status)
- Smoking Status (>10, ≤10 pack-years)
- Primary tumor site (oral cavity, oropharynx, hypopharynx, larynx)
- Prior radiation therapy (Yes, No)
- Use of chewing tobacco, oral snuff, and sublingual nicotine (Yes, No)
- Smoking history (current, former, never)
- Time to recurrence from last dose of platinum in a platinum-containing multimodality therapy (≤6 months, >6 months)
- Sex (male and female)
- Age at randomization (<65, ≥65 – <75, and ≥75 years of age)
- Race (Asian, non-Asian)
- Standard of Care (cetuximab, taxane, methotrexate, fluoropyrimidine-based regimen) if there is sufficient data for the analysis

- ECOG Performance status (0,1)
- Prior lines of systemic therapy for treatment of SCCHN (1, 2, ≥3)
- Extent of Disease (recurrent, recurrent and metastatic)

The comparisons will include MEDI4736 + tremelimumab combination therapy versus SoC (in all patients regardless of PD-L1status and in PD-L1-negative patients) and MEDI4736 monotherapy versus SoC (in all patients regardless of PD-L1 status). Treatment effect will be estimated by the HR together with its corresponding 95% CI using an unstratified Cox model with treatment as the only covariate. For standard of care subgroup analysis, only the SoC of interest will be included as a treatment factor (e.g. for comparison of MEDI4736 monotherapy versus cetuximab, the treatment factors will be MEDI4736 monotherapy and cetuximab).

Other baseline variables may also be assessed if there is clinical justification or if an imbalance is observed between the treatment arms. The purpose of the subgroup analyses is to assess the consistency of treatment effect across expected prognostic and/or predictive factors. Only HR estimate along with 95% CI will be presented. No adjustment to the significance level for testing of the subgroup and sensitivity analyses will be made since all these analyses will be considered supportive of the analysis of OS.

If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 20 events in a subgroup), the relationship between that subgroup and the primary endpoint (OS) will not be formally analysed. In this case, only descriptive summaries will be provided.

A forest plot will be presented comparing OS for MEDI4736 + tremelimumab combination therapy vs. SoC (in all patients regardless of PD-L1 status and in PD-L1 negative patients) and MEDI4736 monotherapy vs. SoC (in all patients regardless of PD-L1 status) within each subgroup.

8.5.1.4 Analysis of OS12, OS18, and OS24

OS12, OS18, and OS24 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 OS at 12 months (18 months, and 24 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 deaths 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).

8.5.1.5 Assumptions of Proportionality

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.

8.5.1.6 Sensitivity Analyses for OS

A sensitivity analysis for OS will examine the censoring patterns to rule out attrition bias, achieved by a Kaplan-Meier plot of time to censoring where the censoring indicator of OS is reversed.

Cox proportional hazards modelling will be employed to assess the effect of covariates on the HR estimate. Details will be presented in the SAP.

Impact of changing (crossover outside of this study) to immunotherapies (or other potentially active investigational agents) on overall survival analyses

Exploratory analyses of OS adjusting for the impact of subsequent immunotherapy or other investigational treatment may be performed if a sufficient proportion of patients change therapy. Methods such as Rank Preserving Structural Failure Time (Robins and Tsiatis 1991), Inverse Probability of Censoring Weighting (Robins 1993), and other methods in development will be explored. The decision to adjust and the final choice of methods will be based on a blinded review of the data and the plausibility of the underlying assumptions. Baseline and time-dependent characteristics will be explored, and summaries of baseline characteristics will be generated by treatment arm, designating between those that have and haven't changed immunotherapies at the time of the analyses. Further detail will be provided in the SAP and Payer Analysis Plan. These analyses are intended to support reimbursement appraisals.

8.5.2 Progression-free survival

PFS analyses will be based on the programmatically derived RECIST 1.1 data using the Investigator tumor assessments. The data will be analyzed from all patients, regardless of PD-L1 status, using stratified log-rank test as described for OS analyses in Section 8.5.1.1, above.

The effect of treatment will be estimated by the HR together with its corresponding CI and p-value. Kaplan-Meier plots of PFS will be presented by treatment arm, and by treatment arm and PD-L_1 tumor status subgroup. 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 for each treatment.

The assumption of proportionality will be assessed in the same way as for OS.

8.5.3 Objective response rate

The ORR will be based on the programmatically derived RECIST 1.1 using the site Investigator data. The ORR will be compared between MEDI4736 + tremelimumab combination therapy versus SoC and MEDI4736 monotherapy versus SoC using logistic regression models adjusting for the same factors as the co-primary objectives. The results of the analysis will be presented in terms of an odds ratio together with its associated profile likelihood 95% CI and p-value (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model).

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

8.5.4 Duration of response

In order to analyze the DoR descriptive data will be provided for the DoR in responding patients, including the associated Kaplan-Meier curves (without any formal comparison of treatment arms or p-value attached).

8.5.5 Proportion of patients alive and progression free at 6 months and 12 months

The APF6 and APF12 will be summarized (using the Kaplan-Meier curve) and presented by treatment arm. APF6 and APF12 will be compared between treatments by using the Kaplan-Meier estimator of PFS at 6 months and 12 months, respectively 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, where d_i and n_i refer to the number of deaths 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 (Weber et al 2012, Whitehead and Whitehead 1991)

8.5.6 Time from randomization to second progression

Second progression (PFS2) will be analyzed using identical methods as outlined for the analysis of PFS and adjusting for the same set of covariates, but no subgroup analysis will be performed. Medians and Kaplan–Meier plots will be presented to support the analysis.

8.5.7 Time from randomization to first subsequent therapy or death

For supportive purposes, the time to the start of subsequent therapy will be analyzed using the same methodology and model. The HR for the treatment effect together with its 95% CI will be presented. In addition, a Kaplan-Meier plot of the time to the start of subsequent therapy will be presented by treatment arm and the time between progression and starting subsequent therapy will be assessed. This interval will be summarized per treatment arm, but no formal comparisons will be made. No multiplicity adjustment will be applied as these are viewed as supportive endpoints.

In patients who received subsequent anticancer therapy, a summary table of first subsequent anticancer therapies by treatment arm will be provided, as well as response to first subsequent anticancer therapy by treatment arm (if available). A summary table of first subsequent therapies by treatment arm will be provided, as well as response to first subsequent therapy by treatment arm.

The number of patients prematurely censored will also be summarized.

8.5.8 Patient reported outcomes

The PRO endpoints that have been identified as secondary objectives are EORTC QLQ-C30 time to HRQoL deterioration for global health status, time to symptom deterioration for functional physical domain, time to symptom deterioration for fatigue, and QLQ-H&N35 time to symptom deterioration for these 2 symptoms; pain and swallowing. These are not part of the main MTP, and as supportive endpoints will need a Bonferroni adjustment to the significance level to aid interpretation. Therefore, these 5 endpoints will be tested at a 1.0% significance level and 99% CIs will be produced.

The other time to symptom deterioration endpoints will be tested at a 5% significance level and 95% CIs will be produced.

8.5.8.1 EORTC QLQ-C30

Time to symptom deterioration, for each of the 3 symptom scales (fatigue, pain, and nausea/vomiting). Time to HRQoL/function deterioration will be analyzed for the 5 function scales (physical, role, emotional, cognitive, and social) and global health status/QoL. These analyses will be done using a stratified log-rank test at the 5% significance level as described for the primary analysis of OS.

The treatment effect will be estimated by the HR together with its corresponding CI and p-value, using an unstratified Cox model with treatment as the only covariate. Time to deterioration will be presented using a Kaplan-Meier plot 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 by treatment group. Summaries of the number and percentage of patients who have an event as well as who were censored, will be provided along with the medians for each treatment.

A summary of the symptom improvement rate for each of the 3 symptom scales (fatigue, pain and nausea/vomiting) 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. Symptom improvement rate and HRQoL/function improvement rate will be analyzed by comparing between treatment arms using a logistic regression model as described for the analysis of ORR.

Summaries of absolute and change from baseline values for each of the 3-symptom scale/item (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 for each treatment arm. Graphical presentations may also be produced as appropriate.

8.5.8.2 EORTC QLQ-H&N35

Time to symptom deterioration for each of the 4 symptom scales/items in the QLQ-H&N35 (pain, swallowing, senses and speech) will be compared between treatment arms using a stratified log-rank test at the 5% significance level as described for the primary analysis of OS.

The treatment effect will be estimated by the HR together with its corresponding CI and p-value, using an unstratified Cox model with treatment as the only covariate.

For each of the above 4 symptom scales/items in the QLQ-H&N35, time to deterioration in symptoms will be presented using a Kaplan-Meier plots. 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 for each of the 4 symptom scales/items mentioned above will be produced. The symptom improvement rate will be compared between treatment groups using a logistic regression model as described for ORR.

Summaries of absolute and change from baseline values of each of the 7 symptom scale/item (pain, swallowing, senses, speech, social eating, social contact and sexuality) and 11 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 for each treatment group. Graphical presentations may also be produced as appropriate.

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8.5.10 Safety data

Safety and tolerability data will be presented by treatment arm using the safety population.

Data from all cycles of treatment will be combined in the presentation of safety data. AEs (both in terms of MedDRA preferred terms and CTCAE Grade) will be listed individually by patient. The number of patients experiencing each AE will be summarized by treatment arm and CTCAE Grade. Additionally, data presentations of the rate of AEs per person-years at risk may be produced. Any safety summaries examining retreatment with MEDI4736 will be produced separately.

Other safety data will be assessed in terms of physical examination, clinical chemistry, hematology, vital signs, and ECGs. Exposure to MEDI4736, MEDI4736 + tremelimumab, and SoC will be summarized. Time on study, MEDI4736, MEDI4736 + tremelimumab, and SoC dose delays/interruptions and dose reductions in the SoC arm will also be summarized. At the end of the study, appropriate summaries of all safety data will be produced, as defined in the SAP.

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8.5.14 Interim analysis

Interim safety monitoring will be conducted by an IDMC. Details of the plan and communication process will be provided in an IDMC Charter.

In addition, 1 interim analysis for OS will be performed for superiority when a total of approximately 300 death events (80% of required events) have been accumulated across the MEDI4736 + tremelimumab combination therapy and SoC arms in all patients, regardless of PD-L1 status; it is expected that approximately 300 death events have accumulated across the MEDI4736 monotherapy and SoC arms at this time.

The Lan-DeMets spending function that approximates an O'Brien Fleming approach will be used to account for the multiplicity introduced by including the interim analysis for superiority (Lan and DeMets 1983).

If exactly 80% of target death information is available at the time of the interim analysis, that is, 300/375 death events have been accumulated across MEDI4736 + tremelimumab combination therapy and SoC arms; and approximately 300/375 death events have been accumulated across MEDI4736 monotherapy and SoC arms, in all patients, regardless of PD-

L1 status, the 2-sided significance level to be applied for the interim and final analyses would be 1.0% and 2.2%, respectively for each co-primary objective.

If the interim analyses indicate superiority in either of the co-primary objective, then subsequent analysis of the secondary objective will be performed in accordance with the multiple testing strategy. A separate Lan-DeMets (O'Brien Fleming) spending function will be used to determine the alpha levels at the interim and final analyses for the secondary objective, as applicable. If the interim analysis results do not meet the criterion for stopping for superiority in either of the co-primary objective, then follow-up will continue until approximately 375 death events have been accumulated across MEDI4736 +tremelimumab combination therapy and SoC arms regardless of PD-L1 status; and approximately 375 death events have accumulated across MEDI4736 monotherapy and SoC arms in all patients, regardless of PD-L1 status. OS will be analyzed in all patients, regardless of PD-L1 status and in PD-L1-negative populations at the final analysis. Similarly, if the criterion for stopping for superiority is met at the interim in either of the co-primary objective, but is not met in the secondary objective (PD-L1-negative population) at that time, then follow-up will continue until the final target number of deaths in the PD-L1-negative population has been observed. The final analysis in the PD-L1-negative population will then be conducted.

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 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, 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 (medical, nursing, and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the 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 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 the location of source data.

9.2.2 Direct access to source data in Japan

The Head of the study site and the Principal Investigator/Investigator will cooperate for monitoring and audit by AstraZeneca and accept inspection by the Institutional Review Board (IRB) or regulatory authorities. All study documents such as raw data will be open for direct access to source data at the request of the monitor and the auditor of AstraZeneca, the IRB, or regulatory authorities.

The monitor will verify data from the eCRFs against source data before the Principal Investigator signs the eCRFs to ensure accuracy and completeness of documentation and ensure that the Principal Investigator has submitted the eCRFs to AstraZeneca. If the Investigator wishes to amend the collected eCRFs, the monitor will ensure that the Principal Investigator has recorded the amendment with signature and date and has provided this to AstraZeneca.

9.2.3 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 and the Principal Investigator should be in place before any study-related procedures can take place, or before any patients are enrolled.

9.2.4 Archiving of study documents

The Investigator will follow the principles outlined in the CSA.

9.3 Study timetable and end of study

The end of the study is defined as the "last visit of the last patient undergoing the study." The Investigator will be notified by the Sponsor when recruitment is complete.

The study is expected to start in Q2 2015 and end by Q2 2018.

The study may be terminated at individual centers if the study procedures are not being performed according to Good Clinical Practice (GCP) or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study involving MEDI4736.

9.4 Data management by AstraZeneca or delegate

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 Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed, and locked, a clean file will be declared. Any treatment-revealing data may be added thereafter, and the final database will be locked.

Serious adverse event reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

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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. The applicable regulatory requirements in Japan are 'Good Clinical Practice for Trials on Drugs' (Minister of Health, Labor, and Welfare [MHLW] Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications).

10.2 Patient data protection

The ICF 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. Even so, the patient's medical information and the genetic files would remain physically separate.

10.3 Ethics and regulatory review

An Ethics Committee (EC)/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 before enrolment of any patient into the study.

The EC/IRB should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC/IRB annually.

Before enrolment 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 will handle the distribution of these documents to the national regulatory authorities.

AstraZeneca 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 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.

For sites in Japan only

If any new information on the study medication becomes available that may influence the decision of the patient to continue the study, the Investigator should inform the patient of such information immediately, record this in a written form, and confirm with the patient if he or she wishes to continue the participation in the study. In addition, if the Investigator deems it necessary to revise the ICF, they should revise it immediately (Refer to Section 10.6). The Investigator should re-explain to the patients using updated ICF even if the patients have already been informed of the new information verbally. Written informed consent to continue participation in the study should be provided separately.

10.5 Changes to the protocol and informed consent form

For sites outside Japan

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 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 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 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.

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.

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APPENDIX D ACTIONS REQUIRED IN CASES OF COMBINED INCREASE OF AMINOTRANSFERASE AND TOTAL BILIRUBIN - HY'S LAW

1. 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.

2. 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.

3. Identification of potential hy's law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any 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 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

4. Follow-up

4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment in the presence of liver metastases (see Section 6)
- 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

5. Review and Assessment of potential hy's law cases

The instructions in this section should be followed for all cases where PHL criteria are met.

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

6. 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 0 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.

7. 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 6?

If No: follow the process described in Section 0 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 0 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.

8. 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)

1. Introduction

This appendix details the implementation of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines (**Eisenhauer et al 2009**) for the D4193C00002 study with regards to Investigator assessment of tumor burden including protocol-specific requirements for this study.

2. Definition of Measurable, Non-Measurable Target and Non-Target Lesions

Only patients with measurable disease at baseline should be included in the study. Measurable disease is defined by the presence of at least one measurable (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, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.

[1] Nodes with <10 mm short axis are considered non-pathological and should not be recorded or followed as non-target lesions (NTLs).

- 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. Lymph nodes, in any location, are collectively considered as a single organ, with a maximum of 2 lymph nodes as TLs. A bilateral organ is considered as a single organ.

Non-target lesions:

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

3. Methods of Assessment

The same method of assessment and the same technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits.

A summary of the methods to be used for RECIST assessment is provided in Table 16, and those excluded from tumor assessments for this study are highlighted with the rationale provided.

[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.

Table 16 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.

3.1 CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and identification of any new lesions.

In the D4193C00002 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.

3.2 Clinical examination

In the D4193C00002 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.

3.3 X-ray

3.3.1 Plain X-ray

In the D4193C00002 study plain X-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

3.4 Ultrasound

In the D4193C00002 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.

3.5 Endoscopy and laparoscopy

In the D4193C00002 study, endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor assessment.

3.6 Tumor markers

In the D4193C00002 study, tumor markers will not be used for tumor response assessments as per RECIST 1.1.

3.7 Cytology and histology

In the D4193C00002 study histology will not be used as part of the tumor response assessment as per RECIST 1.1.

3.8 Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

In the D4193C00002 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.

3.9 FDG-PET scan

In the D4193C00002 study,[18] F-Fluorodeoxyglucose 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]F-Fluorodeoxyglucose 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 CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

[3] A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT are of limited use in anatomically-based efficacy assessments, and it is therefore suggested that they should not substitute for dedicated diagnostic contrast-enhanced CT scans for tumour measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed, as part of a PET/CT examination, is of identical diagnostic quality (with intravenous contrast) to a dedicated diagnostic CT scan, then the CT portion of the PET/CT can be used for RECIST measurements. However, this is not recommended because the PET portion of the CT introduces additional (PET) data that may bias an Investigator if it is not routinely or serially performed.

4. Tumor response evaluation

4.1 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 and Table 3 of the Clinical Study Protocol). Follow-up assessments will be performed every 8 weeks (relative to the date of randomization), until 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 IMT 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.

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.

4.2 Target lesions

4.2.1 Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes collectively considered as a single organ), 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 and the intervention recorded in the RECIST case report form.

4.2.2 Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumor visit response for TL (see Table 17).

Table 17 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.

4.3 Non-target lesions

4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit (see Table 18).

Table 18 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.

4.4 New lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: 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.

4.5 Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

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

4.6 Evaluation of overall visit response

The overall visit response will be derived using the algorithm shown in Table 19.

Table 19 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).

5. Confirmation of progression

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.

Objective disease progression according to RECIST 1.1 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 scan timepoints with an absolute increase of 5mm [(1)]
- *and/or* significant progression (worsening) of NTLs at the confirmatory scan time-point compared with the first time point where progression of NTLs was identified (Note: new lesions identified at the previous scan timepoints are considered non-target lesions at the confirmatory scan timepoint)
- and/*or* additional new unequivocal lesions at the confirmatory scan time-point.

[(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 significant clinical deterioration the investigator should continue IMT treatment until progression is confirmed. If progression is not confirmed then the patient should continue on IMT treatment and on treatment assessments. Treatment through PD in the Standard of Care group is at the Investigator's discretion; however, a confirmatory scan is required for all patients in the Standard of Care group even if a subsequent treatment is started.

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 confirmed objective disease progression.

6. Specifications for radiological imaging

These notes are recommendations for use in clinical studies. The use of standardized protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

6.1 CT scan

CT scans of the chest and abdomen (and pelvis when indicated) should be contiguous throughout all the anatomic region of interest.

The most critical CT image acquisition parameters for optimal tumor evaluation using RECIST 1.1 are *anatomic coverage, contrast administration,* and *slice thickness and reconstruction interval.*

a. Anatomic coverage: Optimal anatomic coverage for most solid tumors is the chest, abdomen, and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumor measurements but also identification of new disease.

b. Intravenous (IV) contrast administration: Optimal visualisation and measurement of metastases in solid tumors requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow- up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumor type and anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution with these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study, then the recommended methods are: CT thoracic (chest) examination without contrast and abdominal (and pelvis) MRI with contrast. If MRI cannot be performed, then CT without IV contrast is an option for the thorax and abdomen (and pelvis) examination. For brain imaging, MRI with IV contrast is the preferred method.

c. Slice thickness and reconstruction interval: It is recommended that CT scans be performed at 5mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Exceptionally, institutions

may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the tumor lesion should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not **"selected" images of the apparent lesion.**

6.2 MRI scan

MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium-enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression, and fast sequences should be optimised for the specific body part being imaged as well as the scanner utilized. It is beyond the scope appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the imaging modality of choice.

6.3 CT portion of PET/CT scans

At present, low dose or attenuation correction CT portions of a combined PET/CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for tumor measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed as part of a PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET/CT can be used for RECIST 1.1 measurements. However, this is not recommended because the PET portion of the CT introduces additional data that may bias an investigator, if it is not routinely or serially performed.

7. 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, EORTC QLQ-H&N35, [redacted] AND [redacted] PATIENT REPORTED OUTCOMES:

ENGLISH

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

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 QLO - 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

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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ITCHY SKIN

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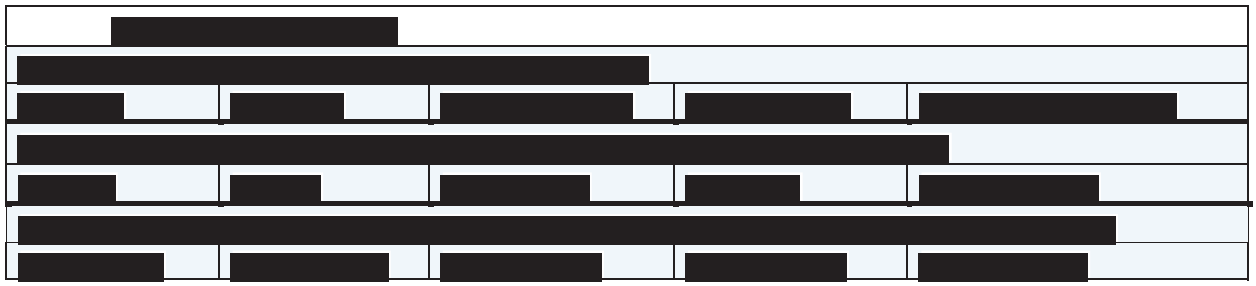

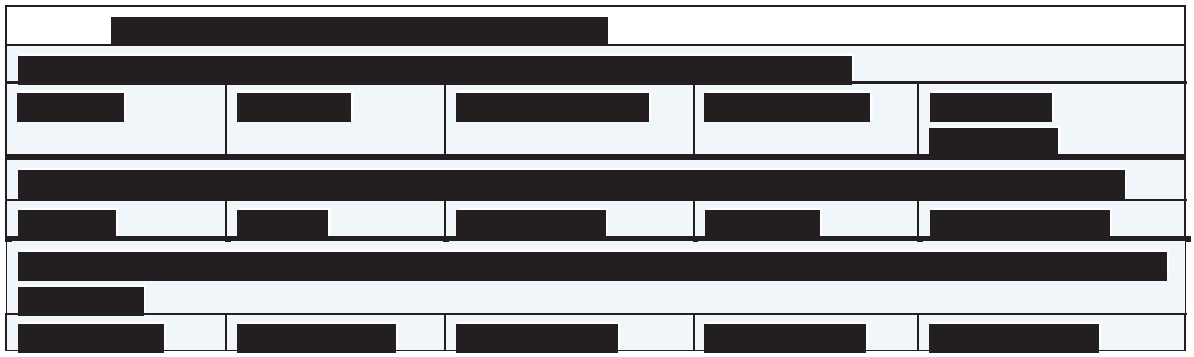

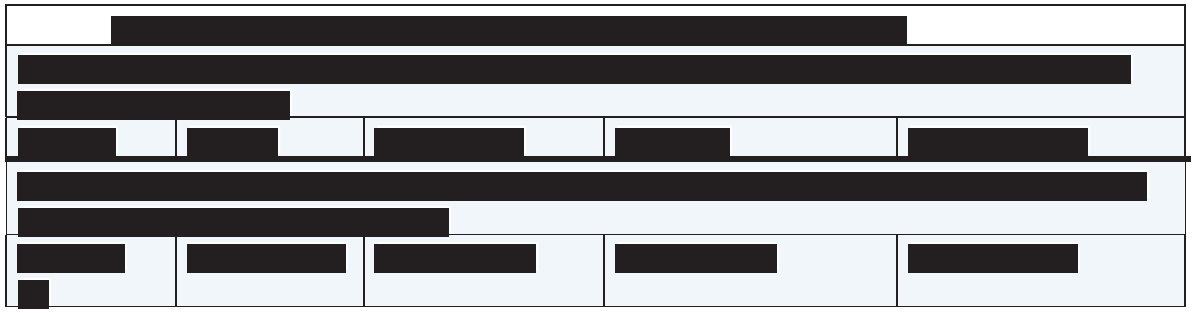

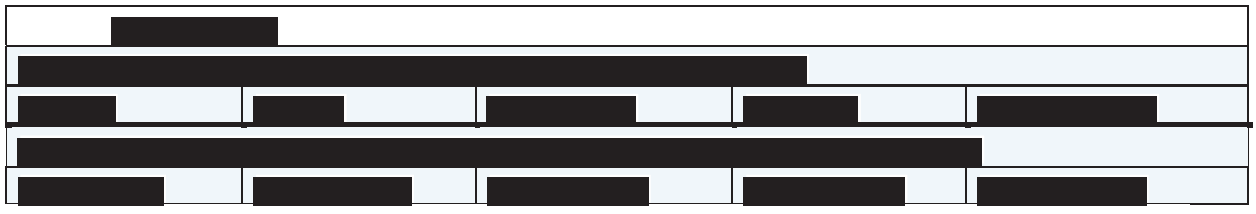

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Drug Substance MEDI4736 and tremelimumab
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SIGNATURE PAGE

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