Clinical Study Protocol

Drug Substance	MEDI4736 and Tremelimumab
Study Code	D419LC00001
Version	12.0
Date	29 June 2020

A Phase III Randomized, Open-label, Multi-center, Global Study of MEDI4736 Alone or in Combination with Tremelimumab versus Standard of Care in the Treatment of First-line Recurrent or Metastatic Squamous Cell Head and Neck Cancer Patients

Sponsor:

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VERSION HISTORY

Version 12.0, 29 June 2020
Changes to the protocol are summarized below.

Change of primary objective from MEDI4736 monotherapy versus Standard of Care (SoC) in patients who are at low risk of early mortality based on baseline laboratory values according to a model developed by AstraZeneca in terms of SoC, to MEDI4736 versus SoC in a biomarker-selected population (PD-L1 TC/IC high subgroup) in terms of overall survival (OS).

The primary objective of the study has been changed from MEDI4736 monotherapy versus SoC in patients who are at low risk of early mortality based on baseline laboratory values according to a specific prognostic model developed by AstraZeneca CCI [redacted] to MEDI4736 versus SoC in a biomarker-selected subgroup (PD-L1 TC/IC high) in terms of OS. MEDI4736 monotherapy versus SoC in the population at low risk of early mortality will be included as a secondary objective in order to maximize the information generated on the utility of this model. The multiple testing procedure (MTP) has been updated accordingly to reflect this change. In line with the changes to the primary objective, the analysis of OS will be performed when approximately 147 death events have occurred in approximately 172 patients (85% maturity) across the MEDI4736 monotherapy and SoC treatment groups in the biomarker-selected population (PD-L1 TC/IC high subgroup).

All relevant sections throughout the protocol have been updated to reflect these changes. This includes the Synopsis, Section 1.2.5 (Study population rationale), Section 1.2.6 (Rationale for endpoints), Section 2.1 (Primary objective), Section 2.2 (Secondary objectives), Section 2.3 (Safety objective), Section 8.2 (Sample size estimate), Section 8.3 (Definitions of analysis sets), 8.4 (Outcome measures for analysis) and Section 8.5 (Methods for statistical analysis).

This revision to the primary objective to focus on the PD-L1 high subgroup (TC/IC) is intended to address feedback from the US FDA regarding the use of the prognostic model to define a primary analysis population in KESTREL. The resulting changes are informed based on data external to the KESTREL study. Specifically, the phase 3 KEYNOTE-048 study, which demonstrated that pembrolizumab monotherapy improved OS when compared with the EXTREME regimen in patients whose tumors had PD-L1 expression ≥1 and ≥20 by Combined Positive Score (CPS) [hazard ratio (HR) 0.78 (0.64–0.96), P=0.0086 and HR 0.61 (0.45– 0.83), P=0007, respectively] (Burtness et al., 2019). The PD-L1 high cut-point (TC50/IC25) was previously defined (see KESTREL CSPv7.0). Additional data analysis from the Sponsor's Phase 3 D4193C00002 (EAGLE) study in second line squamous cell head and neck cancer (HNSCC) appear to further support the utility of PD-L1 to select patients with improved outcome when treated with MEDI4736. CCI [redacted] When controlling for prognostic factors, the multivariate analysis of patients treated with MEDI4736 shows a tendency to better OS in the PD-L1 high (TC/IC) vs PD-L1 low

subgroup [HR=0.80 (95% CI 0.58–1.09)]. The primary objective will include the MEDI4736 monotherapy arm vs SoC (EXTREME), as the body of evidence described above supports that the primary utility of PD-L1 blockade in treatment of recurrent or metastatic HNSCC appears to be as in patients whose tumors express sufficient levels of PD-L1.

Changes not related to the analysis of the primary objective include the following:

Synopsis, Section 8.5 (Methods for statistical analysis). These sections have been updated to include OS analysis in MEDI4736 + tremelimumab ctDNA TMB≥16 mut/Mb as the fourth tier in the MTP based on ctDNA TMB results from the EAGLE study (Li et al 2020) and growing evidence of the value of this biomarker for identifying patients who may benefit from MEDI4736 + tremelimumab treatment.

Synopsis, Section 1.2.6 (Rationale for endpoints), Section 2.2 (Secondary objectives), Section 8.2 (Sample size estimate), Section 8.3 (Definition of analysis sets), Section 8.5 (Methods for statistical analysis). These sections have been updated to remove OS noninferiority analysis for MEDI4736 versus SoC in all randomized patients (all-comers) as a secondary objective and as the second level of the MTP.

Synopsis, Section 2.3 (Safety objective), 8.3 (Definition of analysis sets), 8.5 (Methods for statistical analysis). These sections have been updated to include the low risk of early mortality subgroup in the safety objectives.

In addition to the changes listed above, minor administrative corrections have been made throughout the protocol and are not detailed here further.

Version 11.0, 04 October 2019
Changes to the protocol are summarized below.

Change of primary objective from MEDI4736 monotherapy versus SoC in all randomized patients (all-comers) in terms of OS to MEDI4736 monotherapy versus SoC in patients who are at low risk of early mortality based on baseline characteristics in terms of OS.

The primary objective of the study has been changed from MEDI4736 monotherapy versus SoC in all randomized patients (all-comers) to MEDI4736 monotherapy versus SoC in patients who are at low risk of early mortality based on baseline characteristics (hereafter referred to as "primary analysis population") in terms of OS. The primary analysis population consists of patients identified by a model developed by AstraZeneca as having low risk of early mortality. The multiple testing procedure has been updated accordingly to reflect this change. In line with the changes to the primary objective, the analysis of OS will be performed when approximately 254 death events have occurred in approximately 304 patients (84% maturity) across the MEDI4736 monotherapy and SoC treatment groups in the primary analysis population.

All relevant sections throughout the protocol have been updated to reflect these changes. This includes the Synopsis, Section 1.2 (Rationale for study design, doses and control

groups), Section 1.2.5 (Study population rationale), Section 1.2.6 (Rationale for endpoints), Section 2.1 (Primary objective), Section 2.2 (Secondary objectives), Section 8.2 (Sample size estimate), Section 8.3 (Definitions of analysis sets) and Section 8.5 (Methods for statistical analysis).

This change has been made based on emerging data that are external to the KESTREL study. Immune checkpoint inhibitors (ICIs) are profoundly changing the treatment of many types of cancer, including melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma (UC), and Hodgkin's lymphoma, and have been associated with long-lasting tumor responses. However, an early mortality (EM) phenomenon has been observed in many randomized clinical trials comparing ICIs with active comparator arms in advanced or metastatic cancer patients, even with overall benefit ultimately favoring ICI therapy (Champiat et al 2018). While the precise etiology of this phenomenon is not clearly established, it is characterized by what seems to be disproportionately higher mortality in the early treatment period favoring the active control arm, followed by subsequent benefit in overall survival (OS) favoring the ICI treatment arm. This is often reflected in the clinical data by the "crossing of the Kaplan-Meier curves" suggesting a subpopulation of patients at a higher risk of EM whose advanced rate of tumor growth may require the cytotoxic tumor-debulking effect of chemotherapy. Accordingly, it is of great therapeutic interest to better predict the risk of early mortality for a given patient to better inform the appropriate treatment for their individual clinical state. To aid in this objective, AstraZeneca has developed and implemented a model that predicts a patient's risk of early mortality to optimize the benefit:risk profile for treatment of patients with ICIs.

Changes not related to the analysis of the primary objective include the following:

Synopsis, Section 1.2.6 (Rationale for endpoints), Section 2.2 (Secondary objectives), Section 8.2 (Sample size estimate), Section 8.3 (Definition of analysis sets), Section 8.5 (Methods for statistical analysis). These sections have been updated to include OS noninferiority analysis for MEDI4736 versus SoC in all randomized patients (all-comers) as a secondary objective and as the second level of the MTP.

Synopsis, Section 1.2.6 (Rationale for endpoints), Section 2.2 (Secondary objectives), Section 8.2 (Sample size estimate), Section 8.3 (Definition of analysis sets) and Section 8.5 (Methods for statistical analysis). These sections have been updated to include OS analysis in the ctDNA Tumor Mutation Burden (TMB) subgroups for MEDI4736 versus SoC as the third level of the MTP and to specify the cutoff value for the ctDNA TMB high subgroup.

In addition to the changes listed above, minor administrative corrections have been made throughout the protocol and are not detailed here further.

Version 10.0, 25 January 2019
Changes to the protocol are summarized below.

Change of primary objective from MEDI4736 + tremelimumab combination therapy versus SoC in a biomarker-selected subgroup (PD-L1 TC/IC), to MEDI4736 monotherapy versus SoC in all randomized patients (all-comers) in terms of OS.

The primary objective of the study has been changed from MEDI4736 + tremelimumab combination therapy versus SoC in a biomarker-selected subgroup (PD-L1 TC/IC), to MEDI4736 monotherapy versus SoC in all randomized patients (all-comers) in terms of OS. The multiple testing procedure has been updated accordingly. In line with the changes to the primary objective, the analysis of OS will be performed when approximately 336 death events have occurred in 380 patients (88% maturity) across the MEDI4736 monotherapy and SoC treatment groups in the all-comers population, and also when approximately 147 death events from the PD-L1 TC/IC subgroup have occurred in 172 patients (85% maturity) across the MEDI4736 monotherapy therapy and SoC treatment groups.

All relevant sections throughout the protocol have been updated to reflect these changes. This includes the Synopsis, Section 1.2 (Rationale for study design, doses and control groups), Section 1.2.6 (Rationale for endpoints), Section 1.4 (Study design), Section 2.1 (Primary objective), Section 2.2 (Secondary objectives), Section 8.1 (Statistical considerations), Section 8.2 (Sample size estimate), Section 8.5 (Methods for statistical analysis).

This change has been made based on emerging data in the field that are external to the KESTREL study, specifically recently announced results from a phase 3 study in 2nd line recurrent/metastatic HNSCC patients (EAGLE).

Changes not related to the analysis of the primary endpoints include the following:

Synopsis, Section 1.2.5 (Study Population Rationale), Section 2.2 (Secondary objectives), Section 2.4 (Exploratory Objectives), Section 5.5.2.1 CCI [redacted]**, Section 8.3 (Definition of Analysis Sets). Section 8.5 (Methods for Statistical Analysis)**
These sections have been updated to include ctDNA Tumor Mutational Burden (TMB) as a secondary analysis to investigate TMB as a marker of response to MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy. This analysis has been changed from an exploratory objective to a secondary objective.

Section 2.4 (Exploratory objectives), Section 5.5.2.1 CCI [redacted]

Section 6.3.9 (Safety data to be collected following the final data cut-off of the study) and Section 7.2.2 (Duration of treatment (post final data cut-off)
These sections have been updated to clarify procedures following final data cut-off of the study.

Section 6.7.2 (Specific toxicity management and dose modification information – MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy)

This section has been updated to clarify that the Toxicity Management Guidelines (TMGs) for durvalumab and tremelimumab will be provided to investigative sites as an Annex to the protocol document.

In addition to the changes listed above, minor administrative corrections have been made throughout the protocol and are not detailed here further.

Version 9.0, 03 October 2018

Changes to the protocol are summarized below.

Change of Overall Survival in the all-comer population from primary objective to secondary objective

OS in the all-comer population has been changed from a co-primary objective to a secondary objective of the study. OS in the PD-L1 TC/IC subgroup remains as the sole primary objective. The multiple testing procedure has been updated accordingly. In line with the changes to the primary objective, the requirement for OS analysis to be performed when 495 death events from the all-comers population have occurred in 570 patients (87% maturity) has been removed. OS analysis will be performed when approximately 213 death events from the PD-L1 TC/IC subgroup population have occurred in 257 patients (83% maturity) across the MEDI4736 + tremelimumab combination therapy and SoC treatment groups and also when approximately 147 death events from the PD-L1 TC/IC subgroup population have occurred in 172 patients (85% maturity) across the MEDI4736 monotherapy therapy and SoC treatment groups.

All relevant sections throughout the protocol have been updated to reflect these changes. This includes the Synopsis, Section 1.2.6 (Rationale for endpoints), Section 2.1 (Primary objective), Section 2.2 (Secondary objectives), Section 2.3 (Safety objective), Section 8.2 (Sample size estimate), Section 8.3 (Definitions of analysis sets), Section 8.4 (Outcome measures for analysis), Section 8.5 (Methods for statistical analysis), Section 11 (References).

This change has been made based on emerging data in the field that are external to the KESTREL study. Specifically, recently announced interim analysis results from a phase 3 study in 1st line recurrent/metastatic HNSCC patients (KEYNOTE-048) demonstrated that the PD-1 inhibitor Pembrolizumab monotherapy in patients with PD-L1 expression (Combined Positive Score (CPS) $\geq$ 20) resulted in significantly longer OS compared to the current standard of care for HNSCC in the first-line treatment setting. At the time of the interim analysis, the dual-primary endpoint of PFS for patients whose tumors expressed PD-L1 (CPS $\geq$ 20) had not been reached. In addition, recent analysis of mature HAWK (D4193C00001)/CONDOR (D4193C00003) data using the TC50/IC25 algorithm confirmed that OS was signicantly improved in the PD-L1 (TC50/IC25) population.

Changes not related to the analysis of the primary endpoints include the following:

Synopsis, Section 1.2.6 (Rationale for endpoints), Section 2.2 (Secondary objectives), Section 8.3 (Definition of analysis sets) and Section 8.5 (Methods for statistical analyses)
These sections have been updated to include DoR, BoR, TFST, TSST, APF6 and APF12 as secondary objectives to assess the efficacy of MEDI4736 monotherapy compared to SoC. This change has been made to aid clinical interpretation of the MEDI4736 monotherapy data following the update to the multiple testing procedure, and for consistency with the secondary efficacy objectives for the MEDI4737 + tremelimumab combination therapy.

Section 1.3.2.1 (MEDI4736), Section 4 (Study plan and timing of procedures), Section 6.7.1. (MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy adverse events of special interest), Section 6.7.2 (Specific toxicity management and dose modification information – MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy)
These sections have been updated to inform Investigators that the Toxicity Management Guidelines (TMGs) for durvalumab and tremelimumab have been removed from the protocol (Table 8) and have become a standalone document. The most current version of these guidelines is to be maintained within the Site Master File. In addition, a version of the current TMG is available via https://tmg.azirae.com

Section 8.3.1 (PD-L1 TC/IC subgroup analysis)
This section has been updated to clarify the definition of PD-L1 high and PD-L1 low.

Section 11 (References)
The following reference was removed in order to be consistent with changes made elsewhere in the protocol: Burman et al 2009.

In addition to the changes listed above, minor administrative corrections have been made throughout the protocol and are not detailed here further.

Version 8.0, 13 Feb 2018
Changes to the protocol are summarized below.

Change of Progression Free Survival from primary objective to secondary objective
PFS in the all-comer population has been changed from a primary objective to a secondary objective of the study. Accordingly, the primary analysis of the secondary objective of PFS will now be conducted using investigator assessments and the sensitivity analysis will now be conducted by BICR.

All relevant sections throughout the protocol have been updated to reflect these changes. This includes the Synopsis, Section 1.2.6 (Rationale for endpoints), Section 1.4 (Study design), Section 2.1 (Primary objective), Section 2.2 (Secondary objectives), Section 8.2 (Sample size), Section 8.4.1 (Calculation or derivation of efficacy variables) and Section 8.5 (Methods for statistical analyses). Table 12 (Summary of statistical assumptions)

has been updated. Appropriate changes have been made throughout Section 8.5 (Methods for statistical analysis), including revision of the multiple testing procedure (Figure 6) and removal of PFS analyses based on subgroups within the full analysis set.

This change has been made based on emerging data in the field that are external to the KESTREL study. Specifically, recently published data from 2 phase 3 trials in 2nd line R/M HNSCC patients demonstrated that despite showing improvements for PD-1 inhibitors compared to standard of care in terms of OS, there was no such improvement for PD-1 for PFS (Ferris et al, N Engl J Med 2016, 375:1856-1867; Cohen et al, Annals of Oncology 2017, 28(suppl_5):v372-v394). Numerically similar results were obtained in two phase 2 studies with durvalumab in a similar patient population (Zandberg et al, Annals of Oncology 2017, 28(suppl_5):v372-v394; data on file). Consequently, PFS is not considered to be a useful primary endpoint in this disease setting with such therapies. Investigator assessments are considered acceptable for secondary objectives and therefore the outcome measure for PFS has been changed from BICR to investigator assessments.

Removal of interim analysis for Overall Survival
The interim analysis for overall survival has been removed. All relevant sections throughout the protocol have been updated to reflect this change. This includes the Synopsis, Section 8.2 (Sample size), Section 8.4.1 (Calculation or derivation of efficacy variables) and Section 8.5 (Methods for statistical analyses); and Section 8.5.8 (Interim analysis). Table 12 (Summary of statistical assumptions) has been updated to reflect the statistical assumptions for the primary objectives following the removal of the interim analysis for OS. This change has been made in order to allocate the full alpha on the final OS analysis, which is considered optimal when comparing against an active standard of care regimen.

Increase in maturity level for the analysis of Overall Survival
The timing of the analysis of overall survival remains event driven. In order to increase the maturity of overall survival events to ~85% in both the all-comers and the PD-L1 TC/IC subgroup, the number of events required for the analysis has been increased (thereby increasing the power for the assumed average HR). All relevant sections throughout the protocol have been updated to reflect this change. This includes the Synopsis, Section 8.2 (Sample size), Section 8.4.1 (Calculation or derivation of efficacy variables) and Section 8.5 (Methods for statistical analyses). This change has been made in order to maximize the amount data available for the analysis of overall survival, which is considered optimal for immune checkpoint inhibitors which appear to be associated with long term clinical benefit.

Changes not related to the analysis of the primary endpoints include the following:

Synopsis, Section 2.2 – Secondary objectives, Section 8.4.1.2 – RECIST-based secondary endpoints, and Section 8.5 – Methods for statistical analysis
These sections have been updated to reflect that investigator assessments, rather than BICR, will be used to derive the secondary objectives of ORR, DoR, BoR, APF6 and APF12. In accordance with this change, the sensitivity analysis for PFS has been

updated to reflect that it is now based on BICR assessment rather than investigator assessment. The change from BICR to investigator assessments was made to align with the outcome measure of the secondary objective of PFS.

Synopsis, Section 2.2 – Secondary objectives, and Section 8.4.1.2 – RECIST-based secondary endpoints
These sections have been updated to include APF6, OS12 and OS18 as secondary objectives, as the proportion of patients alive, or alive and progression free, at these time points is considered to be a clinically meaningful objective.

Section 1.3.2 – Identified and potential risks
The identified and potential risks associated with MEDI4736, tremelimumab, and MEDI4736 in combination with tremelimumab have been updated in order to align with the recently revised Investigator Brochures (MEDI4736 IB edition 12, 03 November 2017; tremelimumab IB edition 8, 02 November 2017)

Section 3.10.3 – Survival status for withdrawn consent and lost to follow up patients
This section has been updated to clarify the reasons patients should be documented as "lost to follow-up" or "withdrawal of consent", and that in order to support the primary endpoint of OS, the survival status of all patients should be re-checked and the case report forms updated if appropriate.

Section 6.7.1 – MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy adverse events of special interest
This section has been updated to include the following as adverse events of special interest for MEDI4736 as monotherapy or in combination with tremelimumab: myocarditis, myositis/polymyositis, and other inflammatory responses that are rare but with a potential immune mediated aetiology. In addition, the AESI of colitis was expanded to include diarrhea and intestinal perforation and the AESI of endocrinopathies was expanded to include hypopituitarism and type I diabetes mellitus. These changes were made in order to align with the recently revised Investigator Brochure (MEDI4736 IB edition 12, 03 November 2017).

Section 6.7.2 – Specific toxicity management and dose modification information – MEDI4736 + tremelimumab combination therapy and MEDI473 monotherapy
This section has been updated to inform investigators that the most current version of the Toxicity Management Guidelines (TMGs) is also available through the following link: https://tmg.azirae.com. In addition, clarification has been provided regarding the importance of thoroughly evaluating patients for potential alternate etiologies when assessing immune-mediated adverse events, and that in the absence of a clear alternative etiology, events should be considered potentially immune related.

Table 8 has been updated to include toxicity management guidelines for events of myocarditis, myositis/polymyositis, as well as for hepatitis-related events in patients with hepatocellular carcinoma; pediatric considerations are also included, although these are not relevant to the current study population. In addition, the toxicity management guidelines have clarified that study drug/study regimen should be permanently discontinued for Grade 3 events with high likelihood for morbidity and/or mortality,

even if they are not currently noted in the guidelines. It has also been clarified that permanent discontinuation of study drug is not required for Grade 4 events of hyperthyroidism, hypothyroidism, or Type 1 diabetes mellitus. These changes have been made in order to align with the toxicity management guidelines across the durvalumab development program.

Section 7.2.2 – Duration of treatment
This section has been updated to clarify that patients who continue to receive benefit from their assigned treatment at the time of database closure may continue to receive treatment for as long as they are gaining clinical benefit, and that such patients are recommended to continue scheduled site visits and be monitored in order to manage AEs in accordance with the toxicity management guidelines. In addition, any patient that may be proposed to move to a safety extension or roll-over study would be given a new Informed Consent Form.

Section 8.3.2 – PD-L1 TC/IC subgroup analysis set
This section has been updated to clarify that the assay used to define patients in the PD-L1 TC/IC subgroup analysis set is the analytically validated VENTANA PD-L1 (SP263) assay.

Section 8.5.2.4 – Proportion of patients alive and progression free at 6 and 12 months
This section has been updated to to clarify that proportion of patients alive and progression free at 6 and 12 months will be summarized using the Kaplan-Meier curve. This change was made to be consistent with standard statistical methodology.

Section 8.5.2.7 – Proportion of OS 12, 18, and 24
This section has been updated to clarify that the proportion of patients alive at 12, 18 and 24 months will be summarized using the Kaplan-Meier curve. This change was made to be consistent with standard statistical methodology.

Section 11 – References
The following references were removed in order to be consistent with changes made elsewhere in the protocol: Klein 2007, Lan and DeMets 1983, Pazdur 2008, Sun and Chen 2010, and Whitehead and Whitehead 1991.

In addition to the changes listed above, minor administrative corrections have been made throughout the protocol and are not detailed here further.

Version 7.0, 10 May 2017
Changes to the protocol are summarized below.

Addition of Primary Objective for Overall Survival in a Biomarker Selected Subgroup
A primary objective has been added for OS in a PD-L1 TC/IC-selected subgroup, defined as those patients having PD-L1 expression at any intensity in ≥ 50% of tumor

cells or ≥25 % of tumor-associated immune cells (PD-L1 TC/IC subgroup; TC≥50 or IC≥25). In order to control the family wise error rate, the MTP has been adjusted. The wording to describe the primary endpoints has also been adjusted to avoid using the term "co-primary" (as this is more correctly applied only for situations where all the primary endpoints need to be significant, where-as we have used an MTP that enables a claim if only one is significant). Furthermore, secondary objectives assessing the same endpoints for the all-comers have been added for the PD-L1 TC/IC-selected subgroup. The timing of the PFS analysis has been moved to coincide with the same time as the 80% of death events interim analysis of OS, thereby removing the first interim analysis of OS from the protocol.

All relevant sections throughout the protocol have been updated to reflect these changes. This includes the Synopsis, Section 1.2.6 (Rationale for endpoints), Section 1.4 (Study design), Section 2.1 (Primary objective), Section 2.2 (Secondary objectives) and Section 2.3 (Safety objective), which have been updated to reflect the PD-L1 TC/IC subgroup as an additional population for the OS primary objective and various secondary objectives; Section 8.2 (Sample size), where the statistical assumptions around the PD-L1 TC/IC-selected subgroup have been added; and Sections 8.2, 8.5 (Methods for statistical analyses) and 8.5.8 (Interim analysis), where the timing of the PFS has been adjusted (thereby removing the first interim of OS) and the timing of the final OS analysis has been adjusted to allow for the required number of events in the PD-L1 TC/IC-selected subgroup. Section 8.3.2 has been adjusted to include the definition of the PD-L1 TC/IC-selected subgroup. Table 12 (Summary of statistical assumptions) has been updated to include the assumptions regarding the PD-L1 TC/IC-selected subgroup, to remove the entries for the PD-L1 negative subgroup, and also to adjust the monotherapy versus SOC entries to reflect the same target hazard ratio as for the combination versus SOC comparisons. Appropriate changes have been made throughout Section 8.5 (Methods for statistical analysis). These include updating of the multiple testing procedure (Figure 6), detailing the new statistical analyses incorporating the PD-L1 TC/IC-selected subgroup (Section 8.5.1.2 Overall survival, Section 8.5.1.3 Subgroup analyses of PFS and OS, Section 8.5.2 Analysis of the secondary variables, Section 8.5.4 Safety data) and removal of the first interim analysis of OS (Section 8.5.8 Interim analysis).

These changes have been made based on emerging data in the field that are external to the KESTREL study. Specifically, recently published data in 2nd line R/M HNSCC patients suggest that PD-L1 expression on both tumor cells and tumor-associated immune cells may be associated with greater clinical benefit to immune checkpoint inhibitors (Chow et al 2016; Ferris et al, 2017). PD-L1 expression on both tumor and tumor-associated immune cells was evaluated in patient samples from two phase 2 studies, D4193C00001 (HAWK) and D4193C00003 (CONDOR). These uncontrolled studies evaluated MEDI4736 alone or in combination with tremelimumab in 2nd line R/M SCCHN patients whose tumors expressed different levels of PD-L1 expression (HAWK: ≥25% PD-L1 tumor cell expression; CONDOR: <25% PD-L1 tumor cell expression). Preliminary overall survival data from a pooled population of patients treated with MEDI4736 monotherapy across the HAWK and CONDOR studies was used to identify patients who appeared to be more likely to derive clinical benefit from MEDI473 treatment based on the level of PD-L1 expression in both tumor and tumor-associated immune cells. Based on this analysis, the biomarker-selected subgroup to be

evaluated for the primary objective of overall survival in the KESTREL study is defined as those patients whose tumors have PD-L1 expression of ≥50% in the tumor cells or ≥25% in the tumor-associated immune cells [PD-L1 TC/IC subgroup; TC ≥50% or IC ≥25%].

Other changes not related to the addition of the PD-L1 TC/IC-selected subgroup include the following:

Synopsis, Section 2.2 – Secondary objectives, Section 8.5 – Methods for statistical analysis (Table 16)
These sections have been updated to include the secondary objectives of Best objective response, Time to first subsequent therapy, and Time to second subsequent therapy, in order to be consistent with the existing secondary endpoints described in Section 8.4.1.4.

Section 3.10.3 – Survival status for withdrawn consent and lost to follow up patients
This new section has been created to clarify that at the time of PFS and OS analyses, site personnel should attempt to obtain the survival status for all patients in the full analysis set and the safety analysis set who had previously withdrawn consent or were considered lost to follow-up using publicly available resources.

Section 5.1 – Efficacy assessments
This section has been updated to ensure consistency within the protocol and reflect that the baseline assessment should be performed no more than 28 days before randomization, rather than start of IP.

Section 7.1.1 – MEDI4736
This section has been updated to include instructions for preparation of MEDI4376 doses for patients whose weight falls to <30 kg during the study.

Section 7.1.2 – Tremelimumab
This section has been updated to include instructions for preparation of tremelimumab doses for patients whose weight falls to <30 kg during the study.

Section 7.2.1 – Dose and treatment regimens
This section has been updated to clarify the appropriate dosing procedures to be followed if a patient's weight falls below 30 kg during the study.

Section 7.7 – Concomitant and other treatments
This section has been updated to clarify that the restriction on the use of monoclonal antibodies against PD-1, PD-L1 or CTLA-4 no longer applies to the 90 day period after the patient has discontinued IP. This change is implemented in order to be consistent with the durvalumab program and to ensure that patients who are randomized to the SOC arm are not denied approved therapies in the 2nd line recurrent/metastatic setting which have previously demonstrated a survival benefit.

Section 8.4.1.2 – Primary endpoint (PFS) and Section 8.5 –Methods for statistical analysis

These sections have been updated to indicate that the sensitivity analysis of PFS based on RECIST 1.1 modified for confirmation of progression will be performed using site Investigator assessments, rather than BICR assessments.

Section 8.4.3.1 – EORTC QLQ-C30
The population for the analysis of time to symptom deterioration has been updated to reflect those patients who have baseline scores of ≤90, in order to accommodate an increase of at least 10 points which is the minimum deterioration considered to be clinically meaningful.

The population for the analysis of time to QoL/function deterioration has been updated to reflect those patients who have baseline scores of ≥10 in order to accommodate a decrease of at least 10 points, which is the minimum deterioration considered to be clinically meaningful.

Section 8.4.4 – Calculation or derivation of pharmacokinetic variables
This section has been updated to reflect that PK parameters, such as peak and trough concentration of MEDI4736 and tremelimumab, will be derived from raw data measurements and that no formal non-compartmental PK analysis methods will be used as only sparse PK is being collected in this study.

Section 8.5.7 – Pharmacokinetic/Pharmacodynamic relationships
This section has been removed because the PK/PD modeling is already covered in Section 8.4.4.1.

Appendix E – Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors)
This section has been updated to ensure consistency with the protocol and reflect that the baseline assessment should be performed no more than 28 days before randomization, rather than start of IP.

In addition, minor administrative corrections have been made throughout the protocol and are not detailed here further.

Version 6.0, 31 August 2016
Changes to the protocol are summarized below.

Synopsis, Section 8.2 – Sample Size Estimate
The sample size has been increased in order to power the co-primary endpoint of overall survival to 90%. The revised sample size requires approximately 1016 patients to be screened in order to randomize 760 patients across the three treatment arms. The requirement for a minimum number of patients with PD-L1-negative disease has been removed because the primary endpoints are based on natural PD-L1 prevalence and the increased sample size ensures a sufficient number of PD-L1-negative patients will be enrolled to allow sufficient power for the secondary analyses.

The section has also been updated to reflect a change in the alpha split between the PFS and OS co-primary endpoints, such that an alpha level of 0.01 will be used for PFS analysis and an alpha level of 0.04 will be used for OS analysis. This change has been made to ensure both OS and PFS are powered to 90% while minimizing the number of patients exposed. As a consequence, most of the alpha is spent on OS which is now considered to be the most important endpoint.

The recruitment period has been updated to 13 months to reflect the current rate of enrolment into the trial, and the follow-up period and expected analysis timeframes have been updated accordingly.

The 18 month landmark OS analyses have been replaced with 24 month landmark OS analyses to be consistent with other trials.

Synopsis, Section 8.2 – Sample size estimate, Section 8.5 – Methods for statistical analysis
The text has been updated to reflect that the primary PFS analysis will not require a minimum number of progression/death events in the PD-L1-negative population, as this secondary endpoint has been removed from the multiple testing procedure.

Section 1.3.2.1 – Potential Risks, MEDI4736
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 – Potential Risks, Tremelimumab
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 – Study Design
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. This section has also been updated to reflect the revised sample size for both enrolled and randomized patients, as well as to remove the requirement for a minimum number of patients with PD-L1-negative disease accordingly. Finally, Figure 1 has been revised to reflect the increased sample size (n=760).

Section 4 – Study Plan and Timing of Procedures
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. 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 remain on treatment at the time of final OS analysis will be followed, in order to provide clarity on data entry and SAE reporting processes when this occurs. CCI [redacted]

CCI Footnote 'f' in Table 2 has been updated to clarify that for patients on the MEDI4736+tremelimumab combination treatment arm, ADA samples collected at cycle 7 will be for MEDI4736 only. Footnote 'g' in Table 2 has been updated to clarify that pre-dose pharmacokinetic samples for both MEDI4736 and tremelimumab may be obtained within 60 minutes prior to the start of the tremelimumab infusion; this change has been made to simplify the procedures at the site on days of PK sample collection. In addition, footnotes have been added in Table 2 and 3 to clarify that the +/- 3 day window is relative to the day of dosing and that the PGIC patient-reported outcome assessment will not be collected at screening or at cycle 1 as this questionnaire refers to a change from baseline status. The tumor assessment schedule in Table 4 has been corrected to reflect that assessments will be performed every 6 weeks for the first 24 weeks relative to the date of randomization and every 8 weeks thereafter, until a patient has confirmed disease progression; this correction is made to align Table 4 with the text in Section 5.1.

Section 5.1 – Efficacy Assessments
The criteria for confirming radiographic progression have been clarified and aligned across the MEDI4736 program. Specifically, the text now clarifies that new lesions identified at the previous scan timepoint are considered non-target lesions at the confirmatory scan timepoint.

Section 5.1.1 – Central reading of scans
The list of guidelines available to sites for the central reading of scans has been updated. In addition, the text has been updated to reflect that results of either investigator assessments or of blinded central reviewer assessments will not be shared with the other party; this has been done for clarity around the central review process.

Section 5.5.1 – Collection of exploratory biomarker data
CCI

Section 5.5.2.1 – Collection of exploratory biomarker data, CCI

Section 6.7.2 – Management of IP-related toxicities; MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy
Table 8 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 8 that prednisone can be given orally (PO).

Section 7.7 – Concomitant and other treatments
The table of prohibited medications has been updated to indicate that short term use of immunosuppressive medications, including corticosteroids, for the acute management of non-IP-related emergencies (e.g., COPD, asthma, etc) is permitted.

Section 8.2 – Sample size estimate
The text describing the PFS analyses being conducted under alpha control for both the MEDI4736 + tremelimumab combination therapy versus SoC in the PD-L1-negative population and the MEDI4736 monotherapy versus SoC in all-comers has been deleted because these comparisons have been removed from the multiple testing procedure. The text describing the OS analysis for monotherapy MEDI4736 versus SoC in all-comers has been deleted because this comparison is not part of the initial levels of the MTP and this will instead be described in the statistical analysis plan. The target hazard ratios, critical values, number of events, maturity, and power for the co-primary and secondary endpoints have been updated in Table 12 to reflect the values associated with an increased sample size.

Section 8.3.2 – Definition of analysis sets; PD-L1-negative analysis set
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 8.3.4 – Definition of analysis sets; PK analysis set
The definition of the PK analysis set has been updated to reflect that all patients who receive at least 1 dose of IP and for whom any post-dose data are available will be included.

Section 8.5 – Methods for statistical analysis
Table 16 has been updated to indicate that both stratified log-rank tests and Cox proportional method will be used for both PFS and OS endpoints, and that Duration of Response will be analyzed using descriptive statistics and Kaplan-Meier plot, in order to be consistent with changes in Section 8.5.1.

The Multiple Testing Procedure has been updated to deprioritize the PFS analyses for the comparisons of MEDI4736 + tremelimumab combination therapy vs. SoC in the PD-L1-negative population and the MEDI4736 monotherapy vs. SoC in the all-comer population, relative to the OS analyses. In addition, it has been clarified that only the initial levels of the MTP are included in the protocol and that a full description of the detailed MTP, including the comparison of MEDI4736 monotherapy vs. SoC, is provided in the SAP. This section has also been updated to clarify that the comparisons of MEDI4736 + tremelimumab combination therapy vs. MEDI4736 monotherapy will not be included in the MTP and therefore will not be conducted under strict alpha control.

Section 8.5.1.1 – Analysis of the co-primary endpoints; Progression-free survival

The methods for PFS 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 – Analysis of the co-primary endpoints; Overall survival
Description of a sensitivity analysis for OS, examining the censoring patterns to rule out attrition bias, has been moved into this section from elsewhere in the protocol, for clarity.

Section 8.5.1.3 – Analysis of the co-primary endpoints; subgroup analysis of PFS and OS
The age at randomization subgroups have been further divided into 3 separate groups, in order to be consistent with other phase 3 clinical trials (<65, ≥65 to <75, and ≥75). The following subgroups have been added to this section based on potential prognostic implications: ECOG performance status (0, 1) and Extent of Disease (only locoregionally recurrent, metastatic with or without locoregional recurrence). Methods for subgroup analyses have been updated to reflect that a forest plot will be presented for the subgroup comparisons between MEDI4736 + tremelimumab combination therapy versus SoC in all-comers.

Section 8.5.2.2 – Analysis of secondary variables; Duration of response
The methods for analysis for duration of response have been updated to reflect that descriptive data will be provided rather than formal statistical analysis as the number of responders is expected to be small.

Section 8.5.3.1– Patient-reported outcomes; EORTC QLC-30
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 8.5.3.2 – Patient-reported outcomes; EORTC QLQ-H&N35
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 8.5.9 – Interim analysis
The expected amount of full death information and events to have occurred at the time of OS interim analyses, in both the all-comer and PD-L1-negative populations, have been updated to reflect the increased sample size. The 2-sided alpha level to be applied at the interim and final analyses have been updated as a result of the overall increase in alpha applied to the co-primary endpoint of OS. This section has been modified in order to clarify that the final OS analysis is dependent only on a specific number of death events that would have occurred in the all-comer population across the MEDI4736 + tremelimumab combination therapy and the SoC treatment groups, rather than the all-comer and PD-L1-negative populations.

Appendix E – Guidelines for Evaluation of Objective Tumor Response Using RECIST1.1 Criteria

The following items have been added for clarity; 1) definition of the short axis, 2) statement that lymph nodes are collectively considered as a single organ, 3) A bilateral organ is considered a single organ for purposes of target lesions, 4) criteria for confirmation of progression have been updated to be consistent with main body of protocol, 5) details regarding which guidelines will be prepared for study sites, 6) a list of guidelines available to sites for the central reading of scans has been updated, and 7) updated text to reflect that results of either investigator assessments or of BICR assessments will not be shared with the other party.

In addition, minor administrative corrections have been made throughout the protocol and are not detailed here further.

Version 5.0, 02 March 2016

Changes to the protocol are summarized below.

Protocol Synopsis: This section has been modified to clarify the patient population and eligibility criteria. Additionally, this section has been updated to clarify that patients with progressive disease (PD) in target lesions that had previously shown an objective response are not eligible to continue immunotherapy treatment. Text has also been added to clarify when radiographic documentation of PD is required. This section has also been updated to reflect that patients must commence study drug within 5 working days of randomization. The definitions of progression-free survival (PFS) and overall survival (OS) have been added. Additionally, the text has been modified to reflect that Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), according to Blinded Independent Central Review (BICR) assessments, will be used instead of Investigator assessments to derive the co-primary variable of progression-free survival (PFS) and the secondary variables of PFS, objective response rate (ORR), duration of response (DoR), and proportion of patients alive and progression free at 12 months (APF12). Additionally, the timing and details pertaining to the two interim analyses for OS and for the final analysis of PFS and OS have been updated. Non-inferiority analysis has been removed from this section. The secondary objectives have been updated to add MEDI4736 monotherapy as a comparison to Standard of Care (SoC) in regard to the assessment of disease-related symptoms and health-related quality of life. Furthermore, in the outcome measures for secondary objectives, various items in the European Organisation for Research and Treatment of Cancer (EORTC) 30-item Core Quality of Life Questionnaire (QLQ-C30) and the 35-item Head and Neck Quality of Life Questionnaire (QLQ-H&N35) module have been prioritized. Finally, specific instructions as to how the 440 PD-L1 negative patients will be distributed among the treatment arms have been removed.

Section 1.1.3 (MEDI4736 [Durvalumab]): This section has been updated to included "durvalumab," the generic name for MEDI4736.

Section 1.1.6 (Rationale for Conducting this Study): This section has been modified to clarify the patient population and eligibility criteria.

Section 1.2 (Rationale for Study Design, Doses, and Control Groups): This section has been modified to clarify the patient population and eligibility criteria. OS has also been added to the efficacy analysis in order to remain consistent with the rest of the protocol.

Section 1.2.5 (Study Population Rationale): This section has been modified to clarify the patient population and eligibility criteria.

Section 1.2.6 (Rationale for Endpoints): CCI [redacted]

Section 1.4 (Study Design): This section (including Figure 1) has been modified to clarify the patient population and eligibility criteria. Additionally, the requirement for human papilloma virus (HPV) testing to be done exclusively using the p16 immunohistochemistry (IHC) assay has been updated to also allow testing according to local standards. Furthermore, this section has been updated to clarify that patients with PD in target lesions that had previously shown an objective response are not eligible to continue immunotherapy treatment. The text has also been modified to reflect that BICR assessments according to RECIST 1.1 will be used instead of Investigator assessments to derive the co-primary variable of PFS and the secondary variables of PFS, ORR, DoR, and APF12. Furthermore, the sensitivity analyses of RECIST 1.1 measurements per BICR has been removed from this section. Figure 3 has been updated to reflect that soluble programmed cell death ligand 1 (sPD-L1) testing is no longer required. Figure 3 has also been modified to clarify the timing of the baseline tumor assessment for patients restarting treatment. Finally, specific instructions as to how the 440 PD-L1 negative patients will be distributed among the treatment arms have been removed.

Section 2.1 (Primary Objective): The text has been updated to reflect that BICR assessments according to RECIST 1.1 will be used instead of Investigator assessments to measure the co-primary objective of PFS.

Section 2.2 (Secondary Objectives): The text has been modified to reflect that BICR assessments according to RECIST 1.1 will be used instead of Investigator assessments to measure the secondary objectives of PFS, ORR, DoR, and APF12. In the outcome measures for secondary objectives, various items in the EORTC QLQ-C30 and QLQ-H&N35 module have been prioritized.

Section 2.4 (Exploratory Objectives): CCI [redacted]

Section 3.1 (Inclusion Criteria): This section has been modified to clarify the patient population and eligibility criteria. Additionally, the requirement for HPV testing to be done exclusively using the p16 IHC assay has been removed. The SI values for platelet

count and absolute neutrophil count have also been added to this section. Finally, age-specific requirements for evidence of post-menopausal status have also been updated.

Section 3.2 (Exclusion Criteria): This section has been modified to clarify the patient population and eligibility criteria. The exclusion of patients who have received prior systemic therapy for recurrent or metastatic SCCHN has been removed as it duplicates the corresponding inclusion criterion. The permissibility of steroid usage by patients in the SoC arm has also been updated. The exclusion criteria have also been modified to include patients with active tuberculosis, as well as those who have been involved in the planning/conduct of the study.

Section 3.3 (Patient Enrollment and Randomization): The requirement for HPV testing in patients with oral cavity tumors has been removed and it has been clarified that HPV results can be collected from historical medical records of any age. Additionally, the requirement for HPV testing to be done exclusively using the p16 IHC assay has been updated to also allow testing according to local standards. A definition of pack-year has been added. This section has also been updated to reflect that patients must commence study drug within 5 working days of randomization.

Section 3.9.1 (Procedures for Discontinuation of a Patient from Investigational Product [IP]): This section has been modified to clarify the procedures that take place when a patient discontinues the IP.

Section 4 (Study Plan and Timing of Procedures): Additional instructions pertaining to the timing of screening, randomization, dose delays, baseline, and laboratory procedures have been added to this section. This section has also been updated to reflect that patients must commence study drug within 5 working days of randomization. The timing of various laboratory assessments has been updated in Table 2. Tables 2, 3, and 4 have been modified to reflect that **either** reflex free triiodothyronine (T_3) or free thyroxine (T_4) will be measured (and not both) if thyroid-stimulating hormone (TSH) is abnormal. Furthermore, the requirement to have urea and TSH results available prior to study drug infusion has been removed from Table 2. In addition, Table 3 has been updated to reflect that only TSH, and not free T_3 and T_4, should be measured in patients who do not complete treatment through Cycle 5. In Tables 2 and 3, the requirement for HPV testing to be done exclusively using the p16 IHC assay and the requirement to have HPV testing completed within the 28 day screening window have been removed. Tables 2 and 3 have also been updated to reflect that sPD-L1 testing is no longer required. CCI [redacted] Additionally, the window for Cycle 1 Day 1 in both Tables 2 and 3 has been changed to "not applicable," and a window of ±3 days has been added for Cycles 7 until PD in Table 3. Furthermore, text has been added to Tables 2 and 3 to clarify when radiographic documentation of PD is required. The frequency and timing of pharmacokinetic and ADA assessments has been modified in Tables 2 and 4. Tables 2, 3, and 4 have also been updated to decrease the frequency of electronic patient-reported outcome (ePRO) assessments.

Section 5.1 (Efficacy Assessments): Text related to the schedule of confirmation of objective tumor response has been deleted. Additionally, text has been added to clarify when radiographic documentation of PD is required. This section has also been

modified to clarify that RECIST 1.1 will be used to determine PFS, ORR, DoR, and APF12 using BICR assessments (as well as Investigator assessments for sensitivity analysis of PFS).

Section 5.1.1 (Central Reading of Scans): This section has been updated to reflect that a full BICR will be performed for the PFS and ORR endpoints, rather than a sample BICR assessment. The text has also been updated to clarify that the results of independent radiologic reviews will not be made available to Investigators, and the management of patients will be based upon Investigator assessments.

Section 5.2.1 (Laboratory Safety Assessments): The procedures involved in clinical laboratory safety tests have been updated (regarding pregnancy and TSH tests in particular). Table 5 has been updated to include the schedule of bicarbonate and chloride testing as well as to remove uric acid from the clinical chemistry laboratory variables that will be measured during this study. The hematology laboratory variables to be measured that are listed in Table 6 have also been updated. Finally, the timing of urinalysis testing has been clarified in Table 7.

Section 5.2.4 (Vital Signs): This section has been modified to include separate procedures for the first infusion and subsequent infusions of MEDI4736 and/or tremelimumab.

Section 6.7 (Management of IP-related Toxicities): Specific guidelines related to toxicity management have been removed from this section. Additionally, text has been added regarding guidelines in case of allergic reactions to dose administration.

Section 6.7.1 (MEDI4736 + Tremelimumab Combination Therapy and MEDI4736 Monotherapy Adverse Events of Special Interest): Language related to the adverse events of special interest has been updated.

Section 6.7.2 (MEDI4736 + Tremelimumab Combination Therapy and MEDI4736 Monotherapy): The title of this subsection has been updated to reflect the content. Language related to immune-related adverse events has been removed from this section; specific guidelines related to toxicity management have been added to this section. Table 8 (Dosing modification and toxicity management guidelines for immune-mediated, infusion-related, and non-immune-mediated reactions) has been updated according to the current Toxicity Management Guidelines.

Section 6.8 (Study Governance and Oversight): This section has been updated to modify the timing of the Independent Data Monitoring Committee meetings.

Section 7.2.1 (Treatment Regimens): This section has been updated to clarify that patients with PD in target lesions that had previously shown an objective response are not eligible to continue treatment. Additionally, text has been added to clarify when radiographic documentation of PD is required.

Section 7.2.3 (Criteria for Retreatment for Patients in the MEDI4736 + Tremelimumab Arm): The timing of the baseline tumor assessment for patients restarting treatment has been clarified.

Section 7.7 (Concomitant and Other Treatments): The first table in this section has been updated to clarify the usage of investigational anticancer therapy concurrent with those under investigation in this study as well as radiation and immunosuppressive steroids during the course of this study.

Section 8.2 (Sample Size Estimate): The timing and details pertaining to the 2 planned interim analyses have been updated. Updates have been made to the text pertaining to sizing superiority analysis; non-inferiority analysis has been removed from this section. Text pertaining to the sizing for PFS of MEDI4736 monotherapy versus Standard of Care (SoC) has also been added. Finally, specific instructions as to how the 440 PD-L1 negative patients will be distributed among the treatment arms have been removed.

Section 8.3.2 (PD-L1-negative Analysis Set): This section has been modified to include a quantitative definition of PD-L1-negative status.

Section 8.4.1.1 (RECIST 1.1-based Endpoints): This section has been updated to reflect that RECIST 1.1 will be used to determine PFS, ORR, DoR, and APF12 based on BICR assessments, rather than investigator assessments. The sample BICR assessment has been removed.

Section 8.4.1.2 (Co-primary Endpoint [PFS]): This section has been updated to clarify that the co-primary endpoint PFS will be assessed by RECIST 1.1 using BICR assessments, whereas a sensitivity analysis of PFS will be performed using Investigator assessments according to RECIST 1.1. In addition, a sensitivity analysis of PFS based on RECIST 1.1 **modified for confirmation of progression** will be performed using BICR assessments.

Section 8.4.1.4 (Secondary Endpoints): This section has been updated to clarify that ORR by irRECIST 1.1 criteria using BICR assessments will not be reported as a secondary endpoint. This section has also been modified to clarify that RECIST 1.1 will determine ORR, DoR, APF12, and best objective response using BICR assessments. Text has also been added regarding time from randomization to the second subsequent therapy or death.

Section 8.5 (Methods for Statistical Analyses): The number of patients with PD-L1-negative tumors across the MEDI4736 + tremelimumab combination therapy and SoC treatment arms needed at the time of the PFS and OS analyses has been corrected. The text has also been updated to clarify that PFS will be assessed by RECIST 1.1 using BICR assessments. Table 16 has been updated to clarify that PFS, ORR, and DoR will be assessed by RECIST 1.1 using BICR assessments rather than investigator assessments; a sensitivity analysis of PFS will be performed using Investigator assessments according to RECIST 1.1 rather than a sample BICR assessment, and a sensitivity analysis of PFS will be performed using BICR assessments according to RECIST 1.1 **modified for confirmation of progression**. Various patient-related outcome (PRO) endpoints have also been removed from Table 16. The MTP has been simplified (both the text and Figure 6) and includes additional detail regarding the timing and assignment of alpha for two interim analyses of OS. Additionally, non-inferiority analysis and the comparisons of the combination arm versus monotherapy arm for both PFS and OS have been removed from the multiple testing

procedure (MTP). Finally, subsections 8.5.1 through 8.5.4 have been combined to reflect analysis of the co-primary endpoints, and subsequent subsections of 8.5 have been re-numbered accordingly.

Section 8.5.1.1 (Progression-free Survival): This section has been updated to clarify that the primary PFS analysis will be assessed by RECIST 1.1 using BICR assessments, that secondary analyses for PFS using BICR assessments will be performed for the comparisons of the combination versus SoC and the combination versus monotherapy in PD-L1-negative patients, and the comparison of monotherapy vs SOC in all comers.

Section 8.5.1.2 (Overall Survival): The parameters for the analyses of OS have been clarified.

Section 8.5.1.3 (Subgroup Analysis of PFS and OS): This section has been updated to clarify that PFS will be assessed by RECIST 1.1 using BICR assessments.

Section 8.5.2.1 (Objective Response Rate): This section has been updated to clarify that ORR will be assessed by RECIST 1.1 using BICR assessments. Details pertaining to the parameters and population to be studied in this analysis have also been clarified.

Section 8.5.2.2 (Duration of Response): This section has been updated to clarify that DoR will be assessed by RECIST 1.1 using BICR assessments.

Section 8.5.2.4 (Time from Randomization to PFS2): A definition of second progression has been added to this section.

Section 8.5.2.5 (Time from Randomization to First and Second Subsequent Therapy or Death): The text has been updated to reflect that time to the start of the first **and** the second therapy or death will be analyzed.

Section 8.5.3 (Patient-reported Outcomes): Details pertaining to the analysis of PRO endpoints have been added.

Section 8.5.9 (Interim Analysis): Text has been updated to reflect that there will be 2 interim analyses for OS performed for superiority. Details regarding the parameters for the interim analyses and potential outcomes have been added.

Section 11 (List of References): References that are not cited in the protocol have been removed; newly cited references have been added.

Appendix E (Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria): This appendix has been updated to reflect changes to the criterion for non-measurable lesions. Preferences for computed tomography and magnetic resonance imaging scans have been updated as well. Additionally, text pertaining to the timing of the imaging for confirmation of response has been removed from this appendix.

Appendix F (Patient-Reported Outcomes): The PRO Common Terminology Criteria for Adverse Events questionnaire has been updated to remove certain symptoms and side effects from the questionnaire.

Version 4.0, 1st December 2015 (D419LC00001CSP Amendment 3) Changes to the protocol are summarized below.
Protocol Synopsis: Per Voluntary Harmonisation Procedure (VHP) review, an interim analysis for OS at the time of PFS analysis has been added. The MTP has also been modified to include 1 interim analysis of OS. Section 8.2 (Sample Size Estimate): Per VHP review, an interim analysis for OS at the time of PFS analysis has been added. The MTP has also been modified to include 1 interim analysis of OS. Section 8.5 (Methods for Statistical Analyses): Per VHP review, an interim analysis for OS at the time of PFS analysis has been added. The Multiple Testing Procedure has also been modified to include 1 interim analysis of OS, and Figure 6 has been updated to reflect this change. Section 8.5.12 (Interim Analysis): Per VHP review, an interim analysis for OS at the time of PFS analysis has been added. The MTP has also been modified to include 1 interim analysis of OS.

Version 3.0, 9th November 2015 (D419LC00001CSP Amendment 2) Changes to the protocol are summarized below.
Section 3.1 (Inclusion Criteria): In response to VHP review comments, the creatinine clearance requirement for patients who will be treated with cisplatin on the SoC arm has been revised to a minimum of 60 mL/min. The age specific requirements for post-menopausal female patients have also been clarified with respect to pregnancy testing. Section 3.2 (Exclusion Criteria): In response to VHP review comments, the time frame allowed for receipt of prior investigational anticancer therapy has been revised to be 28 days or 5 half-lives, whichever is longer, prior to first study treatment. Also in response to VHP review comments, contraception requirements have been modified such that female patients of childbearing potential must agree to use highly effective method of birth control and nonsterilized male patients who are sexually active with a partner of childbearing potential must agree to use condoms with spermicide. Section 3.3 (Patient Enrollment and Randomization): The process for defining SoC at time of randomization has been clarified. Section 3.8 (Restrictions): In response to VHP review comments, Table 1 has been updated to include only highly effective methods of contraception. Section 4 (Study Plan and Timing of Procedures): In response to VHP review comments, the timing of scheduled pregnancy testing in Table 2 has been modified to

reflect that patients assigned to either the MEDI4736 + tremelimumab or MEDI4736 monotherapy arms will undergo pregnancy testing at each study visit when IP is administered.

Section 5.2.1 (Laboratory Safety Assessments): In response to VHP review comments, the timing of scheduled pregnancy testing has been modified to reflect that patients assigned to either the MEDI4736 + tremelimumab or MEDI4736 monotherapy arms will undergo pregnancy testing at each study visit when IP is administered.

Version 2.0, 10th September 2015 (D419LC00001CSP Amendment 1**)**

Changes to the protocol are summarized below,

Title Page: The title has been updated to reflect the 3-arm design of the trial in response to regulatory feedback**.**

Protocol Synopsis: The text has been modified to clarify the distribution of programmed cell death ligand 1 (PD-L1) negative patients across the treatment arms and to reflect that patients in any treatment arm, not only the immunomodulatory therapy (IMT) arms, will not be permitted to continue therapy if they develop PD in a target lesion after a clear response to therapy. The definition of smoking history has also been clarified. Additional detail on the Ventana assay has also been added. The SoC dosing regimen has been updated to correct minor inconsistencies within the text. Also, the timing of confirmatory scans has been updated to be consistent across all treatment arms. The contact information of the Co-International Coordinating Investigators has also been updated. Finally, the title has been updated to reflect the 3-arm design of the trial in response to regulatory feedback.

Section 1.3.2.1 (MEDI4736): The potential risks of nephritis and pancreatitis for MEDI4736 have been updated to align with the most recent Investigator's Brochure.

Section 1.4 (Study Design): This text in this section has been updated, along with Figure 2, to clarify tumor biopsy collection procedures. The text has also been modified to clarify the distribution of PD-L1 negative patients across the treatment arms. Figure 3 has been updated to clarify that retreatment tumor assessments are relative to restarting study treatment. Additionally, the text has been modified to reflect that patients in any treatment arm, not only the IMT arms, will not be permitted to continue therapy if they develop PD in a target lesion after a clear response to therapy. The SoC dosing regimen has been updated to correct minor inconsistencies within the text.

Section 3.1 (Inclusion Criteria): This section has been modified to change the required PD-L1 tumor biopsy sample to a formalin-fixed and paraffin-embedded recently acquired tissue sample (preferred) or an archival tissue <3 years old and to clarify related tumor biopsy collection procedures. Additionally, the text has been modified to reflect that patients in any treatment arm, not only the IMT arms, will not be permitted to continue therapy if they develop PD in a target lesion after a clear response to therapy. Additional detail on the Ventana assay has also been added. This section has

also been revised to clarify that SoC procedures prior to informed consent are not study procedures for this study.

Section 3.2 (Exclusion Criteria): An additional exclusion criterion that clarifies minimum patient weight needed for this study has been added.

Section 3.3 (Patient Enrollment and Randomization): This section has been updated to clarify tumor biopsy collection procedures. The definition of smoking history has also been clarified. This section has also been revised to clarify that patients should have no obvious exclusion parameters before a tumor sample is obtained. The instances in which HPV status will be determined have also been clarified.

Section 3.5 (Methods for Assigning Treatment Arms): The definition of smoking history has been clarified. Additional detail on the Ventana assay has also been added.

Section 3.8 (Restrictions): The contraception restrictions have been updated to be in alignment across the MEDI4736 development program.

Section 4 (Study Plan and Timing of Procedures): In Table 2, TSH has been added to the assessments that must be available before commencing an infusion. Table 2 has also been updated to clarify that the first treatment period continues until PD and that SoC procedures prior to informed consent are not study procedures for this study. In Table 3, the SoC dosing regimen has been updated to correct minor inconsistencies within the text. Table 3 has been further modified to include an assessment on Cycle 1, Day 1, Week 0 for the PRO measures in the SoC arm. Furthermore, Tables 2 and 3 have been modified to change the required PD-L1 tumor biopsy sample to a formalin-fixed and paraffin-embedded recently acquired tissue sample (preferred) or an archival tissue <3 years old and to clarify related tumor biopsy collection procedures. Also, Tables 2 and 3 have been updated to clarify which assessments performed 3 days prior to Day 1 do not need to be repeated at Day 1 and to clarify the timing of pregnancy testing in response to regulatory feedback. Table 4 has been modified to clarify that pharmacokinetics should only be collected for the IMT arms at follow-up.

Section 4.1 (Enrollment/Screening Period): This section has been updated to clarify tumor biopsy collection procedures.

Section 5.1 (Efficacy Assessments): The timing of confirmatory scans has been updated to be consistent across all treatment arms.

Section 5.2.1 (Laboratory Safety Assessments): Table 5 has been modified to clarify that bicarbonate will not be evaluated at South Korean sites.

Section 5.5.1 (Collection of Patient Samples for Stratification by PD-L1): This section has been modified to change the required PD-L1 tumor biopsy sample to a formalin-fixed and paraffin-embedded recently acquired tissue sample (preferred) or an archival tissue <3 years old and to clarify related tumor biopsy collection procedures. Additional detail on the Ventana assay has also been added.

Section 5.5.2.2 CCI [redacted]
Section 6.7.2 (Immune Related Adverse Events): An error in the definition of *Pneumocystis carinii* pneumonia has been corrected in Table 8. Section 7.2.1 (Treatment Regimens): The SoC dosing regimen has been updated to correct minor inconsistencies within the text. The timing of confirmatory scans has also been updated to be consistent across all treatment arms. Section 8.2 (Sample Size Estimate): The text has been modified to clarify the distribution of PD-L1 negative patients across the treatment arms. Additionally, hazard ratio values have been corrected for the MEDI4736 monotherapy versus SoC in all-comers noninferiority analysis. Section 8.3.2 (PD-L1-negative Analysis Set): Additional detail on the Ventana assay has been added. Section 8.4.1.4 (Secondary Endpoints): A definition and description for the analysis of time from randomization to the first subsequent therapy or death has been added. Section 8.5.5.5 (Time from Randomization to the First Subsequent Therapy or Death): A definition and description for the analysis of time from randomization to the first subsequent therapy or death has been added.
Version 1.0, 6th July 2015
Initial creation

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

PROTOCOL SYNOPSIS

A Phase III Randomized, Open-label, Multi-center, Global Study of MEDI4736 Alone or in Combination with Tremelimumab versus Standard of Care in the Treatment of First-line Recurrent or Metastatic Squamous Cell Head and Neck Cancer Patients

Co-International Coordinating Investigators

PPD

Study site(s) and number of patients planned

This study will enroll approximately 1016 patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) who are not amenable to local curative therapy and who have not received prior systemic therapy for recurrent/metastatic disease. Approximately 760 patients will be identified globally and will be randomized in a 2:1:1 ratio (380:190:190 patients) to receive MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, or Standard of Care (SoC).

Study period		Phase of development
Estimated date of first patient enrolled	Q4 2015	III
Estimated date of last patient completed	Q1 2021	III

Q Quarter.

Study design

This is a randomized, open-label, multi-center, 3-arm, global Phase III study to determine the efficacy and safety of MEDI4736 +/- tremelimumab versus SoC (EXTREME regimen) in the treatment of patients with R/M SCCHN who are not amenable to local curative therapy with surgery or radiation and who have not received prior systemic therapy for recurrent/metastatic disease, unless it was given as part of multimodality treatment for locally advanced or locally recurrent disease. Patients will undergo a screening assessment on their tumor tissue sample to determine PD-L1 expression status (defined by an analytically validated immunohistochemistry assay developed by VENTANA in which ≥25% PD-L1 membrane expression in tumoral tissue is considered positive and <25% is considered negative for purposes of stratification; referred to hereafter as patients with PD-L1-positive or –negative tumors, respectively). Patients will be randomized in a 2:1:1 ratio to MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, or SoC in a stratified manner according to PD-L1 tumor expression status (as described above),

tumor location (oropharyngeal cancer [OPC] or non-OPC), and smoking history (>10 vs ≤10 pack-years) to receive treatment with MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, or SoC therapy. Patients with OPC will be further stratified by their human papilloma virus status (positive or negative).

Patients in all arms will continue therapy until progression. Patients in all arms should continue receiving therapy in the setting of equivocal progressive disease (PD), at the Investigator's discretion, until PD is confirmed. Assessments in all arms should continue as per schedule until confirmation of PD. Patients in all arms with confirmed PD by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) who, in the Investigator's opinion, continue to receive benefit from their assigned treatment and who meet the criteria for treatment in the setting of PD may continue to receive their assigned treatment. However, patients in the immunotherapy arms will not be permitted to continue immunotherapy if progression occurs after objective response (defined by RECIST 1.1) to immunotherapy treatment in the target lesions. Patients who have discontinued treatment due to toxicity or symptomatic deterioration, clinical progression, or who have commenced subsequent anticancer therapy, will be followed up until confirmed disease progression and for survival.

Tumor assessments will be performed on computed tomography scans or magnetic resonance imaging scans, preferably with intravenous (IV) contrast. Efficacy for all patients will be assessed by objective tumor assessments every 6 weeks for the first 24 weeks, then every 8 weeks thereafter (relative to the date of randomization) until treatment discontinuation due to progression or toxicity. All patients will be followed every 3 months for survival after progression is confirmed. If an unscheduled assessment is performed, and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits, but scans would not need to be repeated if obtained within 2 weeks of the scheduled assessment. Patients with confirmed PD who discontinue treatment should have scans conducted according to local practice.

The primary objective of the study is:

- To assess the efficacy of MEDI4736 monotherapy versus SoC (EXTREME) in a prespecified biomarker-selected subgroup of patients (PD-L1 TC/IC high subgroup) in terms of overall survival (OS)

The primary endpoint of the study is OS which will be assessed in a prespecified biomarker-selected subgroup of patients with tumors expressing PD-L1 in ≥50% of tumor cells (TC) or in ≥25% of tumor-associated immune cells (IC) (PD-L1 TC/IC high subgroup; TC≥50 or IC≥25) using the VENTANA PD-L1 SP263 assay.

Categorization of objective tumor response assessment at each post-screening imaging timepoint will be based on RECIST 1.1: complete response, partial response, stable disease (SD), and PD. Investigator assessments according to RECIST 1.1 will be used to programmatically derive the secondary variables of progression-free survival (PFS), objective response rate (ORR), duration of response (DoR), best objective response (BoR), time to response (TTR) and proportion of patients alive and progression free at 6 (APF6) and 12 months (APF12). Additional secondary objectives will include proportion of patients alive at 12 (OS12), 18 (OS18) and 24 months after randomization (OS24), second

progression (PFS2), safety and tolerability, pharmacokinetics (PK), anti-drug antibody (ADA), and health-related quality of life. Exploratory objectives will also be assessed.

Timepoint assessments showing PD for patients in the immunomodulatory therapy treatment arms should be confirmed preferably at the next scheduled imaging visit and no earlier than 4 weeks after the preceding assessment of PD in the absence of clinically significant deterioration. Timepoint assessments showing PD for patients in the SoC arm should be confirmed preferably at the next scheduled imaging visit and no earlier than 4 weeks after the preceding assessment of PD in the absence of clinically significant deterioration, if clinically feasible. Treatment with MEDI4736 + tremelimumab combination therapy or MEDI4736 monotherapy will continue between the assessment of progression and its confirmation. If progression is not confirmed, then the patient should continue receiving study treatment and participating in study assessments. For patients randomized to the SoC arm in whom equivocal findings of progression are observed (eg, very small and uncertain new lesions, cystic changes, or necrosis in existing lesions), treatment should continue until the next scheduled assessment. Patients with clinical evidence of progression who do not meet PD criteria by RECIST 1.1 should have radiographic documentation of PD.

Objectives

Primary Objectives:	**Outcome Measure:**
To assess the efficacy of MEDI4736 monotherapy compared to SoC (EXTREME) in terms of OS	OS in the PD-L1 TC/IC high subgroup

Secondary Objectives:	**Outcome Measures:**
To further assess the efficacy of MEDI4736 monotherapy compared to SoC (EXTREME) in terms of OS, PFS, ORR, DoR, BoR, TTR, TFST, TSST, APF6, APF12, PFS2, OS12, OS18 and OS24	OS in low risk of early mortality (EM) subgroup, ctDNA TMB high subgroup (≥16 mut/Mb) and all-comers OS12, OS18, OS24 in the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high subgroup (≥16 mut/Mb) and all-comers PFS, ORR, APF6 and APF12 using site investigator assessments according to RECIST 1.1 in the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high subgroup (≥16 mut/Mb) and all-comers DoR, BoR and TTR, using site investigator assessments according to RECIST 1.1 in the PD-L1 TC/IC high subgroup and all-comers PFS2 using local standard clinical practice in the PD-L1 TC/IC high subgroup and all-comers TFST and TSST in the PD-L1 TC/IC high subgroup and all-comers

Secondary Objectives:	**Outcome Measures:**
To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC (EXTREME) in terms of OS, PFS, ORR, DoR, BoR, TTR, TFST, TSST, APF6, APF12, PFS2, OS12, OS18 and OS24	OS, OS12, OS18, OS24 in the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high subgroup (≥16 mut/Mb) and all comers PFS, ORR, APF6 and APF12 in the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high subgroup (≥16 mut/Mb) and all-comers using site investigator assessments according to RECIST 1.1 DoR, BoR and TTR, using site investigator assessments according to RECIST 1.1 in the PD-L1 TC/IC high subgroup and all-comers PFS2 using local standard clinical practice in the PD-L1 TC/IC high subgroup and all-comers TFST and TSST in the PD-L1 TC/IC high subgroup and all-comers
To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to MEDI4736 monotherapy in terms of PFS, ORR, and OS	PFS and ORR using site investigator assessments according to RECIST 1.1 in the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high subgroup (≥16 mut/Mb) and all-comers OS in the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high subgroup (≥16 mut/Mb) and all-comers
To assess disease-related symptoms and health-related quality of life in patients treated with MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy compared to SoC (EXTREME) using the European Organisation for Research and Treatment of Cancer (EORTC) 30-item Core Quality of Life Questionnaire (QLQ-C30) version 3 and the 35-item Head and Neck Quality of Life Questionnaire (QLQ-H&N35) module	EORTC QLcQ-C30: global health QoL, functioning (physical) and symptoms (fatigue) in the PD-L1 TC/IC high subgroup and all-comers EORTC QLQ-H&N35: symptoms (pain, swallowing) in the PD-L1 TC/IC high subgroup and all-comers Changes in World Health Organization/Eastern Cooperative Oncology Group performance status in the PD-L1 TC/IC high subgroup all-comers
To assess the PK of MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy	Concentration of MEDI4736 and tremelimumab in blood and PK parameters, such as peak concentration and trough (as data allow; sparse sampling)
To investigate the immunogenicity of MEDI4736 and tremelimumab	Presence of ADAs for MEDI4736 and tremelimumab

Safety Objective:	Outcome Measures:
To assess the safety and tolerability profile of MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy compared to SoC (EXTREME) in the first-line setting for treatment of SCCHN	Adverse events, physical examinations, laboratory findings (including clinical chemistry, hematology, and urinalysis), vital signs (including blood pressure and pulse), and electrocardiograms in PD-L1 TC/IC high subgroup, low risk of EM subgroup and all-comers.

Target patient population

Males and females aged 18 and over with histologically or cytologically confirmed PD-L1-positive or -negative, recurrent or metastatic SCCHN (oral cavity, oropharynx, hypopharynx, or larynx) and who are not amenable to local curative therapy with surgery or radiation and who have not received prior systemic therapy for recurrent/metastatic disease, unless it was given as part of multimodality treatment for locally advanced or locally recurrent disease.

Duration of treatment

Treatment with MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, or SoC will commence within 5 working days of randomization and continue until confirmed progression, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met at the Investigator's discretion. Patients in the SoC arm will be treated with SoC for a maximum of six 3-week cycles of cetuximab, a platinum, and 5-fluorouracil (5FU), with continuation of maintenance cetuximab in patients who have achieved SD or better until confirmed PD, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

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

Patients in the MEDI4736 + tremelimumab combination therapy group 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: (1500 mg) will be administered via IV infusion every 4 weeks (q4w) until PD.

MEDI4736 + tremelimumab combination therapy: Tremelimumab (75 mg) will be administered via IV infusion q4w for a maximum of 4 doses, and MEDI4736 (1500 mg) will be administered via IV infusion q4w until PD.

SoC (EXTREME): Either cisplatin (at a dose of 100 mg/m^2 of body surface area as an IV infusion) or carboplatin (at an area under the curve of 5 mg/mL/min as an IV infusion) on Day 1 of up to six 3-week cycles, and an infusion of 5FU (at a dose of 1000 mg/m^2/day on Days 1 through 4) every 3 weeks, along with 400 mg/m^2 of cetuximab on Cycle 1 Day 1 and 250 mg/m^2 weekly for up to 6 cycles and maintenance cetuximab at 250 mg/m^2

administered via IV infusion weekly thereafter in patients who achieve SD or better upon completion of chemotherapy until PD, toxicity, or withdrawal of consent.

Statistical methods

The primary objective of this study is to assess the efficacy of MEDI4736 monotherapy treatment compared with SoC (EXTREME) in terms of OS in a prespecified biomarker-selected subgroup of patients with tumors expressing PD-L1 in ≥50% of tumor cells or ≥25% of tumor-associated immune cells (PD-L1 TC/IC high subgroup), who have not received prior systemic therapy for recurrent/metastatic disease, unless it was given as part of multimodality treatment for locally advanced or locally recurrent disease.

OS will be defined as the time from the date of randomization until death due to any cause.

Secondary efficacy variables include

- OS (assessed in the low risk of EM subgroup, ctDNA TMB high subgroup (≥16 mut/Mb) and all-comers), PFS, ORR, APF6, APF12, OS12, OS18 and OS24 (assessed in the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high subgroup (≥16 mut/Mb) and in all-comers), PFS2, DoR, BoR, TTR, TFST, TSST (assessed in the PD-L1 TC/IC high subgroup and all-comers) for MEDI4736 monotherapy versus SoC

- OS, PFS, ORR, APF6, APF12, OS12, OS18 and OS24 (assessed in the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high subgroup (≥16 mut/Mb) and in all-comers), PFS2, DoR, BoR, TTR, TFST and TSST (assessed in the PD-L1 TC/IC high subgroup and all-comers) for MEDI4736 + tremelimumab combination therapy versus SoC

- OS, PFS and ORR (assessed in the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high subgroup (≥16 mut/Mb) and in all-comers) for MEDI4736 + tremelimumab versus MEDI4736 monotherapy.

PFS (per RECIST 1.1 using site investigator assessment) 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 discontinues therapy or receives another anticancer therapy prior to progression. A sensitivity analysis of PFS will be performed based on data from blinded independent central review (BICR) assessments.

Efficacy data will be summarized and analyzed on an intent-to-treat (ITT) basis and the treatment groups will be compared on the basis of randomized 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 ITT population.

Approximately 760 patients will be randomized in a 2:1:1 ratio (380:190:190 patients) to receive MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, or SoC to assess OS (primary endpoint) in each treatment comparison.

The primary analysis of OS will be performed when approximately 147 death events have occurred in approximately 172 patients (85% maturity) across the MEDI4736 monotherapy and SoC treatment groups in the PD-L1 TC/IC high subgroup. All other endpoints will be analysed at this time. No interim analyses will be performed for any efficacy endpoint.

The primary analysis of OS will test MEDI4736 monotherapy versus SoC in the PD-L1 TC/IC high subgroup at a two-sided 5% level. If superiority over SoC is found, a hierarchical multiple testing procedure will be employed to strongly control for the overall type I error at the 5% level (two-sided). Subsequent hypotheses in the hierarchy will be to test MEDI4736 monotherapy versus SoC for the low risk of EM subgroupand ctDNA TMB high subgroup). Should these tests show statistical significant evidence of superiority, MEDI4736 + tremelimumab combination therapy versus SoC will be tested in the ctDNA TMB high subgroup (≥16 mut/Mb), followed by MEDI4736 monotherapy versus SoC for all-comers. The final hypothesis to be tested, should all previous tests show statistical significant evidence of superiority, will be to test MEDI4736 + tremelimumab combination therapy versus SoC for all-comers. All tests will be at the two-sided 5% level and the procedure will stop at the first failure to find statistically significant evidence of superiority or if tests of all hypotheses show superiority over SoC.

If OS in the PD-L1 TC/IC high subgroup at 24 months was 30% with MEDI4736 monotherapy and 12% with SoC (with a 10.1-month median OS), and assuming the true average OS HR is 0.59, the trial will have approximately 90% power to demonstrate statistical significance at the 5% level (using a 2-sided test) for the comparison of MEDI4736 monotherapy versus SoC in the PD-L1 TC/IC high subgroup, with the smallest treatment difference that could be statistically significant being an average HR of 0.72 With a 17-month recruitment period and a minimum follow-up period of 23.6 months, it is anticipated that the analysis will be performed approximately 40.6 months after the first patient has been recruited.

The primary analysis of OS will use a stratified log-rank test (stratified for PD-L1 expression tumor status [PD-L1 positive vs PD-L1 negative], tumor location [OPC vs non-OPC, with a subsequent adjustment for HPV status in patients with OPC], and smoking history [>10 vs ≤10 pack-years] as entered in the IVRS system). The effect of treatment will be estimated by the HR together with corresponding 95% confidence interval and p-value.

Safety data will be summarized descriptively.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
5FU	5-Fluorouracil
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
APF6	Proportion of patients alive and progression free at 6 months
APF12	Proportion of patients alive and progression free at 12 months
AUC	Area under the curve
AUC_{ss}	Area under the serum drug concentration-time curve at steady state
ASCO	American Society for Clinical Oncology
BICR	Blinded Independent Central Review
BoR	Best objective response
BP	Blood pressure
BSC	Best supportive care
CD	Cluster of differentiation
CI	Confidence interval
$C_{max,ss}$	Maximum serum concentration at steady state
CPS	Combined Positive Score
CR	Complete response
CRF	Case report form
CSA	Clinical study agreement
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	Circulating tumor DNA
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4
$C_{trough,ss}$	Trough concentration at steady state
DBL	Database Lock
DCO	Data Cut-Off

Abbreviation or special term	Explanation
DCR	Disease control rate
DLT	Dose-limiting toxicity
DoR	Duration of response
EBV	Epstein-Barr virus
EC	Ethics Committee, synonymous with Institutional Review Board (IRB)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDoR	Expected duration of response
EGFR	Epidermal growth factor receptor
eCRF	Electronic case report form
EM	Early Mortality
EORTC	European Organisation for Research and Treatment of Cancer
CCI	CCI
ePRO	Electronic patient-reported outcome
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HNSCC	Head and Neck Squamous Cell Carcinoma
HPV	Human papilloma virus
HR	Hazard ratio
HRQoL	Health-related quality of life
IB	Investigator's Brochure
IC	Tumor-associated immune cells
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICI	Immune Checkpoint Inhibitor
IDMC	Independent Data Monitoring Committee
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IHC	Immunohistochemistry

Abbreviation or special term	Explanation
IL	Interleukin
IMT	Immunomodulatory therapy
IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional Review Board, synonymous with Ethics Committee (EC)
irRECIST 1.1	Immune-related response criteria updated with RECIST 1.1
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
mAb	Monoclonal antibody
Mb	Megabase
MDSC	Myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	Micro RNA
MMRM	Mixed effect model repeated measurement
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MTP	Multiple testing procedure
NCI	National Cancer Institute
NE	Not evaluable
CCI	CCI
NSCLC	Non-small cell lung cancer
OPC	Oropharyngeal cancer
ORR	Objective response rate
OS	Overall survival
OS12	Proportion of patients alive at 12 months after randomization
OS18	Proportion of patients alive at 18 months after randomization
OS24	Proportion of patients alive at 24 months after randomization
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PFS	Progression-free survival
PFS2	Second progression

Abbreviation or special term	Explanation
CCI	CCI
PK	Pharmacokinetic(s)
PR	Partial response
PRO	Patient-reported outcome
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks
QC	Quality check
QLQ-C30 v3	30-item core quality of life questionnaire, version 3
QLQ-H&N35	35-item head and neck quality of life questionnaire
QoL	Quality of life
QTcF	QT interval corrected for Fridericia's formula
RCC	Renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
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
TC	Tumor cells
TC/IC high subgroup	Patients with tumor expressing PD-L1 in TC≥50 or IC≥25
TFST	Time to the first subsequent therapy
TSST	Time to second subsequent therapy
Th1	Helper T cell
TMB	Tumor Mutational Burden
TMG	Toxicity management guidelines
TTR	Time to response
TSH	Thyroid-stimulating hormone

Abbreviation or special term	Explanation
UC	Urothelial cancer
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 (squamous cell carcinoma of the head and neck [SCCHN]) with risk factors primarily attributed to prior alcohol or tobacco use or exposure to human papilloma virus (HPV). HPV infection has been associated with oropharyngeal tumors specifically and is increasingly becoming the predominant risk factor for oropharyngeal SCCHN in the Western world.

The majority of patients who present with SCCHN will be diagnosed with either localized disease or locally advanced disease. SCCHN diagnosed at a localized stage (Stage I/II) can be effectively treated with single-modality treatment (either surgery or radiation) and has a 5-year survival rate over 80%. However, about 70% of SCCHN patients are diagnosed with locally advanced disease and 10% with metastatic disease, for which the survival rates are poor (Siegel et al 2014). Patients with locally advanced disease typically receive multimodality treatment with curative intent, involving varied combinations of surgical resection, radiation therapy, and chemotherapy. Five-year survival rates of up to 30% to 40% have been seen with this treatment. However, most of these patients eventually relapse with either locoregional recurrence, metastatic disease (20% to 30% of patients), or both (Vermorken and Specenier 2010).

For patients who relapse with no localized salvage surgical or radiation options or who develop or present with metastatic disease, there is no likelihood of cure. Standard treatment options include a platinum doublet with either carboplatin or cisplatin along with a variety of chemotherapy agents, such as 5-fluorouracil (5FU) or taxanes. In 2008, Vermorken et al established the superiority of the EXTREME regimen to these platinum doublets (Vermorken et al 2008). The EXTREME regimen consists of triplet therapy with cetuximab, a recombinant human/mouse chimeric monoclonal antibody (mAb) to the epidermal growth factor receptor (EGFR), along with 5FU, and either carboplatin or cisplatin. After completing six 3-week cycles of triplet therapy, patients with no evidence of progressive disease (PD) were able to continue single-agent cetuximab until progression of disease. In a Phase III randomized study of cisplatin or carboplatin and 5FU compared to EXTREME, the EXTREME regimen was able to achieve an almost 3-month improvement in overall survival (OS) (10.1 months vs 7.4 months, hazard ratio [HR]=0.80; 0.64 to 0.99; p=0.04), a 2-month improvement in progression-free survival (PFS) (5.5 months vs 3.3 months; HR=0.54; p<0.001), and an increased response rate (RR) from 20% to 36% (p<0.001). Based on these results, this regimen has become the standard first-line therapy for patients in the recurrent/metastatic setting.

While the toxicities of EXTREME were similar to the chemotherapy doublet, the rate and type of Grade 3 and 4 toxicities can make delivering these regimens especially challenging for the majority of head and neck cancer patients. The most common Grade 3 or 4 adverse events (AEs) in the EXTREME arm were also common to chemotherapy and included

anemia (13%), neutropenia (22%), and thrombocytopenia (11%) with sepsis seen in 9 of 222 patients in the EXTREME group. Additionally, cetuximab-specific toxicities were observed, with Grade 3 skin reactions reported in 9% of patients and Grade 3 or 4 infusion-related reactions reported in 3% of patients (Vermorken et al 2008). While an 80% dose intensity was noted with the regimen as a whole, in reality, this regimen can only be effectively delivered to younger, fitter patients with a 0 to 1 Eastern Cooperative Oncology Group (ECOG) performance status. Unfortunately, the majority of patients diagnosed with head and neck cancer are older with a median age of 62 and have multiple comorbidities as a result of prior alcohol and tobacco use, including compromised cardiac and pulmonary function. Furthermore, as a result of therapy for this disease, such as radiation and/or surgery along with the disease itself, many also have compromised nutritional status that further makes delivering aggressive therapy with a favorable outcome difficult.

This population is therefore in need of therapies that are not only more efficacious in offering a longer survival benefit or even cure but can also be delivered with less toxicity than traditional chemotherapy regimens such as EXTREME.

1.1.2 Immunotherapies

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors (Dunn et al 2004). Studies in mouse models of transplantable tumors have demonstrated that manipulation of co-stimulatory or co-inhibitory signals can amplify T-cell responses against tumors (Peggs et al 2009). This amplification may be accomplished by blocking co-inhibitory molecules, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) or programmed cell death 1 (PD-1), from binding with their ligands, B7 or B7-H1 (programmed cell death ligand 1 [PD-L1]). Biologically, SCCHN has attributes that suggest susceptibility to immune checkpoint blockade. Multiple lines of evidence suggest that SCCHN tumors create a highly immunosuppressive environment and that the PD-1/PD-L1 axis and inhibition of the activation of T cells play an important role, and may be amenable to therapeutic intervention with immune-modulating agents (Badoual et al 2010, Badoual et al 2013, Larkin et al 2015, Litwin et al 1998, Lyford-Pike et al 2013). Virally driven tumors, including HPV-associated SCCHN, express viral antigens that may be recognized by the immune system. In HPV-associated cancers, the E6 and E7 tumor-specific antigens are known to be immunogenic, and studies have shown that HPV-specific T-cell responses form upon vaccination with these proteins (Kaufmann et al 2002). Administering an immunotherapeutic agent to patients with HPV-positive SCCHN may result in an anti-tumor immune response versus HPV tumor-specific antigens. In patients with HPV-negative SCCHN, the driving etiology is thought to be tobacco use. Data suggest that cancers associated with smoking such as non-small cell lung cancer (NSCLC), small-cell lung cancer, and SCCHN may carry a high mutational burden (Alexandrov et al 2013, Vogelstein et al 2013). Tumors with high mutational burden produce neoantigens, which may generate T-cell immunity. This hypothesis may explain the observation that patients with NSCLC with a history of heavy smoking may be more prone to respond to anti-PD-1 or anti-PD-L1 therapy as compared to light or never smokers (Li et al 2018; Norum et al 2018). Specifically, higher objective response rates (ORRs) following treatment with an anti-PD-L1 mAb were observed in patients with NSCLC with a history of smoking as compared to those without a history of smoking (**Champiat**

et al 2014). These data suggest that application of immune-modulating therapies in SCCHN may have a positive impact on clinical outcomes (Badoual et al 2010, Badoual et al 2013, Larkin et al 2015, Litwin et al 1998, Lyford-Pike et al 2013).

1.1.3 MEDI4736 (Durvalumab)

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

MEDI4736 has been given to humans as part of ongoing studies as a single drug or in combination with other drugs. As of June 2014, 509 patients have been enrolled and treated in 10 ongoing clinical studies of MEDI4736 (5 employing MEDI4736 as monotherapy and 5 as combination therapy). Details on the safety profile of MEDI4736 monotherapy are summarized in Section 1.3.2.1. Refer to the MEDI4736 Investigator's Brochure (IB) for a complete summary of non-clinical and clinical information; see Section 6.7 for guidance on management of MEDI4736-related toxicities.

1.1.4 Tremelimumab

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

An extensive program of non-clinical and clinical studies has been conducted for tremelimumab both as monotherapy and combination therapy with conventional anticancer agents to support various cancer indications using different dose schedules. As of the data cut-off date of 12 November 2014 (for all studies except D4190C00006 [hereafter referred to as Study 006], which has a cut-off date of 4 December 2014), 973 patients have received tremelimumab monotherapy (not including 497 patients who have been treated in the blinded Phase 2b study, D4880C00003) and 208 patients have received tremelimumab in combination with other agents. Details on the safety profile of tremelimumab monotherapy are summarized in Section 1.3.2.2. Refer to the current tremelimumab IB for a complete summary of non-clinical and clinical information; see Section 6.7 for guidance on management of tremelimumab-related toxicities.

1.1.5 MEDI4736 in combination with tremelimumab

Targeting both PD-1 and CTLA-4 pathways may have additive or synergistic activity (Pardoll 2012), because the mechanisms of action of the CTLA-4 and PD-1 pathways are non-redundant and therefore ultimately lead to stimulation of an immune response. Support for this is seen in mouse syngeneic models of transplantable solid tumors, demonstrating superior anticancer activity of the combination therapy compared with monotherapy. (Refer to the MEDI4736 IB for a full description of these results.) Furthermore, clinical data from the combination of CTLA-4 and PD-1 blockades in melanoma have resulted in higher 1-year survival and an ORR of 40% compared to either agent alone, with rapid, deep, and durable responses (Wolchok et al 2013). Recent data also demonstrate that inhibiting both the PD-1 and CTLA-4 pathways is associated with enhanced clinical activity in patients with PD-L1-negative disease compared to PD-1 inhibition alone, with median PFS of 11.2 months in patients with PD-L1-negative tumors who received ipilimumab and nivolumab compared to 2.8 months and 5.3 months for patients with PD-L1-negative tumors who received ipilimumab or nivolumab, respectively (Larkin et al 2015). Therefore, AstraZeneca is investigating the use of MEDI4736 + tremelimumab combination therapy for the treatment of cancer.

Study 006 is a Phase Ib dose-escalation study to establish safety, pharmacokinetic (PK)/pharmacodynamics, and preliminary antitumor activity of MEDI4736 + tremelimumab combination therapy in patients with advanced NSCLC. Preliminary efficacy, safety, and clinical data are summarized in Sections 1.3.1.3 and 1.3.2.3 demonstrate that the combination can be safely combined, with evidence of clinical activity.

The combination of MEDI4736 + tremelimumab is currently being evaluated in multiple ongoing Phase II and Phase III trials in patients with NSCLC and SCCHN (NCT02352948, NCT02453282, NCT02319044, and NCT02369874).

Details on the safety profile of MEDI4736 + tremelimumab combination therapy is summarized in Section 1.3.2.3.

1.1.6 Rationale for conducting this study

Patients with recurrent or metastatic head and neck cancer are considered incurable. Even with the established standard EXTREME regimen, consisting of cetuximab, a platinum, and 5FU, the expected survival is only 10 months with progression expected within 6 months. Hence, there is still a need for more efficacious therapies. Furthermore, delivery of the EXTREME regimen can be challenging in a population of patients who are older and have multiple comorbidities. Therefore, a regimen that is more efficacious and better tolerated would be of value.

SCCHN tumors, like many other malignancies, create a highly immunosuppressive environment and are amenable to therapeutic intervention with immune-modulating agents. Clinical data from the Sponsor and competitor molecules indicate that anti–PD-1/anti-PD-L1 agents can effectively achieve disease stabilization and durable responses when administered as monotherapy in pretreated patients. Efficacious interventions to initiate and sustain an immune response will likely require a number of agents that harness different immune mechanisms to successfully mount an immune response. Two specific

pathways, the PD-1–PD-L1 axis and the CTLA-4 pathway, have been successfully targeted by IMTs to obtain tumor reduction.

MEDI4736, an antibody that blocks the interaction between PD-L1 and its receptors, may relieve PD-L1-dependent immunosuppressive effects seen in SCCHN tumors and, therefore, enhance the cytotoxic activity of anti-tumor T-cells. This hypothesis is supported by emerging clinical data from other mAbs targeting the PD-L1/PD-1 pathway, which provide early evidence of clinical activity and a manageable safety profile in multiple tumor types (Brahmer et al 2012, Topalian et al 2012). Currently available data from the first-time-in-human, single-agent study (Study CD-ON-MEDI4736-1108; referred to hereafter as Study 1108) in patients with advanced solid tumors using MEDI4736 monotherapy indicates encouraging RRs and duration of response (DoR) with a manageable safety profile in patients with a variety of solid malignancies, including patients with SCCHN. Preliminary data in the SCCHN expansion cohort demonstrated a confirmed ORR of 11% (7 out of 62 partial response [PR]) and a disease control rate (DCR) at 24 weeks of 15% (9 out of 62 patients) based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) (Segal et al 2015).

The CTLA-4 and PD-1 pathways are non-redundant; therefore, while MEDI4736 monotherapy has shown efficacy in pretreated SCCHN patients, the combination of MEDI4736 + tremelimumab may have synergistic activity that may further improve upon the RRs, clinical benefit, and PFS achieved with standard chemotherapy (Pardoll 2012). Phase II and Phase III studies of MEDI4736 monotherapy and the combination of MEDI4736 + tremelimumab in the second-line recurrent/metastatic population are being conducted to establish that this combination is active and safe. Clinical data from competitor molecules utilizing the combination of CTLA-4 and PD-1 blockade in melanoma have demonstrated enhanced efficacy of this approach compared with either monotherapy agent (Postow et al 2015; Wolchok et al 2013).

Based on the preliminary clinical efficacy and safety data observed in patients with solid tumors, including advanced SCCHN, from Study 1108 with MEDI4736 monotherapy and the data from Study 006 of the MEDI4736 + tremelimumab combination therapy in NSCLC, the Sponsor has a comprehensive program to develop MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy for the treatment of SCCHN across multiple lines of therapy. The objective of earlier trials in this program was to determine the activity of MEDI4736 as monotherapy and also to establish the role of MEDI4736 in combination with tremelimumab in patients who had failed platinum-based therapy for recurrent/metastatic SCCHN. As part of this comprehensive development program, this Phase III study will determine the activity of MEDI4736 monotherapy compared to Standard of Care (SoC) in patients with PD-L1–positive and -negative R/M SCCHN who are not amenable to local curative therapy with surgery or radiation and who have not received prior systemic therapy for recurrent/metastatic disease, unless it was given as part of multimodality treatment for locally advanced or locally recurrent disease.

1.2 Rationale for study design, doses, and control groups

In this study, the efficacy of MEDI4736 with or without tremelimimab in terms of OS compared to SoC is being evaluated in SCCHN patients with R/M SCCHN who are not amenable to local curative therapy with surgery or radiation and who have received no

prior systemic therapy for recurrent/metastatic disease, unless it was given as part of multimodality treatment for locally advanced or locally recurrent disease. The contribution of MEDI4736 monotherapy to the efficacy of combination treatment regimen and the efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC will also be evaluated in a prospective, randomized fashion.

1.2.1 MEDI4736 monotherapy dose rationale

A dose of MEDI4736 1500 mg (corresponding to 20 mg/kg) every 4 weeks (q4w) is supported by in-vitro, non-clinical, clinical PK/pharmacodynamics, biomarkers, and activity data from Study 1108 in patients with advanced solid tumors and from a Phase I trial performed in Japanese patients with solid tumors (NCT01938612).

PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg every 2 weeks (q2w) or 15 mg/kg every 3 weeks (q3w), MEDI4736 exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg q2w, suggesting near complete target saturation (membrane-bound and soluble programmed cell death ligand 1 [sPD-L1]), and further shows that the MEDI4736 dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg q2w is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of MEDI4736 with PD-L1. Dose-related changes in a variety of peripheral biomarkers have been observed over the dose range of 0.1 to 15 mg/kg. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to MEDI4736. Of the 220 patients who received MEDI4736 monotherapy and for whom PK/anti-drug antibody (ADA) data were available as of 14 July 2014, five were ADA positive, with an impact on PK/pharmacodynamics reported in 1 patient at the 3 mg/kg dose.

Data from Study 006 also show an approximately dose-proportional increase in PK exposure for MEDI4736 over the dose range of 3 to 20 mg/kg MEDI4736 q4w or q2w. (For further information on PK observations in Study 006, please refer to Section 1.2.2).

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg q2w or 15 mg/kg q3w; Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg q2w and 20 mg/kg q4w regimens, as represented by area under the serum drug concentration-time curve at steady state (AUC_{ss}; 4 weeks). Median maximum serum concentration at steady state ($C_{max,ss}$) is expected to be higher with 20 mg/kg q4w (~1.5 fold) and median trough concentration at steady state ($C_{trough,ss}$) is expected to be higher with 10 mg/kg q2w (~1.25 fold). Clinical activity with the 20 mg/kg q4w dosing regimen is anticipated to be consistent with 10 mg/kg q2w, with the proposed dose of 20 mg/kg q4w expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Clinical data

As of 8 April 2015, there is initial safety data for 16 patients receiving the 20 mg/kg q4w dosing regimen (12 patients from Study 1108 and 4 patients from the Japan Phase I trial). The toxicities observed with 20 mg/kg q4w are consistent with the 10 mg q2w regimen, and there were no dose-limiting toxicities (DLTs) observed. Of the 12 patients in Study 1108, 42% of patients have experienced any grade AE, with 2 being Grade 3 and above (17%). None of the Grade 3 and higher events was considered treatment-related. No patients on the Japan Phase I trial have experienced a Grade 3 or above AE. At present, the data do not suggest that the safety profile of MEDI4736 will be different in the 20 mg/kg q4w dosing regimen when compared to 10 mg/kg q2w regimen. Data presented at the American Society for Clinical Oncology (ASCO) Meeting 2015, with a cut-off date of 7 April 2015, showed that MEDI4736 was well tolerated at a dose of 10 mg/kg q2w in the SCCHN subset of patients enrolled into Study 1108, with drug-related Grade ≥3 AEs reported in 10% of patients and no drug-related AEs leading to discontinuation or death. No drug-related colitis of any grade and no Grade ≥3 pneumonitis were reported (Segal et al 2015).

Efficacy data on the SCCHN patients in Study 1108, presented at ASCO 2015 (cut-off date: 7 April 2015), showed a DCR of 15% at 24 weeks (18% and 11% in patients with PD-L1-positive and -negative tumors, respectively) and ORR of 11% among 62 evaluable patients. The ORR was higher (18%; 4 complete response [CR]/PR; n=22) in patients with PD-L1-positive tumors, defined as those with ≥25% of tumor cells with membrane staining for PD-L1, compared to patients with PD-L1-negative tumors (8%; 3 CR/PR; n=37) (Segal et al 2015).

Given the available clinical data (the similar AUC_{ss} [4 weeks], the modest differences in median $C_{max,ss}$ and $C_{trough,ss}$, and the observation that both regimens maintain complete sPD-L1 suppression at trough), the 20 mg/kg (1500 mg) q4w and 10 mg/kg (750 mg) q2w regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 1500 mg q4w.

While treatment has been continued for a maximum of 1 year in the majority of patients treated to date with MEDI4736, dosing will continue until confirmed PD in this study to ensure a balanced comparison to the SoC arm.

1.2.2 MEDI4736 + tremelimumab combination therapy dose rationale

The MEDI4736 + tremelimumab combination therapy doses and regimen selected for this study are based on the goal of selecting an optimal combination dose of MEDI4736 and tremelimumab that would yield sustained target suppression (ie, sPD-L1), demonstrate promising efficacy, and have an acceptable safety profile.

PK/Pharmacodynamics data

In order to reduce the dosing frequency of MEDI4736 to align with the q4w dosing of tremelimumab, while ensuring an acceptable PK/pharmacodynamics, safety, and efficacy profile, cohorts in Study 006 were narrowed to 15 and 20 mg/kg MEDI4736 q4w. PK simulations from the MEDI4736 monotherapy data indicated that a similar AUC_{ss} (4 weeks) was expected following both 10 mg/kg q2w and 20 mg/kg q4w MEDI4736. The observed MEDI4736 PK data from the Study 006 were well in line with the predicted

monotherapy PK data developed preclinically. This demonstrates similar exposure of MEDI4736 20 mg/kg q4w and 10 mg/kg q2w, with no alterations in PK when MEDI4736 and tremelimumab (doses ranging from 1 to 3 mg/kg) are dosed together. While the median $C_{max,ss}$ is expected to be higher with 20 mg/kg q4w (approximately 1.5 fold) and median $C_{trough,ss}$ is expected to be higher with 10 mg/kg q2w (approximately 1.25 fold), this is not expected to impact the overall safety and efficacy profile, based on existing preclinical and clinical data.

Monotonic increases in pharmacodynamic activity were observed with increasing doses of tremelimumab relative to the activity observed in patients treated with MEDI4736 monotherapy. There was evidence of augmented pharmacodynamic activity relative to MEDI4736 monotherapy with combination doses containing 1 mg/kg tremelimumab, inclusive of both the 15 and 20 mg/kg MEDI4736 plus 1 mg/kg tremelimumab combinations.

Clinical data

As of 15 April 2015, a total of 102 patients with advanced NSCLC have been treated in Study 006 (Antonia et al 2015). Various dose combinations were explored, with doses of tremelimumab ranging from 1 to 10 mg/kg and doses of MEDI4736 ranging from 3 to 20 mg/kg. Seventy-four of these patients were in the q4w dosing schedule and 28 patients were in the q2w dosing schedule, with the goal of identifying the dose combination that best optimizes the risk:benefit profile in an acceptable range of PK and pharmacodynamic values.

Patients treated with doses of tremelimumab above 1 mg/kg had a higher rate of AEs, including discontinuations due to AEs, serious AEs (SAEs), and severe AEs. The number of patients reporting any AE, Grade 3 AEs, SAEs, and treatment-related AEs was higher in the 10 mg/kg MEDI4736 + 3 mg/kg tremelimumab q2w cohort than the 10 mg/kg MEDI4736 + 1 mg/kg tremelimumab q2w cohort. A similar pattern was noted in the q4w regimens, suggesting that, as the dose of tremelimumab is increased above 1 mg/kg, a higher rate of treatment-related events may be anticipated. Further, the SAEs frequently attributed to IMT, pneumonitis and colitis, were more commonly seen in cohorts using either 3 mg/kg or 10 mg/kg of tremelimumab compared to the 1-mg/kg dose cohorts. Together, these data suggest that a combination using a tremelimumab dose of 1 mg/kg appeared to minimize the rate of toxicity when combined with MEDI4736. As a result, all combination doses utilizing either the 3 or 10-mg/kg doses of tremelimumab were eliminated in the final dose selection.

In contrast, cohorts assessing higher doses of MEDI4736 with a constant dose of tremelimumab did not show an increase in the rate of AEs. The data suggested that increasing doses of MEDI4736 may not impact the safety of the combination as much as the tremelimumab dose. Further, safety data between the 10-mg/kg and 20-mg/kg cohorts were similar.

In Study 006, of all treatment cohorts in which clinical activity was observed, the cohort of 18 patients treated in the 20 mg/kg MEDI4736 + 1 mg/kg tremelimumab group had the fewest AEs, Grade ≥3 AEs, SAEs, and treatment discontinuations due to AEs. In this cohort, there was 1 treatment-related discontinuation due to sepsis, and no DLTs or treatment-related deaths were reported (Antonia et al 2015).

Preliminary clinical activity of the MEDI4736 + tremelimumab combination did not appear to change with increasing doses of tremelimumab. The 10-, 15-, and 20-mg/kg MEDI4736 q4w cohorts demonstrated objective responses at all doses of tremelimumab, and increasing doses of tremelimumab did not provide deeper or more rapid responses (Antonia et al 2015).

Efficacy data suggested that the 20 mg/kg MEDI4736 + 1 mg/kg tremelimumab dose cohort may demonstrate equivalent clinical activity to other dose combinations. A total of 8 of 18 patients in the 20 mg/kg MEDI4736 + 1 mg/kg tremelimumab cohort were evaluable for efficacy with at least 16 weeks of follow-up. Of these, 50% (4 out of 8 patients) had PR. The DCR rate at 16 weeks was 50% (Antonia et al 2015).

All together, the data suggested that a 20 mg/kg (1500 mg) MEDI4736 + 1 mg/kg (75 mg) tremelimumab dose combination should be selected for further development.

While treatment has been continued for a maximum of 1 year in the majority of patients treated to date with MEDI4736 + tremelimumab combination therapy, dosing will continue until confirmed PD in this study to ensure a balanced comparison to the SoC arm.

1.2.3 Rationale for fixed dosing

A population PK model was developed for MEDI4736 using monotherapy data from Study 1108 (Phase I study; N=292; doses=0.1 to 10 mg/kg q2w or 15 mg/kg q3w; solid tumors). Population PK analysis indicated only a minor impact of body weight on the PK of MEDI4736 (coefficient of ≤0.5). The impact of body weight-based (10 mg/kg q2w) and fixed dosing (750 mg q2w) of MEDI4736 was evaluated by comparing predicted steady-state PK concentrations (5^{th}, median, and 95^{th} percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on a median body weight of approximately 75 kg). A total of 1000 patients were simulated using a body weight distribution of 40 to 120 kg. Simulation results demonstrated that body weight-based and fixed dosing regimens yield similar median steady state PK concentrations, with slightly less overall between-patient variability with the fixed dosing regimen.

Similarly, a population PK model was developed for tremelimumab using data from Phase I through III studies (N=654; doses=0.01 to 15 mg/kg q4w or every 90 days; metastatic melanoma; Wang et al 2014). A population PK model indicated a minor impact of body weight on the PK of tremelimumab (coefficient of ≤0.5). The body weight-based (1 mg/kg q4w) and fixed dosing (75 mg q4w; based on a median body weight of approximately 75 kg) regimens were compared using predicted PK concentrations (5^{th}, median, and 95^{th} percentiles) using a population PK model in a simulated population of 1000 patients with a body weight distribution of 40 to 120 kg. Similar to MEDI4736, simulations indicated that both body weight-based and fixed dosing regimens of tremelimumab yield similar median steady-state PK concentrations, with slightly less overall between-patient variability with the fixed dosing regimen.

Similar findings have been reported by others (Narwal et al 2013, Ng et al 2006, Wang et al 2009, Zhang et al 2012). Wang and colleagues investigated 12 mAbs and found that fixed and body weight-based dosing perform similarly, with fixed dosing being superior for 7 of 12 antibodies (Wang et al 2009). In addition, they investigated 18

therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/pharmacodynamics parameters (Zhang et al 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given the expectation of similar PK exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens. Based on an average body weight of 75 kg, a fixed dose of 1.5 g q4w MEDI4736 (equivalent to 20 mg/kg q4w) and 75 mg q4w tremelimumab (equivalent to 1 mg/kg q4w) is included in the current study.

1.2.4 Standard of Care dose rationale

Based on the significant 3-month survival benefit established by the EXTREME regimen by Vermorken et al, this regimen will serve as the control therapy for this study (Vermorken et al 2008). As per the original publication, the Investigator will have the choice of using either carboplatin or cisplatin for the platinum component and any drug within the triplet regimen (cetuximab, a platinum, and 5FU) can be discontinued at any time due to toxicity at the discretion of the Principal Investigator.

1.2.5 Study population rationale

This study will enroll patients with recurrent or metastatic SCCHN who are not amenable to local curative therapy with surgery or radiation and who have not received prior systemic therapy for recurrent/metastatic disease, unless it was given as part of multimodality treatment for locally advanced or locally recurrent disease. Approximately 70% of newly diagnosed SCCHN cancer patients will be diagnosed with locally advanced or local disease that is amenable to therapy with radiation, surgery, chemotherapy, or combination of the three. However, for patients with recurrent disease that is not amenable to localized therapy or those who present with metastatic disease, no cure is currently available even with the current SoC regimen, EXTREME. An unmet medical need exists for this patient population.

Current experience with single-agent studies utilizing PD-1 or PD-L1 inhibitors suggests that clinical responses may be restricted to a subset of any given patient population and that it might be beneficial to enrich the patient population by selecting patients likely to respond to therapy. To date, no assay has been established or validated, and no single approach has proven accurate for patient enrichment. However, independent data from multiple sources using different assays and scoring methods suggests that PD-L1 expression on tumor cells and/or tumor-infiltrating cells may be associated with greater clinical benefit.

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

Data presented by AstraZeneca at the 2015 ASCO meeting (Segal et al 2015) demonstrate that treatment with MEDI4736 resulted in an ORR of 18% and 8% in patients with PD-L1-positive and -negative SCCHN tumors, respectively. Therefore, it appears that the

selection of patients based on PD-L1 expression levels within the tumor microenvironment may improve the probability and/or quality of responses to PD-1 pathway-targeting agents and, therefore, may have merit as a patient enrichment tool. Competitors have presented similar data with this class of agents. Specifically, the phase 3 KEYNOTE-048 study, which demonstrated that pembrolizumab monotherapy improved OS when compared with the EXTREME regimen in patients whose tumors had PD-L1 expression ≥1 and ≥20 by Combined Positive Score (CPS) [hazard ratio (HR) 0.78 (0.64–0.96), P=0.0086 and HR 0.61 (0.45– 0.83), P=0007, respectively] (Burtness et al., 2019). CCI [redacted] Based on these 2 studies, durvalumab monotherapy results in better OS in the PD-L1 high subgroup (TC50/IC25) when compared to the PD-L1 low population (HR=0.70; p=0.039). Median survival was 9.8 months versus 5.4 months in the PD-L1 high and PD-L1 low subgroups respectively. Additional data analysis from the Sponsor's Phase 3 D4193C00002 (EAGLE) study in second line HNSCC appear to further support the utility of PD-L1 to select patients with improved outcome when treated with durvalumab. CCI [redacted] When controlling for prognostic factors, the multivariate analysis of patients treated with durvalumab shows a tendency to better OS in the PD-L1 high (TC/IC) vs PD-L1 low subgroup [HR=0.80 (95% CI 0.58–1.09)].

Nevertheless, PD-L1-negative patients still appear to derive clinical benefit from PD-L1-directed therapies. Segal et al noted DCRs (stable disease [SD] or better) at 24 weeks of 18% and 11% in PD-L1-positive and -negative patients, respectively (Segal et al 2015). For patients in the late line of disease with a median PFS of only 3 months and OS of 6 months, maintaining at least SD is clinically beneficial. These data demonstrate that clinical benefit can be achieved in both PD-L1-positive and -negative SCCHN patients.

MEDI4736 + tremelimumab combination therapy may further enhance RRs and clinical benefit rates in both PD-L1-negative and -positive patients and may be able to improve the probability and quality of response in PD-L1-negative patients compared to those who receive MEDI4736 alone. As of 15 April 2015 from Study 006 investigating the clinical activity of combination of MEDI4736 + tremelimumab in NSCLC, data show that across a range of doses, the addition of tremelimumab to MEDI4736 results in an ORR of 27% in patients with PD-L1-negative NSCLC (Antonia et al 2015). This compares favorably to the 5% ORR observed with MEDI4736 monotherapy in pretreated PD-L1-negative NSCLC patients (Rizvi et al 2015). Increases in ORR may also be achieved in patients with PD-L1-positive disease, as an ORR of 27% was observed with MEDI4736 monotherapy (Rizvi et al 2015), while an ORR of 33% was observed over the range of doses evaluated for the combination of MEDI4736 + tremelimumab (Antonia et al 2015). Acknowledging the limitations and necessary caveats associated with cross-trial comparisons, there appears to be an incremental benefit regardless of PD-L1 status in patients with NSCLC treated with the combination therapy; however, this benefit appears to be greater in the PD-L1-negative population. Similar patterns are anticipated with SCCHN.

Based on this information, both PD-L1-negative and -positive SCCHN cancer patients with recurrent or metastatic disease who are not amenable to local curative therapy with surgery or radiation and who have not received prior systemic therapy for recurrent/metastatic disease may be enrolled in all arms of this study, as clinical benefit may be seen in both populations with monotherapy and combination immunotherapy.

Immune checkpoint inhibitors (ICIs) are profoundly changing the treatment of many types of cancer, including melanoma, NSCLC, renal cell carcinoma (RCC), SCCHN, urothelial carcinoma (UC), and Hodgkin's lymphoma, and have been associated with long-lasting tumor responses. However, an early mortality (EM) phenomenon has been observed in many randomized clinical trials comparing ICIs with active comparator arms in advanced or metastatic cancer patients, even with overall benefit ultimately favoring ICI therapy (Champiat et al 2018). While the precise etiology of this phenomenon is not clearly established, it is characterized by what seems to be disproportionately higher mortality in the early treatment period favoring the active control arm, followed by subsequent benefit in OS favoring the ICI treatment arm. This is often reflected in the clinical data by the "crossing of the Kaplan-Meier curves" suggesting a subpopulation of patients at a higher risk of EM whose advanced rate of tumor growth may require the cytotoxic tumor-debulking effect of chemotherapy. Accordingly, it is of great therapeutic interest to better predict the risk of early mortality for a given patient to better inform the appropriate treatment for their individual clinical state. To aid in this objective, AstraZeneca has developed and implemented a model that predicts a patient's risk of early mortality to optimize the benefit:risk profile for treatment of patients with ICIs.Tumor mutational burden (TMB) has been associated with response in patients treated with PD-1 and CTLA-4 inhibitors in several tumour types (Rizvi et al 2015b, Snyder et al 2014). In a retrospective analysis of HNSCC patients treated with pembrolizumab, TMB was significantly associated with best overall response (BoR) (Siewert et al 2018). Hanna et al (2018) also observed a significant difference in mutational load between responders and non-responders to anti-PD-1/PD-L1 agents (17.7 mut/Mb versus 7.1 mut/Mb). Furthermore, TMB was correlated with increased median overall survival. In patients with TMB>10mut/Mb mOS was 20 months, compared to 6 months in patients with TMB<5mut/Mb, p=0.01).

There are numerous benefits of minimally invasive, blood-based biomarkers. TMB assays using circulating tumour DNA (ctDNA) are under development. Recently, in the MYSTIC study, high TMB measured in ctDNA was associated with improved OS in NSCLC patients treated with durvalumab and tremelimumab (Rizvi et al 2018). There is no published data on the use of ctDNA TMB in HNSCC (Oliva et al 2018), however ctDNA is present in the blood in detectable quantities in patients with head and neck cancers (Bettegowda et al 2014). In this study patient plasma samples will be analysed for ctDNA TMB using the Guardant OMNI panel.

1.2.6 Rationale for endpoints

The primary aim of this study is to determine the efficacy of MEDI4736 monotherapy versus SoC (EXTREME) in a pre-specified PD-L1 TC/IC high subgroup in terms of OS.

Testing for improvements in OS as a primary endpoint provides a non-biased assessment of direct clinical benefit to the patient (FDA Guidance 2011).

Secondary efficacy endpoints include the following:

- MEDI4736 monotherapy versus SoC: OS in the low risk of EM subgroup, ctDNA TMB high subgroup (≥16 mut/Mb) and all-comers. PFS, ORR, APF6, APF12, OS12, OS18 and OS24 assessed in the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high subgroup (≥16 mut/Mb) and all-comers. PFS2, DoR, BoR, TTR, TFST and TSST in the PD-L1 TC/IC high subgroup and all-comers.
- MEDI4736 + tremelimumab combination therapy versus SoC: OS, PFS, ORR, APF6, APF12, OS12, OS18 and OS24 in the PD-L1 TC/IC high subgroup , low risk of EM subgroup, ctDNA TMB high subgroup (≥16 mut/Mb) and all-comers. PFS2, DoR, BoR, TTR, TFST and TSST in the PD-L1 TC/IC high subgroup and all-comers.
- MEDI4736 + tremelimumab versus MEDI4736 monotherapy: PFS, ORR and OS in the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high subgroup (≥16 mut/Mb) and all-comers.

CCI [redacted] IrRECIST 1.1 will take into account the unique kinetics of responses that have been observed and well characterized with this class of agents, including those observed in the ongoing Study 1108.

The secondary endpoints of 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 [QLQ-H&N35]) will show the overall influence of the benefits and toxicity of the treatment from a patient's perspective and will aid in the understanding of the benefit/risk evaluation. These patient-reported outcome (PRO) questionnaires are well-established instruments that have been previously included in cancer clinical studies.

The PK and immunogenicity of MEDI4736 + tremelimumab combination therapy are being examined to assess the PK and immunogenicity profiles of the combination of both agents and to determine the impact of each on PK, pharmacodynamics, and safety and efficacy parameters. Biological samples will be used to explore potential biomarkers in tumor, plasma, and/or serum, which may influence the progression of cancer (and associated clinical characteristics) and/or response.

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. Of the 414 patients treated with MEDI4736 (all dose levels) in all tumor types in Study 1108 as of 14 July 2014, a total of 169 patients were evaluable for response analysis, which included patients who had at least 24 weeks of follow-up as of 14 July 2014 and had either at least 1 post-baseline tumor assessment or experienced clinical PD or death. Nineteen patients (11.2%) had a best overall response of confirmed and unconfirmed CR/PR. The DCR (CR + PR + SD ≥12 weeks) was 32% (54 of 169 patients). PD-L1 status (based on VENTANA/MedImmune assay) was known for 143 of 169 evaluable patients, of whom 30 had PD-L1-positive tumors (defined by tumor staining ≥25%). A best overall response of CR/PR (confirmed and unconfirmed) was observed in 7 of 30 (23.3%) patients with PD-L1-positive tumors and in 6 of 113 (5.3%) patients with PD-L1-negative tumors.

Recent data are available for patients with SCCHN in the expansion cohort of Study 1108 (Segal et al 2015). Sixty-two SCCHN patients were treated with MEDI4736 as monotherapy at 10 mg/kg q2w and evaluable for disease assessments as of the data cut-off date of 7 April 2015. Tissue samples were retrospectively tested for PD-L1 expression using an immunohistochemistry (IHC) assay. Of 62 SCCHN patients, an ORR of 11% was observed in the PD-L1-unselected population and in 18% and 8% of patients with PD-L1-positive (n=22) and PD-L1-negative disease (n=37), respectively, with DCR at 24 weeks achieved in 18% and 11% of patients with PD-L1-positive and –negative disease, respectively. DoRs ranged from 41 to 53 weeks in patients with PD-L1 positive disease and 16 to 54 weeks in patients with PD-L1-negative disease, with responses noted in both HPV-positive and -negative patients and in smokers and non-smokers.

1.3.1.2 Tremelimumab

In a single-arm, Phase II study (Study A3671008) of tremelimumab administered at 15 mg/kg every 90 days to patients with refractory melanoma, a RR of 7% and a median OS of 10 months in the second-line setting (compared to approximately 6 months with best supportive care [BSC] 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 a RR of 11% and median OS of 12.58 months in the first-line setting compared to 10.71 months with standard chemotherapy (Ribas et al 2013). Additionally, in a Phase II maintenance study in patients with NSCLC (Study A3671015), PFS at 3 months was 22.7% in the tremelimumab arm (15 mg/kg) compared with 11.9% in the BSC arm.

1.3.1.3 MEDI4736 + tremelimumab combination therapy

Preliminary efficacy data from Study 006 have demonstrated that this combination is clinically active and well tolerated. As of 15 April 2015, 63 patients were evaluable for response across various MEDI4736 + tremelimumab combination therapy dose regimens. Of these, 27% (17 out of 63 patients) had a best response of PR and 41% (26 out of

63 patients) had disease control (CR, PR, SD ≥16 weeks). In the MEDI4736 20 mg/kg plus tremelimumab 1 mg/kg q4w cohort, a total of 8 of 18 patients were evaluable for efficacy with at least 16 weeks of follow-up. Of these, both the ORR and DCR at 16 weeks were 50% (4 out of 8 patients) (Antonia et al 2015).

A number of ongoing studies are assessing the activity of agents in patients with PD-L1-positive tumors. There is also an unmet medical need in patients with PD-L1–negative tumors that needs to be addressed. Data, as of 15 April 2015 from Study 006, show that with the addition of tremelimumab to MEDI4736, the ORR of 27% was achieved in patients with PD-L1-negative NSCLC. As patients with PD-L1-positive disease also appear to achieve higher ORR with the combination (27% with MEDI4736 monotherapy compared with 33% with MEDI4736 + tremelimumab combination therapy; Antonia et al 2015; Rizvi et al 2015), this study will enroll all patients with SCCHN, with an emphasis on those determined to be PD-L1 negative.

1.3.2 Identified and Potential risks

Overall risks

Monoclonal antibodies directed against immune checkpoint proteins, such as programmed cell death ligand 1 (PD-L1) as well as those directed against programmed cell death-1 (PD-1) or cytotoxic T-lymphocyte antigen-4 (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 AEs such as colitis and diarrhoea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis and endocrinopathies including hypo- and hyper-thyroidism.

1.3.2.1 MEDI4736

Risks with MEDI4736 include, but are not limited to, diarrhea/colitis and intestinal perforation, pneumonitis/ILD, endocrinopathies (hypo- and hyper-thyroidism, 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 durvalumab 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 durvalumab 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 (see the Dosing Modification and Toxicity Management Guidelines referenced in Section 6.7.2).

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

1.3.2.2 Tremelimumab

Risks with tremelimumab monotherapy include, but are not limited to, GI effects (colitis, diarrhoea, enterocolitis and intestinal perforation), endocrine disorders (hypo and hyperthyroidism, hypophysitis and adrenal insufficiency), skin effects (rash, and pruritus), elevations in lipase and amylase and clinical manifestations of pancreatitis, other gastrointestinal events e.g. ulcerative colitis, dehydration, nausea and vomiting; hepatic events including hepatitis, and liver enzyme elevations; pneumonitis and ILD; nervous system events including encephalitis, peripheral motor and sensory neuropathies, Guillain-Barre 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.

Further information on these identified and potential risks can be found in 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, dyspnoea, constipation, cough, pyrexia, abdominal pain, decreased weight, headache, asthenia, and anaemia. Approximately 16% of patients experienced an AE that resulted in permanent discontinuation of tremelimumab and approximately 45% of patients experienced an SAE.

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

1.3.2.3 MEDI4736 + tremelimumab combination therapy

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

Approximately 15% of patients experienced an AE that resulted in permanent discontinuation of study drug and approximately 15% of patients experienced an SAE that was considered to be related to 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 are not amenable to local curative therapy with surgery or radiation and who have not received prior systemic therapy in the metastatic setting.

The study design aims to minimize potential risks; 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 + tremelimumab combination therapy, MEDI4736 monotherapy, and SoC).

Based upon the available non-clinical and clinical safety data, the limited survival benefit provided by the currently available treatment options to patients, the limited life expectancy due to malignant disease, and the strength of the scientific hypotheses under evaluation, MEDI4736 monotherapy and in combination with tremelimumab 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.

Therefore, the investigation of the potential therapeutic efficacy of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination in patients with PD-L1-positive and -negative tumors is acceptable, and the overall benefit/risk assessment supports the proposed study design.

1.4 Study design

This is a randomized, open-label, multi-center, 3-arm, global Phase III study to determine the efficacy and safety of MEDI4736 +/- tremelimumab compared to SoC in the treatment of patients with recurrent or metastatic SCCHN who are not amenable to local curative therapy with surgery or radiation and who have not received prior systemic therapy for

recurrent/metastatic disease, unless it was given as part of multimodality treatment for locally advanced or locally recurrent disease. A schematic diagram of the overall study design is shown in Figure 1, a flow chart of the study design treatment periods is presented in Figure 2, and a flow chart of the optional retreatment period for the MEDI4736 + tremelimumab combination therapy arm is presented in Figure 3.

Patients will undergo an assessment on their tumor tissue sample to determine PD-L1 status. Patients with tumoral PD-L1 expression above or below a pre-specified cut-off level of ≥25%, as determined by an IHC assay (referred to hereafter as PD-L1–positive or -negative tumors, respectively), will be enrolled in the study. If the patient has already been tested as a part of the screening process for any AstraZeneca study using the VENTANA assay, this test result can be used for the determination of eligibility. The specified expression cut-off level of ≥25% in the tumor cells will be used for the purpose of stratification and therefore included in the stratified log rank tests for OS and PFS. HPV status will be assessed according to local standards or by the p16 IHC assay.

Emerging data from 2nd line SCCHN studies suggests that PD-L1 expression on tumor tumor-infiltrating immune, as well as tumor cells, may be associated with greater clinical benefit with PD-1/PD-L1 inhibitors compared to tumor cell expression alone (Chow et al 2016, Ferris et al 2017). The D4193C00001 and D4193C00003 studies were used to identify a subgroup of patients that may be more likely to benefit from MEDI4736 +/- tremelimumab treatment. Based on this data, the pre-specified PD-L1 TC/IC high subgroup used in this study is defined as those patients whose tumors express PD-L1 on ≥50% of tumor cells OR ≥25% of tumor-associated immune cells (TC≥50 or IC≥25) as assessed by the VENTANA PD-L1 (SP263) Assay.

Patients will be randomized in a 2:1:1 manner to either the MEDI4736 + tremelimumab combination arm, the MEDI4736 monotherapy arm, or the SoC arm. Patients randomized to the MEDI4736 + tremelimumab combination arm will receive tremelimumab 75 mg intravenous (IV) q4w for 4 doses and MEDI4736 1500 mg IV q4w until PD, those in the MEDI4736 monotherapy arm will receive MEDI4736 1500 mg IV q4w monotherapy until PD, while patients in the SoC arm will receive up to six 3-week cycles consisting of a platinum [cisplatin 100 mg/m^2 or carboplatin area under the curve (AUC) of 5 mg/mL/min IV] on 1, 5FU 1000 mg/m^2/day on Days 1 through 4, and weekly cetuximab. Cetuximab will be administered at 400 mg/m^2 on Day 1 of Cycle 1, and then 250 mg/m^2 weekly for up to six 3-week cycles and 250 mg/m^2 IV weekly for maintenance until progression, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met (see Section 3.9).

Patients in all arms with confirmed PD by RECIST 1.1 who, in the Investigator's opinion, continue to receive benefit from their assigned treatment and who meet the criteria for treatment in the setting of PD may continue to receive their assigned treatment (see Section 7.2.3). Since the phenomenon of pseudoprogression in patients treated with immunotherapy is well documented and the limitations of RECIST 1.1 in identifying those who are achieving clinical benefit with immunotherapies are known, patients enrolled in the IMT arms will be permitted to continue therapy even in the presence of PD as per RECIST 1.1 (Weber et al 2012). However, patients in the immunotherapy arms will not be permitted to continue immunotherapy if progression occurs after objective response (defined by RECIST 1.1) to immunotherapy treatment in the target lesions. Patients in the

SoC arm may continue therapy in the setting of PD if they remain clinically stable, meet criteria for treatment in the setting of PD, and continue to receive some clinical benefit in the Investigator's opinion.

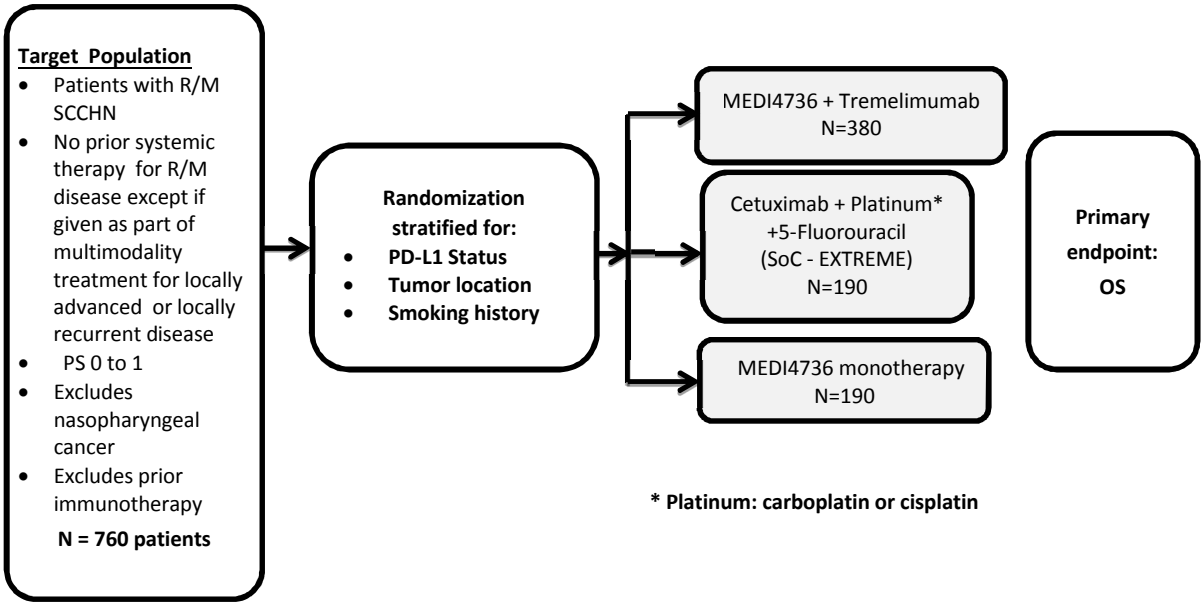
Patients in all arms with a symptomatic solitary lesion, a brain lesion, or a lesion of clinical importance (eg, impending fracture, etc) may be treated with radiation after approval from the Sponsor. Non-irradiated lesions need to continue to be measurable by RECIST 1.1. The time interval between the last systemic treatment and radiation should be 10 days, and systemic treatment can be resumed 1 week post radiation.

Patients who have discontinued therapy due to disease progression will enter follow-up until death (see Table 4). Patients who have discontinued treatment due to toxicity will be followed up until confirmed disease progression and for survival (see Table 4).

Tumor assessments will be performed on images from computed tomography (CT) or magnetic resonance imaging (MRI) scans, preferably with IV contrast, at the times specified in Table 2, Table 3, and Table 4. RECIST 1.1 assessments using the investigator assessments will be used to derive the secondary variables of PFS, ORR, DoR, and proportion of patients alive and progression free at 6 and 12 months (APF6 and APF12). CCI [redacted] See Section 5.1 and Appendix E for further information regarding RECIST 1.1 tumor assessments in this study.

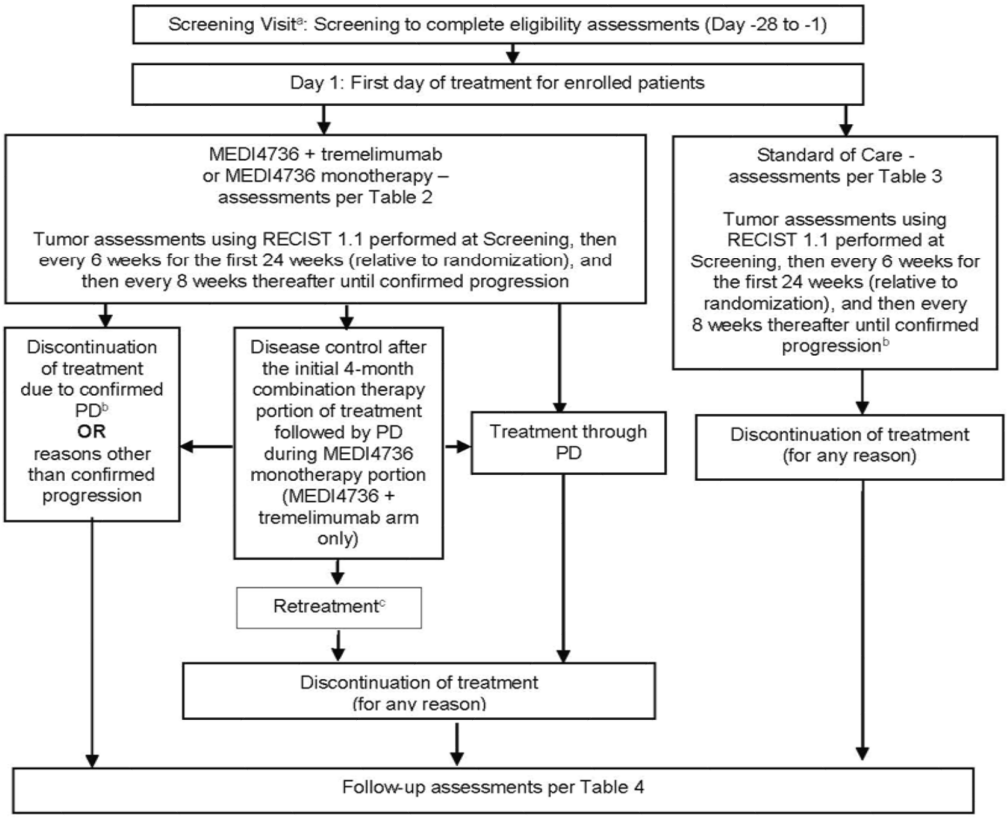
This study will enroll approximately 1016 patients with PD-L1-positive and -negative disease at sites globally to obtain 760 patients who are likely to be evaluable for the primary endpoint.

Figure 1 Overall study design



OS Overall survival; PD-L1 Programmed cell death ligand 1; PS Eastern Cooperative Oncology Group performance status; SCCHN Squamous cell cancer of the head and neck; SoC Standard of Care.

Figure 2 Study flow chart - treatment periods



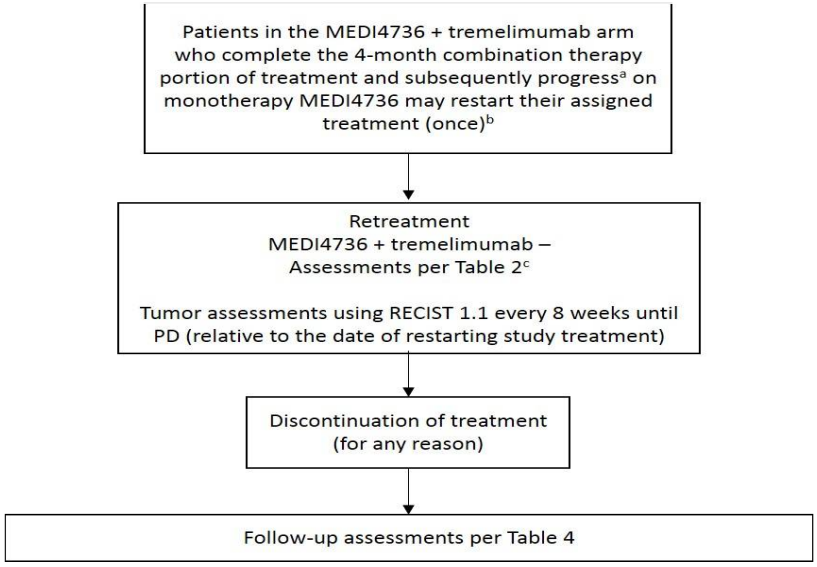
[a] Informed consent of study procedures and tumor sample acquisition may be obtained prior to the 28-day screening window, if necessary, in order to permit tumor sample acquisition and analysis prior to randomization.

[b] Disease progression requires confirmation for patients receiving IMT. Disease progression in patients in the SoC arm should be confirmed if clinically feasible (see Section 5.1 for more information).

[c] Patients in the MEDI4736 + tremelimumab combination therapy arm who are eligible for retreatment will be treated according to Figure 3.

IMT Immunomodulatory therapy; PD Progressive disease; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1.

Figure 3 Study flow chart – optional retreatment for MEDI4736 + tremelimumab arm



[a] With or without confirmation.

[b] Before restarting MEDI4736 + tremelimumab combination therapy, the Investigator should ensure that the patient does 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 prior to restarting study treatment; all further scans should occur q8w until PD (relative to the date of restarting study treatment).

[c] PK, ADA, and MDSC assessments do not need to be collected during retreatment.

ADA Anti-drug antibody; MDSC Myeloid-derived suppressor cell; PK Pharmacokinetics; q8w Every 8 weeks; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objectives:	**Outcome Measure:**
To assess the efficacy of MEDI4736 monotherapy compared to SoC in terms of OS	OS in the PD-L1 TC/IC high subgroup

OS Overall survival; SoC Standard of Care.

2.2 Secondary objectives

Secondary Objectives:	Outcome Measures:
To further assess the efficacy of MEDI4736 monotherapy compared to SoC (EXTREME) in terms of OS, PFS, ORR, DoR, BoR, TTR, TFST, TSST, APF6, APF12, PFS2, OS12, OS18 and OS24	OS in low risk of early mortality (EM) subgroup, ctDNA TMB high subgroup (≥16 mut/Mb) and all-comers OS12, OS18, OS24 in the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high subgroup (≥16 mut/Mb) and all-comers PFS, ORR, APF6 and APF12 using site investigator assessments according to RECIST 1.1 in the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high subgroup (≥16 mut/Mb) and all-comers DoR, BoR and TTR, using site investigator assessments according to RECIST 1.1 in the PD-L1 TC/IC high subgroup and all-comers PFS2 using local standard clinical practice in the PD-L1 TC/IC high subgroup and all-comers TFST and TSST in thePD-L1 TC/IC high subgroup and all-comers
To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC (EXTREME) in terms of OS, PFS, ORR, DoR, BoR, TTR, TFST, TSST, APF6, APF12, PFS2, OS12, OS18 and OS24	OS, OS12, OS18, OS24 in the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high subgroup (≥16 mut/Mb) and all comers PFS, ORR, APF6 and APF12 in the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high subgroup (≥16 mut/Mb) and all-comers using site investigator assessments according to RECIST 1.1 DoR, BoR and TTR, using site investigator assessments according to RECIST 1.1 in the PD-L1 TC/IC high subgroup and all-comers PFS2 using local standard clinical practice in the PD-L1 TC/IC high subgroup and all-comers TFST and TSST in the PD-L1 TC/IC high subgroup and all-comers
To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to MEDI4736 monotherapy in terms of PFS, ORR, and OS	PFS and ORR using site investigator assessments according to RECIST 1.1 in the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high subgroup (≥16 mut/Mb) and all-comers OS in the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high subgroup (≥16 mut/Mb) and all-comers

Secondary Objectives:	Outcome Measures:
To assess disease-related symptoms and health-related quality of life in patients treated with MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy compared to SoC (EXTREME) using the European Organisation for Research and Treatment of Cancer (EORTC) 30-item Core Quality of Life Questionnaire (QLQ-C30) version 3 and the 35-item Head and Neck Quality of Life Questionnaire (QLQ-H&N35) module	EORTC QLQ-C30: global health QoL, functioning (physical) and symptoms (fatigue) in the PD-L1 TC/IC high subgroup and all-comers EORTC QLQ-H&N35: symptoms (pain, swallowing) in the PD-L1 TC/IC high subgroup and all-comers Changes in World Health Organization/Eastern Cooperative Oncology Group performance status in the PD-L1 TC/IC high subgroup all-comers
To assess the PK of MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy	Concentration of MEDI4736 and tremelimumab in blood and PK parameters, such as peak concentration and trough (as data allow; sparse sampling)
To investigate the immunogenicity of MEDI4736 and tremelimumab	Presence of ADAs for MEDI4736 and tremelimumab

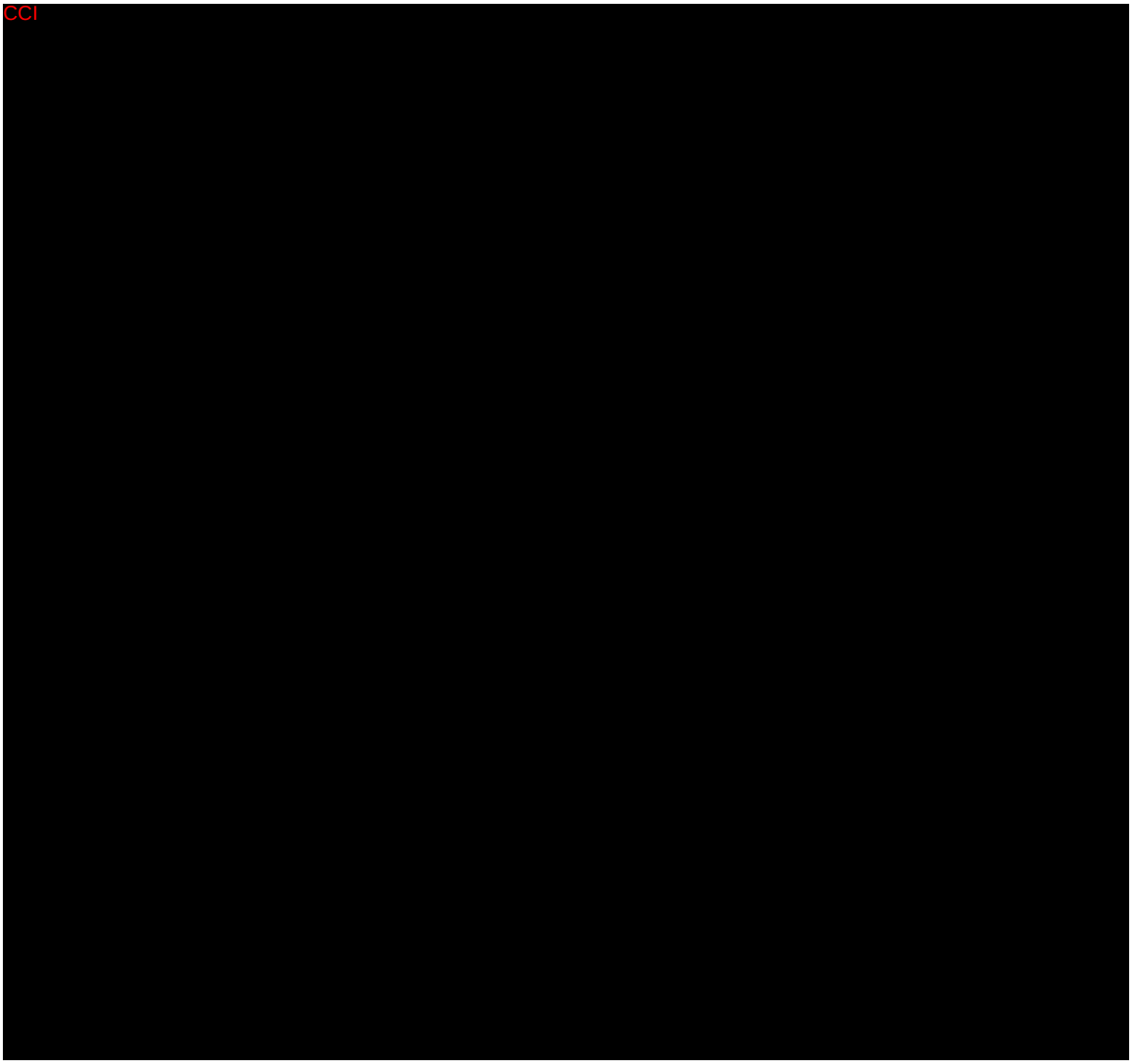
ADA Anti-drug antibody; APF6 Proportion of patients alive and progression free at 6 months; APF12 Proportion of patients alive and progression free at 12 months; BoR Best objective response; ctDNA Circulating tumor DNA; DNA Deoxyribonucleic acid; DoR Duration of response; ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; HRQoL Health-related quality of life; IC tumor-associated immune cells; ORR Objective response rate; OS Overall survival; OS12 Proportion of patients alive at 12 months after randomization; OS18 Proportion of patients alive at 18 months after randomization; OS24 Proportion of patients alive at 24 months after randomization; PD-L1 Programmed cell death ligand 1; PFS Progression-free survival; PFS2 Second progression; PK Pharmacokinetics; QLQ-C30 v3 30-item core quality of life questionnaire, version 3; QLQ-H&N35 35-item head and neck quality of life questionnaire; QoL Quality of life; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1; SCCHN Squamous cell carcinoma of the head and neck; SoC Standard of Care; TC tumor cells; TFST Time to first subsequent therapy; TMB Tumor mutation burden (The ctDNA TMB cutpoint of 16mut/Mb for MEDI4736+tremelimumab and MEDI4736 monotherapy was derived from the EAGLE study (Li et al 2020) Li W, Wildsmith S, Ye J, Si H, Morsli N, He P et al. Plasma-based tumor mutational burden (bTMB) as predictor for survival in phase III EAGLE study: Durvalumab (D) +/- tremelimumab (T) versus chemotherapy (CT) in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) after platinum failure. J Clin Oncol 2020;38:15_suppl, 6511-6511.)).; TTR Time to response; TSST Time to second subsequent therapy; WHO World Health Organization.

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 in the first-line setting for treatment of SCCHN	AEs, physical examinations, laboratory findings (including clinical chemistry, hematology, and urinalysis), vital signs (including BP and pulse), and ECGs in the PD-L1 TC/IC high subgroup, low risk of EM subgroup and all-comers

AE Adverse event; BP Blood pressure; ECG Electrocardiogram; IC tumor-associated immune cells; SoC Standard of Care; TC tumor cells.

2.4 Exploratory objectives



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:

SoC procedures obtained prior to informed consent for other purposes may be used for screening if the patient/legal representative consents to allow use of these procedures for screening purposes.

Patients must meet all of 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 local curative therapy with surgery or radiation therapy.

4. No prior systemic therapy for recurrent/metastatic disease. Systemic therapy given as part of multimodality treatment for locally advanced or locally recurrent disease is allowed.

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

6. For patients with OPC only: known HPV status prior to randomization.

7. Confirmed PD-L1–positive or –negative SCCHN by the VENTANA 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 analytically validated VENTANA assay as a part of the screening process for another AstraZeneca/MedImmune study, this test result can be used for the determination of eligibility.

   – Note: A 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 determined by 0% to 24% of tumor cells with membrane staining for PD-L1.

8. World Health Organization (WHO)/ECOG performance status of 0 or 1

9. 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 and the lesion measures at least 20 mm.

10. Patients must have no prior exposure to immune-mediated therapy, including anti-CTLA-4, anti-PD-1, anti–PD-L1, or anti–programmed cell death ligand 2 antibodies, excluding therapeutic anticancer vaccines. Exposure to other investigational agents may be permitted after discussion with the Sponsor.

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

    - Hemoglobin ≥9 g/dL
    - Absolute neutrophil count ≥1500/mm^3 (1.5×10^9/L)
    - Platelet count ≥100000/mm^3 (100×10^9/L)
    - Serum bilirubin ≤1.5 × the upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia [predominantly unconjugated bilirubin] in the absence of evidence of hemolysis or hepatic pathology), who will be allowed in consultation with their physician.
    - ALT and AST ≤2.5 × ULN; for patients with hepatic metastases, ALT and AST ≤5 × ULN
    - Calculated creatinine clearance >40 mL/min as determined by Cockcroft-Gault (using actual body weight) (creatinine clearance of 60 mL/min is needed if cisplatin is used)

      Males:

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

      Females:

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

12. 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 if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution, or 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).

Criteria for continuation of treatment in the setting of progressive disease

For all patients who are treated through progression at the Investigator's discretion, the Investigator should ensure that patients still meet all of the inclusion criteria and none of the exclusion criteria for this study, and that 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

   The IP should be discontinued if there is confirmed PD while receiving treatment following a previous response (CR or PR) to the IP in the target lesions (ie, the response and progression events both occurred in the target lesions while receiving the IP during the treatment period).

Criteria for retreatment in the MEDI4736 + tremelimumab arm

Patients in the MEDI4736 + tremelimumab combination therapy arm are eligible to receive retreatment with the MEDI4736 + tremelimumab combination therapy provided progression occurred in the monotherapy portion of dosing and the patient meets all the criteria specified above for treatment beyond confirmed progression. Patients who discontinue treatment in 1 treatment arm may not switch to treatment in a different group.

Additional details pertaining to retreatment are presented in Section 7.2. Additional details pertaining to restrictions are presented in Section 3.8.

3.2 Exclusion criteria

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

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

2. Tumor progression or recurrence within 6 months of last dose of platinum therapy given as part of multimodality treatment for locally advanced or locally recurrent disease.

3. Receipt of any radiotherapy or hormonal therapy for cancer treatment within 30 days prior to first dose of study treatment.

4. 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. Receipt of any investigational anticancer therapy within 28 days or 5 half-lives, whichever is longer, prior to the first dose of study treatment.

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

7. Any unresolved toxicity National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (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, gastrostomy tube) may be included after consultation with the Study Physician.

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

   – 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) and/or as anti-emetics for the SoC arm

9. History of allogeneic organ transplantation

10. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis, Crohn's disease], diverticulitis with the exception of a prior episode that has resolved or diverticulosis, celiac disease, or other serious gastrointestinal 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 psoriasis not requiring systemic treatment

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

12. History of another primary malignancy within the last 5 years except for the following:

    - Non-invasive malignancies, such as cervical carcinoma in situ or non-melanomatous carcinoma of the skin that has been surgically cured. Other in situ carcinomas that have been adequately treated may be permitted after detailed discussion with the Sponsor.

13. 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

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

15. History of active primary immunodeficiency

16. Active tuberculosis

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

18. 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.

19. Female patients of childbearing potential who are pregnant or breast-feeding or who are not willing to employ a highly effective method of birth control from screening to 90 days after the last dose of MEDI4736 monotherapy or 180 days after the last dose of MEDI4736 + tremelimumab combination therapy and non-sterilized male patients who are sexually active with a female partner of childbearing potential who are not willing to employ male condom plus spermicide from screening to 90 days after the last dose of MEDI4736 monotherapy or 180 days after the last dose of MEDI4736 + tremelimumab combination therapy. For patients randomized to receive SoC treatment, follow the local prescribing information relating to contraception, the time limit for such precautions, and any additional restrictions for agents in the SoC treatment regimen.

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

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

22. For patients randomized to the SoC arm, any contraindication to a specific SoC agent as specified by the accompanying package insert or Summary of Product Characteristics

23. Patient weight of <30 kg

24. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca/MedImmune staff and/or staff at the study site)

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

3.3 Patient enrollment 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. (Informed consent of study procedures may be obtained prior to the 28-day screening window in order to permit tumor sample acquisition, which must be analyzed prior to randomization.)

2. Obtain a unique 7-digit enrollment number (E-code) through the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) in the following format (ECCNNXXX: CC being the country code, NN being the center number, and XXX being the patient enrollment code at the center). This number is the patient's unique identifier and is used to identify the patient on the electronic case report forms (eCRFs).

3. For any patient who does not have obvious exclusion parameters, obtain tumor sample and send for PD-L1 expression status evaluation. (Obtaining the tumor sample should be given the highest priority and, as such, the sample may be obtained and sent for PD-L1 expression status evaluation prior to the 28-day screening window in order to permit analysis prior to randomization.) The PD-L1 result must be available prior to randomization.

4. Determine patient eligibility (see Sections 3.1 and 3.2). Define HPV status if the location of the tumor is oropharyngeal (oropharynx). HPV results can be collected from historical medical records of any age. HPV status will be assessed using local standards or using the p16 IHC assay. If status is unknown and/or unavailable locally, archival or newly acquired tissue specimen must be submitted for testing at a reference laboratory. See Laboratory Manual for detailed instructions in lieu of a separate tumor sample.

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

1. Define the SoC (cetuximab, a platinum [**carboplatin or cisplatin**], and 5FU) treatment (based on the most appropriate option for the patient) that the patient would receive if randomized to SOC therapy. This must be completed for all patients. The information will be recorded in the IVRS/IWRS.

2. Record the patient's PD-L1 status, tumor location (OPC or non-OPC), and smoking history (>10 vs ≤10 pack-years [1 pack-year = 1 pack of 20 cigarettes per day for 1 year or equivalent]) as stratification factors in the IVRS. Include the HPV status (positive or negative) if the tumor is OPC.

3. Obtain a unique randomization number via the IVRS/IWRS. Numbers will start at 001 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 arms. (PD-L1 status results must be received from the central laboratory by the IVRS/IWRS prior to randomization.)

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

Every effort should be made to minimize the time between randomization and starting study drug. Study drug must be administered within 5 working days of randomization (although it is recommended that patients commence study drug on the same day as randomization in the IVRS/IWRS if feasible).

Patients will begin treatment on Day 1. Patients must not be treated unless all eligibility criteria have been met.

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

3.4 Procedures for handling incorrectly enrolled patients

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

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

3.5 Methods for assigning treatment arms

Patients must not be randomized unless all eligibility criteria have been met.

At baseline, patients who satisfy all the entry criteria will be centrally assigned to study drug by the IVRS/IWRS, according to the randomization scheme generated by the Biostatistics Group, AstraZeneca, or delegate.

Patients enrolled in the study will be randomized (2:1:1) to treatment with MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, or SoC (cetuximab, a platinum [carboplatin or cisplatin based on Investigator's choice], and 5FU). Patients will be stratified by PD-L1 status (positive or negative, based on the analytically validated VENTANA/MedImmune assay), tumor location (OPC or non-OPC), and smoking history (>10 vs ≤10 pack-years). Patients with OPC will be further stratified by HPV status.

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 arm.

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.

If a patient discontinues participation in the study, then his/her enrollment/randomization code cannot be reused.

3.6 Methods for ensuring blinding (not applicable)

Not applicable; this study is not blinded.

3.7 Methods for unblinding (not applicable)

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 nonsterilized male partner must use at least 1 highly effective method of contraception (see Table 1) from screening and must agree to continue using such precautions for 90 days after the last dose of MEDI4736 monotherapy or 180 days after the last dose of MEDI4736 + tremelimumab combination therapy; cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Female patients should refrain from breastfeeding and egg cell donation throughout this period. It is strongly recommended for the male partner of a female patient to also use a male condom plus spermicide throughout this period.
   - Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal (defined as 12 months with no menses 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.
2. Nonsterilized male patients who are sexually active with a female partner of childbearing potential must use male condom and spermicide from screening and for 90 days after the last dose of MEDI4736 monotherapy or 180 days after the last dose of MEDI4736 + tremelimumab combination therapy. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout the study period and through 180 days after the last dose of MEDI4736 + tremelimumab combination therapy. It is strongly recommended for the female partner of a male patient to also use an effective method of contraception throughout this period.
3. SoC therapy: Follow the local prescribing information relating to contraception, the time limit for such precautions, and any additional restrictions for agents in the SoC treatment regimen.
4. 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[a] methods of contraception

Barrier/Intrauterine Methods	Hormonal Methods
• Copper T intrauterine device • Levonorgesterel-releasing intrauterine system (eg, Mirena®)[b]	• Etonogestrel implants: eg, Implanon or Norplan • 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] Highly effective (ie, failure rate of <1% per year)
[b] This is also considered a hormonal method

3.9 Discontinuation of investigational product

An individual patient will not receive any further IP (MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, or SoC [cetuximab, a platinum, and 5FU]) if any of the following occur in the patient in question:

- Withdrawal of consent from further treatment with IP.
- 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
- Pregnancy or intent to become pregnant
- Non-compliance that, in the opinion of the Investigator or Sponsor, warrants discontinuation of study treatment (eg, refusal to adhere to scheduled visits)
- Initiation of alternative anticancer therapy including another investigational agent unless specified in the protocol
- Confirmed PD and Investigator determination that the patient is no longer benefiting from treatment with MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, or SoC
- 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/regimen due to a treatment-related toxicity
- Treatment interval of ≥8 weeks of MEDI4736 + tremelimumab combination therapy or MEDI4736 monotherapy due to non-compliance.

3.9.1 Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue the IP without prejudice to further treatment. A patient who decides to discontinue the IP will always be asked about the reason(s) for discontinuation and the presence of any AEs. If possible, they will be seen and assessed by an Investigator. AEs will be followed up (see Section 6). The AstraZeneca 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 from IP will enter follow-up and be asked to come in for every protocol-specified visit and follow all protocol procedures, including imaging and electronic patient-reported outcome (ePRO) questionnaires (see Table 4). All patients will be followed up for survival until the end of the study. Details of any treatment for SCCHN (including surgery or radiation) after the last dose of study treatment must be recorded in the eCRF, including the identity of subsequent anticancer therapies. Patients who decline to return to the site for evaluations should be contacted by telephone every 3 months as an alternative.

Patients who are permanently discontinued from receipt of IP should also be discontinued in the IVRS/IWRS.

3.10 Criteria for withdrawal of the patient from the study

3.10.1 Screen failures

Screening failures are patients who do not fulfill the eligibility criteria for the study, and therefore must not be enrolled and randomized. These patients should have the reason for study withdrawal recorded as "eligibility criteria not fulfilled" (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 re-screened 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 will not receive any further IP or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn his or her consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

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

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

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed (see Section 3.11), 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 any evaluations should resume according to the protocol.

3.10.3 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 the primary endpoint of OS, the survival status of all patients in the full analysis and the safety analysis sets 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 patients' current physician, and a publicly available death registry (if available) to obtain a current survival status. (The applicable 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 AstraZeneca, study patients are placed at undue risk because of clinically significant findings that meet any of the following criteria:

- Meet individual stopping criteria or are otherwise considered significant
- Are assessed as causally related to study drug
- Are not considered to be consistent with continuation of the study

In addition, the study may be stopped based on the findings of the interim safety analysis conducted by the 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 or follow-up must be recorded in the eCRFs. All reasons for discontinuation of treatment must be documented

In terminating the study, AstraZeneca 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 AstraZeneca.

4. STUDY PLAN AND TIMING OF PROCEDURES

The procedures for the screening and treatment periods in this study for the MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy arms are presented in Table 2, for the SoC group is presented in Table 3, and the procedures for the follow-up period are presented in Table 4.

Imaging and standard procedures performed before signing the informed consent form (ICF) may be used for screening purposes if the patient consents to the use of those results for screening purposes. Screening procedures must be performed within 28 days of randomization. Randomization must occur within 28 days of screening procedures and study drug dosing must occur within 5 working days of randomization. Baseline procedures required for Cycle 1, Day 1 need not be repeated if they were performed within 3 days prior to Cycle 1, Day 1.

All visits should be conducted based on the schedules provided in Table 2 through Table 4 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 (as referenced in Section 6.7.2). 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 for 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.

Following the OS analysis, patients still on randomized study treatment will continue to be supplied with study medication and will be managed at the discretion of the Investigator until discontinuation criteria are met. The study database will be closed at this point and only serious adverse event (SAEs) will be reported.

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

	Screening	C1[a]	C2	C3	C4	C5	C6	C7	C8 until PD
Week	**-4 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28, 32, 36, 40, 44 (+4-wk intervals)**
Day	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197, 225, 253, 281, 309 (+28-day intervals)**
Window (days)*	**NA**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Informed consent	X[b]								
Study procedures									
Physical examination (full)	X								
Medical history, past and current	X								
Targeted physical examination (based on symptoms)		X	X	X	X	X	X	X	X
Vital signs[c]	X	X	X	X	X	X	X	X	X
ECG[d]	X	As clinically indicated							
Concomitant medications	<---------- ->								
Demography, including baseline characteristics and tobacco use	X								
HPV for oropharyngeal tumors only[e]	X[b]								
Eligibility criteria	X								
Pharmacokinetics[f]									
MEDI4736 PK sample (serum)		X[h]	X[g]		X[g,h]			X[g]	
Tremelimumab PK sample (serum; combination therapy arm only)		X[h]	X[g]		X[g,h]				
Laboratory assessments									
Clinical chemistry	X	X[i]	X	X	X	X	X	X	X
Hematology	X	X[i]	X	X	X	X	X	X	X

	Screening	C1[a]	C2	C3	C4	C5	C6	C7	C8 until PD
Week	**-4 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28, 32, 36, 40, 44 (+4-wk intervals)**
Day	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197, 225, 253, 281, 309 (+28-day intervals)**
Window (days)*	**NA**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
TSH (and reflex free T_3 or free T_4)[j]	X	X[i]	X	X	X	X	X	X	X
Urinalysis	X	As clinically indicated							
Hepatitis B surface antigen, Hepatitis C antibody, and HIV	X								
Pregnancy test[k]	X	X	X	X	X	X	X	X	X
WHO/ECOG performance status	X	X	X	X	X	X	X	X	X
AE/SAE assessment	<---------- ->								
Drug accountability		X	X	X	X	X	X	X	X
IP administration									
Monotherapy arm									
MEDI4736[l]		X	X	X	X	X	X	X	X
Combination therapy arm									
MEDI4736 (combination therapy)[l,m]		X	X	X	X	X	X	X	X
Tremelimumab[l,m]		X	X	X	X				
Patient-reported outcome assessments[n,f]									
EORTC QLQ-C30, CCI [redacted]	X	X	q8w (±3 days) relative to the date of Cycle 1 Day 1						
EORTC QLQ-H&N35, CCI [redacted]	X	X	q4w (±3 days) relative to the date of Cycle 1 Day 1						
Other laboratory assessments and assays									
Immunogenicity assessment (ADA sampling [including ADA neutralizing antibodies] to identify ADA responses in patient circulation) for MEDI4736 and tremelimumab[f]		X			X			X	

	Screening	C1[a]	C2	C3	C4	C5	C6	C7	C8 until PD
Week	**-4 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28, 32, 36, 40, 44 (+4-wk intervals)**
Day	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197, 225, 253, 281, 309 (+28-day intervals)**
Window (days)*	**NA**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Tumor biopsy or obtain archival tumor tissue <3 years old for PD-L1 status[p]	X[b]								
Tumor evaluation (CT or MRI) (RECIST 1.1)[q,r]	X	First on-treatment scan at 6 weeks (+1 week) and then q6w (±1 week) for the first 24 weeks relative to the date of randomization and then q8w (±1 week) thereafter							
Health economics outcomes									
CCI [redacted]									

* Window for visits is relative to day of dosing, even if dosing is delayed, unless otherwise specified.

a Cycle 1 Day 1 procedures do not need to be repeated if the same procedures were performed for screening purposes 3 days prior to Cycle 1 Day 1.

b Informed consent of study procedures and tumor sample acquisition may be obtained prior to the 28-day screening window, if necessary, in order to permit tumor sample acquisition and analysis prior to randomization. PD-L1 testing will be done from a newly acquired tumor biopsy (preferred) or archival tissue (<3 years old). SoC procedures obtained prior to informed consent for other purposes may be used for screening if the patient/legal representative consents to allow use of these procedures for screening purposes.

c Body weight is recorded along with vital signs. See Section 5.2.4 of the CSP for specific guidelines for measuring vital signs.

d Any clinically significant abnormality detected requires a confirmatory ECG.

e HPV status testing may be performed for oropharyngeal tumors only. Local testing is acceptable and preferred. If HPV status is unknown or unavailable locally, a newly acquired or archived tumor sample must be submitted for central testing at a reference laboratory as described in the Laboratory Manual.

f For patients in the MEDI4736 + tremelimumab combination therapy arm: ADA samples collected at cycle 7 will be for MEDI4736 only. For patients in the MEDI4736 + tremelimumab combination therapy group who go on to retreatment, the same assessments should be done as in the first treatment period with the exception of the PK and ADA assessments, which do not need to be collected for retreatment. All PRO questionnaires and health resource use should be completed q8w during retreatment.

g Pre-dose (within 60 minutes prior to start of infusion). For patients in the MEDI4736 + tremelimumab combination therapy arm: pre-dose samples for both MEDI4736 and tremelimumab can be taken within 60 minutes prior to the start of the tremelimumab infusion.

h Within 10 minutes of the end of infusion.

i If screening assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1.

j 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.

k For women of childbearing potential only. A pregnancy test must be performed within 7 days before Cycle 1 Day 1. A urine or serum pregnancy test is acceptable.

l Results for electrolytes, full blood count, and liver function tests must be available before commencing an infusion (within 3 days).

m During the combination portion of treatment, tremelimumab will be administered first; the MEDI4736 infusion will start approximately 1 hour (maximum 2 hours) after the end of the tremelimumab infusion. If there are no clinically significant infusion reactions with the first cycle, then for all other cycles, MEDI4736 can be given immediately after the tremelimumab infusion has finished.

n Patients will complete PROs using handheld devices at home.

o CCI [redacted]

p MEDI4736 + tremelimumab combination therapy only: The collection of tumor biopsies at the time of progression prior to retreatment is mandated; the Investigator must consult with the Study Physician if such sampling is not feasible.

q RECIST 1.1 assessments will be performed using images from CT/MRI scans, preferably with IV contrast, of the neck (from base of skull) through the chest and abdomen (includes liver and adrenals). Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before the date of randomization and, ideally, should be performed as close as possible to the start of study treatment. The scans for confirmation of progression should be performed preferably at the next scheduled visit and no less than 4 weeks after the initial assessment of 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 next scheduled visit. However, assessments do not need to be repeated if performed within 2 weeks of a scheduled scan. Patients with clinical evidence of progression who do not meet PD criteria by RECIST 1.1 should have radiographic documentation of PD.

r Patients with confirmed PD in the MEDI4736 + tremelimumab combination therapy or MEDI4736 monotherapy arms who continue to receive clinical benefit may continue therapy at the discretion of the Investigator (following consultation with AstraZeneca) until a criterion in Section 3.9 is met. Patients will have scans done at 6 weeks post randomization and then every 6 weeks up to and including 24 weeks and then every 8 weeks thereafter. For retreatment patients in the MEDI4736 + tremelimumab combination therapy arm, scans will be performed q8w post-initiation of therapy until PD.

s CCI [redacted]

t CCI [redacted]

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

ADA Anti-drug antibody; AE Adverse event; C Cycle; CSP Clinical study protocol; CT Computed tomography; CCI [redacted] ctDNA Circulating tumor DNA; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; CCI [redacted] HIV Human immunodeficiency virus; CCI [redacted] HPV Human papilloma virus; IP Investigational product; IV Intravenous; MDSC Myeloid-derived suppressor cell; miRNA micro RNA; MRI Magnetic resonance imaging; mRNA Messenger RNA; NA Not applicable; PBMC Peripheral blood mononuclear cell; PCR Polymerase chain reaction; PD Progressive disease; PD-L1 Programmed cell death ligand 1; CCI [redacted] PK Pharmacokinetics; CCI [redacted] q4w Every 4 weeks; q6w Every 6 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; SoC Standard of Care; TSH Thyroid-stimulating hormone; T_3 Triiodothyronine; T_4 Thyroxine; WHO World Health Organization.

Table 3 Schedule of assessments for the Standard of Care treatment period

	Screening	C1[a]	C2	C3	C4	C5	C6	Cycles 7 until PD[b]
Week	**-4 to -1**	**0**	**3**	**6**	**9**	**12**	**15**	q4w
Day	**-28 to -1**	**1**	**22**	**43**	**64**	**85**	**106**	
Window (days)*	**NA**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Informed consent	X[c]							
Study procedures								
Physical exam (full)	X							
Medical history, past and current	X							
Targeted physical exam (based on symptoms)		X	X	X	X	X	X	q4w
Vital signs[d]	X	X	X	X	X	X	X	q4w
ECG[e]	X	As clinically indicated						
Concomitant medications	<----------							---------->
Demography, including baseline characteristics and tobacco use	X							
HPV for oropharyngeal tumors only[f]	X[c]							
Eligibility criteria	X							
Clinical chemistry[g,h]	X	X	X	X	X	X	X	q4w
Hematology[g,h]	X	X	X	X	X	X	X	q4w
TSH (and reflex free T_3 or free T_4)[j]	X					X[i]		Week 24
Urinalysis	X							
Hepatitis B and C and HIV	X							
Pregnancy test[k]	X	As clinically indicated						
WHO/ECOG performance status	X	X	X	X	X	X	X	q4w
AE/SAE assessment	<----------							---------->

	Screening	C1[a]	C2	C3	C4	C5	C6	Cycles 7 until PD[b]
Week	**-4 to -1**	**0**	**3**	**6**	**9**	**12**	**15**	q4w
Day	**-28 to -1**	**1**	**22**	**43**	**64**	**85**	**106**	
Window (days)*	**NA**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
SoC administration								
Cetuximab[l,m]		400 mg/m^2 IV on Day 1 of Cycle 1, then 250 mg/m^2 IV weekly						Maintenance administration of 250 mg/m^2 IV **weekly**
5FU[l]		1000 mg/m^2/day IV on Days 1 through 4 for up to six 3-week cycles						
Carboplatin or cisplatin[l,n]		Day 1 of up to six 3-week cycles						
Patient-reported outcome assessments[o]								
EORTC QLQ-C30, CCI CCI	X	X	q8w (±3 days) relative to the date of Cycle 1 Day 1					
EORTC QLQ-H&N35, CCI CCI	X	X	q4w (±3 days) relative to the date of Cycle 1 Day 1					
Other laboratory assessments and assays								
Tumor biopsy or obtain archival tumor tissue <3 years old for PD-L1 status	X[c]							
Tumor evaluation (CT or MRI) (RECIST 1.1)[q]	X	First on-treatment scan at 6 weeks (+1 week) and then q6w (±1 week) for the first 24 weeks relative to the date of randomization and then q8w (±1 week) thereafter						

CCI

* Window for visits is relative to day of dosing, even if dosing is delayed, unless otherwise specified.

a Cycle 1 Day 1 procedures do not need to be repeated if the same procedures were performed for screening purposes 3 days prior to Cycle 1 Day 1.
b Patient visits will change from q3w to q4w after completion of chemotherapy.
c Informed consent of study procedures and tumor sample acquisition may be obtained prior to the 28-day screening window, if necessary, in order to permit tumor sample acquisition and analysis prior to randomization. PD-L1 testing will be done from a newly acquired tumor biopsy (preferred) or archival tissue (<3 years old).
d Pre-dose and as clinically indicated before every infusion or administration.
e Any clinically significant abnormality detected requires a confirmatory ECG.
f HPV status testing may be performed for oropharyngeal tumors only. Local testing is acceptable and preferred. If HPV status is unknown or unavailable locally, a newly acquired or archived tumor sample must be submitted for central testing at a reference laboratory as described in the Laboratory Manual.
g To be collected q3w prior to the start of infusion and as clinically indicated. Electrolytes should be monitored with cetuximab therapy as per institution guidelines.

[h] If screening assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1.

[i] If the patient does not complete treatment through Cycle 5, TSH should be obtained after the patient's last cycle.

[j] 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.

[k] For women of childbearing potential only. A pregnancy test must be performed within 7 days before Cycle 1 Day 1. A urine or serum pregnancy test is acceptable.

[l] Patients will receive a maximum of six 3-week cycles of cetuximab, 5FU, and carboplatin or cisplatin. Cetuximab will be administered on Cycle 1 Day 1 at 400 mg/m^2 and then weekly at 250 mg/m^2. 5FU will be administered on Day 1 through 4 and carboplatin or cisplatin will be administered on Day 1 of each 3-week cycle. Patients with SD or better at the end of chemotherapy will then receive weekly cetuximab administration until PD, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

[m] Patients with SD at the end of these 6 cycles of chemotherapy should continue to receive cetuximab 250 mg/m^2 weekly until PD, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

[n] Patients will receive cisplatin 100 mg/m^2 IV on Day 1 or carboplatin AUC of 5 mg/mL/min IV on Day 1 of up to six 3-week cycles.

[o] Patients will complete PROs using handheld devices at home.

[p] CCI [redacted]

[q] RECIST 1.1 assessments will be performed using images from CT/MRI scans, preferably with IV contrast, of the neck (from base of skull) through the chest and abdomen (includes liver and adrenals). Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before the date of randomization and, ideally, should be performed as close as possible to the start of study treatment. The scans for confirmation of progression should be performed preferably at the next scheduled visit and no less than 4 weeks after the initial assessment of 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 next scheduled visit. However, assessments do not need to be repeated if performed within 2 weeks of a scheduled scan. Patients with clinical evidence of progression who do not meet PD criteria by RECIST 1.1 should have radiographic documentation of PD.

[r] CCI [redacted]

[s] CCI [redacted]

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

5FU 5-Fluorouracil; AE Adverse event; AUC Area under the curve; C Cycle; CT Computed tomography; CCI [redacted] ctDNA Circulating tumor DNA; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; CCI [redacted] HIV Human immunodeficiency virus; CCI [redacted] HPV Human papilloma virus; IV Intravenous; MDSC Myeloid-derived suppressor cells; miRNA micro RNA; MRI Magnetic resonance imaging; mRNA Messenger RNA; NA Not applicable; PBMC Peripheral blood mononuclear cell; PCR Polymerase chain reaction; PD Progressive disease; CCI [redacted] CCI [redacted] q3w Every 3 weeks; q4w Every 4 weeks; q6w Every 6 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; SoC Standard of Care; TSH Thyroid-stimulating hormone; T_3 Triiodothyronine; T_4 Thyroxine; WHO World Health Organization.

Table 4 Schedule of assessments for patients who have discontinued treatment with MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, or Standard of Care therapy

	Time since last dose of IP					
	Day (±3)	Months (±1 week)				12 months (±2 weeks)
Evaluation	**30**	**2**	**3**	**6**	**9**	
Physical examination (full)	X					
Vital signs (temperature, respiratory rate, BP, and pulse)	X					
Weight	X					
Pregnancy test[a]	X	As clinically indicated				
AE/SAE assessment	X	X	X			
Concomitant medications	X	X	X			
WHO/ECOG performance status	At timepoints consistent with tumor assessments; at 30, 60, and 90 days following time since the last dose of IP; and then at initiation of subsequent anticancer therapy[b]					
Subsequent anticancer therapy[c] and second progression assessment[d]	<----------					---------->
Survival status[d]			X	X	X	X (every 3 months)
Hematology	X	X	X			
Clinical chemistry	X	X	X			
TSH (and reflex free T_3 or free T_4)[e]	X					
PK assessment for MEDI4736[f] (MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy arms only)			X			
PK assessment for tremelimumab[f] (MEDI4736 + tremelimumab combination therapy arm only)			X			

	Time since last dose of IP					
	Day (±3)	Months (±1 week)				12 months (±2 weeks)
Evaluation	**30**	**2**	**3**	**6**	**9**	
Immunogenicity assessment (ADA sampling [including ADA neutralizing antibodies] to identify ADA responses in patient circulation) for MEDI4736 and tremelimumab[f] (MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy arms only)			X			
CCI	If patients are **not** eligible for retreatment, all questionnaires and health resource use should be completed at Day 30, Month 2, and Month 3 from the date of confirmed PD and then stopped. 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 should be completed relative to the date of **treatment on Cycle 1 Day1** as follows: q8w until confirmed PD.					
CCI						
EORTC QLQ-C30[g]						
EORTC QLQ-H&N35[g]						
CCI						
CCI						
Tumor assessment (CT or MRI)	q6w (±1 week) for the first 24 weeks relative to the date of randomization and then q8w (±1 week) thereafter until confirmed disease progression					

[a] For women of childbearing potential only. A urine or serum pregnancy test is acceptable.

[b] WHO/ECOG 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/ECOG performance status should be provided when information on subsequent anticancer therapy is provided, where possible.

[c] Details of any treatment for SCCHN (including surgery) post the last dose of study treatment must be recorded in the eCRF.

[d] Patients may be contacted in the week following data cut-offs to confirm survival status. Details of any treatment for SCCHN (including surgery) post the last dose of study treatment must be recorded in the eCRF. Patients who discontinue treatment due to PD will be checked for survival status every 3 months. All patients will be followed for survival until the end of the study. Patients who decline to return to the site for evaluations should be contacted by telephone every 3 months as an alternative. Scans conducted on patients with confirmed PD in any treatment arm should be conducted according to local practice and are optional.

[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] For patients with disease control (CR, PR, or SD) only.

[g] Patients will complete PROs using handheld devices at home.

[h] CCI

[i] CCI [redacted]

ADA Anti-drug antibody; AE Adverse event; BP Blood pressure; CT Computed tomography; CCI [redacted] ECOG Eastern Cooperative Oncology Group; eCRF Electronic case report form; EORTC European Organisation for Research and Treatment of Cancer; CCI [redacted] IP Investigational product; MRI Magnetic resonance imaging; PD Progressive disease; CCI [redacted] 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; SAE Serious adverse event; SCCHN Squamous cell carcinoma of the head and neck; TSH Thyroid-stimulating hormone; T_3 Triiodothyronine; T_4 Thyroxine; 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. All patients will be required to provide consent to supply a sample of their tumor (archival or recently obtained biopsy) for entry into this study. This consent is included in the main patient informed consent form (ICF).

All screening/baseline procedures must be performed within 28 days before the first dose of treatment (Days -28 to -1). Screening/baseline evaluations may be performed over more than 1 visit. SoC procedures performed for other purposes prior to informed consent suitable for use as screening evaluations need not be repeated if the patient/legal representative consents to allow use of these procedures for screening purposes. 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.

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 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the exact nominal time.

4.3 Follow-up period

All procedures to be conducted will be performed according to the assessment schedule (see Table 4).

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 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, BoR, TTR, APF6 and APF12 using Investigator assessments (as well as BICR assessments for sensitivity analysis of PFS). The RECIST 1.1 guidelines for measurable, non-measurable, target, and non-target lesions and the objective tumor response criteria (CR, PR, SD, or PD) are presented in Appendix E. Second progression (PFS2) will be defined by local standard clinical practice. OS, OS12, OS18 and OS24 will also be evaluated.

The methods of assessment of tumor burden used at baseline are CT and MRI scans, preferably with IV contrast, of the neck (including the base of skull) through chest and abdomen (includes liver and adrenals). 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 of MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, or SoC, and ideally as close as possible to the start of the IP. Efficacy for all patients will be assessed by objective tumor assessments every 6 weeks (q6w) (±1 week) for the first 24 weeks and then every 8 weeks (q8w) (±1 week) thereafter, relative to the date of randomization (see Table 2 and Table 3), until treatment discontinuation due to progression or toxicity. If an unscheduled assessment is performed, and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. Unscheduled scans do not need to be repeated if performed within 2 weeks of a scheduled scan.

For patients who discontinue therapy due to toxicity in the absence of progression, objective tumor assessments should be continued q6w for the first 24 weeks (relative to the date of randomization) then q8w until confirmed clinical disease progression.

Disease progression for patients in the IMT treatment arms should be confirmed according to RECIST 1.1; timepoint assessments showing PD should be confirmed preferably at the next scheduled imaging visit and no earlier than 4 weeks after the preceding assessment of PD in the absence of clinically significant deterioration. Disease progression in patients in the SoC arm should be confirmed by a scan obtained no earlier than 4 weeks after the initial assessment of PD and preferably at the next scheduled imaging visit, if clinically feasible. Treatment in all arms will continue between the assessment of progression and its confirmation. 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.

Radiographic progression would be considered confirmed if the following criteria are met:

- ≥20% increase in the sum diameters of target lesions compared with the nadir at 2 consecutive 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.

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

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

If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression, then the patient should still continue to be followed until confirmed objective disease progression.

Patients with clinical evidence of progression who do not meet PD criteria by RECIST 1.1 should continue to be followed until there is radiographic documentation of PD.

Patients in all arms with a symptomatic solitary lesion, a brain lesion, or a lesion of clinical importance (eg, impending fracture, etc) may be treated with radiation after approval from the Sponsor. Non-irradiated lesions need to continue to be measurable by RECIST 1.1. The time interval between the last systemic treatment and radiation should be 10 days, and systemic treatment can be resumed 1 week post radiation.

Categorization of objective tumor response assessment at each post-screening imaging timepoint 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, nadir; smallest sum of diameters previously recorded on study). In the absence of progression, tumor response (CR or PR) and SD will be calculated in comparison to the baseline tumor measurements obtained before starting treatment.

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

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

Following confirmed progression, patients should continue to be followed up for survival every 3 months as outlined in the study plan (see Table 4). Patients with confirmed PD who discontinue MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, or SoC should have scans conducted according to local practice; the scans may also be submitted for centralized collection and quality check (QC) and be held until the patient commences a new treatment (these scans are optional; see Table 4).

It is important to follow the assessment schedule as closely as possible. Please refer to the study plans (Table 2, Table 3, and Table 4).

5.1.1 Central reading of scans

A BICR of radiological scans will be performed for a sensitivity analysis for the PFS endpoint.

This sensitivity analysis will use all images, including unscheduled visit scans, collected prior to version 8 of the clinical study protocol (dated 13 Feb 2018), after which no further central collection of the scans will be done. All images, including unscheduled visit scans, will be collected on an ongoing basis and quality checked and assessed centrally. Guidelines for image acquisition, anonymization, submission to the imaging CRO, and local storage will be provided in a separate document. The results of Investigator assessments will not be communicated to the independent central reviewers, nor will the results of independent reviews be communicated to Investigators, and the management of patients will be based solely upon the results of the RECIST 1.1 assessment conducted by the Investigator.

5.1.2 Survival assessments

Assessments for survival must be made every 3 months following treatment discontinuation and/or upon disease progression. Survival information may be obtained via telephone contact with the patient, patient's family, or by contact with the patient's current physician. The details of first and subsequent therapies for cancer, after discontinuation of treatment, will be collected.

In addition, patients on treatment or in survival follow-up will be contacted following the data cut-off for the primary analysis and all subsequent survival analyses to provide complete survival data. These contacts should generally occur within 7 days of the data cut-off.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the assessment schedules (see Table 2, Table 3, and Table 4).

Clinical laboratory safety tests will be performed in a licensed clinical laboratory according to local standard procedures. Hematology, clinical chemistry, and urinalysis tests will be performed by the hospital's local laboratory. Urine pregnancy tests may be performed at the site using a licensed test. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. Clinically significant abnormal 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 5 (clinical chemistry), Table 6 (hematology), and Table 7 (urinalysis).

Note: For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline and as clinically indicated.

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 Screening and subsequent visits as specified in the assessment schedule (see Table 2, Table 3, and Table 4). Tests will be performed by the hospital's local laboratory unless otherwise specified. If results are positive, the patient must not start or continue 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, HIV antibodies, and thyroid-stimulating hormone (TSH). Free triiodothyronine or free thyroxine will also be measured if the results of the TSH are abnormal or if there is clinical suspicion of an AE related to the endocrine system.

Table 5 Clinical chemistry (serum or plasma)

Albumin	Glucose
Alkaline phosphatase[a]	Lactate dehydrogenase
ALT[a]	Lipase
Amylase	Magnesium[b,c]
AST[a]	Potassium
Bicarbonate[b]	Sodium
Calcium	Total bilirubin[a]
Chloride[b]	Total protein
Creatinine clearance[b]	Urea or blood urea nitrogen, depending on local practice
Creatinine	
Gamma glutamyltransferase[b]	

[a] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2 × upper limit of normal (and evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin.

[b] Bicarbonate (where available), chloride, creatinine clearance, gamma glutamyltransferase, and magnesium testing are to be performed at screening, on Day 1 (unless screening laboratory assessments are performed within 3 days prior to Day 1), and if clinically indicated.

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

ALT Alanine aminotransferase; AST Aspartate aminotransferase

Table 6 Hematology

Eosinophils	Neutrophils
Hematocrit	Partial thromboplastin time
Hemoglobin	Platelet count
International normalized ratio	Red blood cell count
Lymphocytes	Total white cell count
Monocytes	

Note: For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline and as clinically indicated.

Table 7 Urinalysis[a]

Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

[a] Urinalysis must be done at baseline and then as clinically indicated.

Note: Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells.

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 6.3.4.

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, Table 3, and Table 4) and will include clinically targeted assessments. Height will be measured at screening only. Situations in which physical examination results should be reported as AEs are described in Section 6.3.4.

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, a mean QT interval corrected for Fridericia's formula (QTcF) 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, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) on the same day or different day to confirm the finding.

Situations in which ECG results should be reported as AEs are described in Section 6.3.4.

5.2.4 Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules (see Table 2, Table 3, and Table 4). Body weight is also recorded along with vital signs.

First infusion of MEDI4736 or tremelimumab:

On the first infusion day, patients in the MEDI4736 + tremelimumab combination therapy group and the MEDI4736 monotherapy group will be monitored prior to, during, and after infusion of IP as presented in the bulleted list below.

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 MEDI4736 + tremelimumab combination therapy group and the MEDI4736 monotherapy group before, during, and after each infusion of IP at the following times (based on a 60-minute infusion):

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion])
- Approximately 30 minutes during the infusion (**halfway** through infusion)
- At the end of the infusion (approximately 60 ±5 minutes)

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. A 1-hour observation period is recommended after the first infusion of MEDI4736 + tremelimumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each MEDI4736 and tremelimumab infusion).

Subsequent infusions of MEDI4736 or tremelimumab:

For subsequent infusions, BP, pulse, and other vital signs should be measured prior to the start of the infusion. Patients should be carefully monitored, and BP and other vital signs should be measured during and after infusion as per institution standard and as clinically indicated. Any clinically significant changes in vital signs should be entered into the unscheduled vital signs case report form (CRF).

Infusions of SoC

Patients in the SoC group will be monitored pre-dose and as clinically indicated per the institutional standard before and after every administration.

Situations in which vital signs results should be reported as AEs are described in Section 6.3.4. For any AEs of infusion reactions, please enter the vital signs values into the CRF.

5.2.5 Other safety assessments

Pregnancy tests on either urine (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). Tests will be performed by the hospital's local laboratory. If results are positive, the patient is ineligible and must be discontinued from the study. In the event of a suspected pregnancy during the study, the test should be repeated.

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

5.3 Other assessments

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), QLQ-H&N35 (head and neck-specific questionnaire), [redacted] see Appendix F).

The PRO instruments will be completed by the patients at home using a handheld ePRO device. All questionnaires should be completed according to the assessment schedules (see Table 2, Table 3 and Table 4). If a patient does complete the questionnaires at a given visit, for example, at screening and at Cycle 1 Day 1, it is preferred that questionnaires be completed before any other study procedures (laboratory tests or imaging) are conducted. 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. For patients receiving retreatment after confirmed PD (MEDI4736 + tremelimumab combination therapy only), questionnaires should be completed according to the assessment schedule in Table 2.

5.3.1.1 EORTC QLQ-C30

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

transformed such that they range from 0 to 100, where higher scores indicate greater functioning, greater QoL, or greater level of symptoms (Aaronson et al 1993).

5.3.1.2 EORTC QLQ-H&N35

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

5.3.1.3 CCI [redacted]

CCI [redacted]

5.3.1.4 CCI [redacted]

CCI [redacted]

5.3.1.5 CCI [redacted]

CCI [redacted]

CCI [redacted]

5.3.2 Administration of the patient-reported outcome questionnaires

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

Each center must allocate the responsibility for the administration of the PRO devices 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 completed per the schedule of assessments (see Table 2, Table 3, and Table 4). Patients will be instructed to bring their handheld devices to every clinic visit. In instances where the PRO assessments coincide with a clinic visit, the research nurse or study coordinator should verify that the questionnaire was completed before the visit. If not, the patient should complete the questionnaire prior to any other study procedures and before discussion of disease progression to avoid biasing the patient's responses to the questions.

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

- The research nurse or appointed site staff must explain the value and relevance of participation to patients and inform them that these questions are being asked in order to find out from them directly how they feel. This can help motivate patients to comply with data collection. The research nurse or appointed site staff should also 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 by the ePRO vendor, and also provide guidance on whom to call if there are problems with the 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.

- 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. If compliance drops below 85%, a check-in call from the site to ask the patient if he/she has any difficulties is highly recommended.

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, Table 3, and Table 4) 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, office work

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

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

4 = Completely disabled; unable to carry out any self-care and totally confined to bed or chair

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

5.4 Pharmacokinetics

5.4.1 Collection of samples and determination of drug concentration

Blood samples for determination of MEDI4736 and tremelimumab concentration in serum will be obtained according to the assessment schedules (see Table 2 and Table 4).

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

5.4.2 Collection of samples to measure for the presence of anti-drug antibodies

The presence of ADA will be assessed in serum samples taken according to the assessment schedules (see Table 2 and Table 4).

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

5.4.3 Storage and destruction of pharmacokinetic/anti-drug antibody samples

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

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

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

CCI [redacted]

5.5 Biomarker analysis

The patient's consent to the use of donated biological samples is mandatory. Tissue samples will be obtained from all screened patients.

Pretreatment tumor PD-L1 expression will be evaluated in all randomized patients. Data will be compared between arms to determine if baseline PD-L1 status is prognostic and/or predictive of outcomes associated with MEDI4736 + tremelimumab combination therapy or MEDI4736 monotherapy versus SoC. Baseline tumor requirements are briefly described in Section 5.5.1.

CCI [redacted]

Details for collection, volumes, storage, and shipment of biologic samples are presented in a separate Laboratory Manual.

All samples collected for biomarker analyses will be stored at the study site, a reference laboratory, or at AstraZeneca facilities and may be used for subsequent research relevant to evaluating biological and/or clinical response to immunotherapy.

The results may be pooled with biomarker data from other MEDI4736 + tremelimumab combination therapy studies to evaluate biological responses across indications and to compare results in monotherapy versus combination settings.

5.5.1 Collection of patient samples for stratification by PD-L1

At screening, there is a mandatory provision of formalin-fixed and paraffin-embedded tissue to be used for determination of eligibility. For the MEDI4736 + tremelimumab combination therapy arm only, **there is a subsequent mandatory provision of tissue if**

retreatment is planned unless, after discussion with Study Physician, biopsy is not clinically feasible:

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

  Samples should be collected via a core needle of 18 gauge or larger or be collected as an excisional tumor biopsy sample. Where institutional practice, in this setting, uses a smaller gauge needle, samples should be submitted in sufficient number to ensure that availability of 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 rises to 3 or 4.

  The tumor specimen submitted to establish eligibility should be of sufficient quantity to allow for PD-L1 IHC analyses (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 recommended. For patients with a single target lesion being used for a screening biopsy for PD-L1 testing, allow approximately 2 weeks before acquiring imaging scans for baseline tumor assessment.

- CCI [redacted]

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

- OPTIONAL: The collection of additional biopsies (other than the mandatory tissue biopsy required prior to retreatment for patients in the MEDI4736 + tremelimumab combination therapy arm) is strongly encouraged.

  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 including sample QC and shipping.

CCI [redacted]

The analytically validated VENTANA PD-L1 SP263 IHC assay will be used to determine PD-L1 IHC status in this study for the purposes of stratification and for the analysis of the original diagnostic sample.

To meet the requirement of FDA approval of a companion diagnostic, sections of the tumor will be retained at VENTANA for potential additional studies, as requested by the FDA, to support potential test approval.

5.5.2 Collection of exploratory biomarker data

5.5.2.1 CCI [redacted]

CCI [redacted]

CCI [redacted]

5.5.2.2 CCI [redacted]

CCI [redacted]

5.5.3 Management of biomarker data

CCI [redacted]

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

Samples will be stored for a maximum of 15 years from the end of study, after which they will be destroyed. The results of this biomarker research may be reported in the CSR itself, as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies involving MEDI4736 to generate hypotheses to be tested in future research.

5.5.5 Labeling and shipment of biological samples

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

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

5.5.6 Chain of custody of biological samples

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

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

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

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

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

5.5.7 Withdrawal of informed consent for donated biological samples

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

The Principal Investigator will:

- Ensure that AstraZeneca is immediately notified of the patients' withdrawal of informed consent to the use of donated samples
- Ensure that biological samples from that patient, if stored at the study site, are immediately identified, disposed of or destroyed and the action documented
- Ensure that the laboratory(ies) holding the samples is/are immediately informed about the withdrawn consent and that samples are disposed of or destroyed, the action is documented, and the signed document is returned to the study site
- Ensure that the patient and AstraZeneca are informed about the sample disposal

5.6 Pharmacogenetics (not applicable)

Not applicable.

5.7 Pharmacodynamics (not applicable)

Not applicable.

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 Definitions of serious adverse events

An SAE is an AE occurring during any study phase (ie, screening, 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 B.

6.2 Recording of adverse events

6.2.1 Time period for collection of adverse events

AEs and SAEs will be collected from the time of signature of informed consent throughout the treatment period and including the follow-up period (up to 90 days after the last dose of IP or until initiation of another therapy). AEs and SAEs collected prior to randomization will be reported as pre-randomization AEs and SAEs.

6.2.2 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.

6.2.3 Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- Changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- Administration of treatment for the AE
- Whether the AE caused the patient's withdrawal from the study (yes or no)
- Outcome

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

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

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria in Section 6.1. 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 6.1. 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 6.1.

6.3 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.

6.3.1 Causality collection

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

6.3.2 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.

6.3.3 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.

6.3.4 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 IP.

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.

6.3.5 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.

6.3.6 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.

6.3.7 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.

6.3.8 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.

6.3.9 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 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 6.7.2). 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 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 IP 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 document for the definition of expectedness or listedness is the IB 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.**

6.5 Overdose

Use of MEDI4736 + tremelimumab combination therapy or MEDI4736 monotherapy in doses in excess of those specified in the protocol are considered to be an overdose. There is currently no specific treatment in the event of overdose of MEDI4736 or tremelimumab, and possible symptoms of overdose are not established.

Please also refer to the local prescribing information for the SoC agents (eg, cisplatin or carboplatin prescribing information, 5FU prescribing information, cetuximab prescribing information).

- 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 IP 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.

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 following 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 the 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 following 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 IP-related toxicities

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

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned IP along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted.
- 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.

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 MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy adverse events of special interest

Adverse events of special interest (AESIs) are events of scientific and medical interest specific to the further understanding of the MEDI4736 and tremelimumab safety profile and require close monitoring and rapid communication by the Investigator to AstraZeneca. MEDI4736 and tremelimumab AESIs may be serious or non-serious. The rapid reporting of these AESIs allows ongoing analysis of these events in order to characterize and understand them in association with the use of these IPs.

AESIs for MEDI4736 +/- tremelimumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants, and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with MEDI4736 monotherapy and combination therapy. An immune-related adverse event (irAE) is defined as an AE that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

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

AESIs observed with MEDI4736 +/- tremelimumab include the following:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- Hepatitis/transaminase increases
- Neuropathy/neuromuscular toxicity (eg, Guillain-Barré, and myasthenia gravis)
- Endocrinopathy (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, and hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis / serum lipase or amylase increases
- Myocarditis
- Myositis / Polymyositis
- Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, haematological and rheumatological events.

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

Further information on these risks (eg, presenting symptoms) can be found in the current versions 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 (as referenced in Section 6.7.2). 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 the study drug/study regimen by the reporting Investigator.

6.7.2 Specific toxicity management and dose modification information - MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy

Comprehensive toxicity management guidelines (TMGs) have been developed to assist investigators with the recognition and management of toxicities associated with use of the immune-checkpoint inhibitors, durvalumab [MED4736] (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor). Given the similar underlying mechanism of toxicities observed with these two compounds, these TMGs are applicable to the management of patients receiving either drug as monotherapy or both drugs in combination. Additionally, these guidelines are applicable when either drug is used alone or both drugs are used in combination and, also other anti-cancer drugs (i.e., antineoplastic chemotherapy, targeted agents) are administered concurrently or sequentially as part of a protocol-specific treatment regimen. The TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune mediated reactions that may be observed with checkpoint inhibitor monotherapy or combination checkpoint inhibitor regimens, with specific instructions for checkpoint inhibitor-specific dose modifications (including discontinuation) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other anti-cancer treatment.

The most current version of the TMGs is provided to the investigative site as an Annex to the Protocol document entitled " 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)" and is maintained within the Site Master File. In addition, a current version of the guidelines is also available through the following link: https://tmg.azirae.com. 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 TMGs).

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. 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 MEDI4736 + tremelimumab combination therapy by the reporting Investigator.

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

6.7.3 Management of toxicity attributable to agents in the Standard of Care arm

IP-related toxicity management, including dose delays, reductions, and adjustments, for patients in the SoC group should be performed as indicated in 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 comprised of independent experts will be convened and will meet approximately 3 months after the study has started or after the first 20 patients have been randomized, whichever occurs first, followed by 2 meetings for safety analysis 3 months apart, and subsequent meetings 6 months apart, to review safety assessments and make recommendations to continue, amend, or stop the study based on safety findings.

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

AstraZeneca will supply MEDI4736 and tremelimumab, while the SoC treatments (cetuximab, carboplatin or cisplatin, and 5FU) are expected to be supplied locally (see Table 8).

Table 8 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
Standard of Care		
Cetuximab[a]	IV (as sourced locally)	Various, depending upon the source
Carboplatin[a]	IV (as sourced locally)	Various, depending upon the source

Investigational product	Dosage form and strength	Manufacturer
Cisplatin[a]	IV (as sourced locally)	Various, depending upon the source
5FU[a]	IV (as sourced locally)	Various, depending upon the source

[a] Under certain circumstances when local sourcing is not feasible, a Standard of Care treatment may be supplied centrally through AstraZeneca.
5FU 5-Fluorouracil; IV Intravenous.

7.1.1 MEDI4736

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

Preparation of MEDI4736 doses for administration with an IV bag

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

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

A dose of 1.5 g (for patients ≥30 kg in weight) 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. Remove 30.0 mL of IV solution from the IV bag prior to addition of MEDI4736. Next, 30.0 mL of MEDI4736 (ie, 1.5 g of MEDI4736) is added to the IV bag such that final concentration is within 1 to 20 mg/mL (IV bag volumes 100 to 1000 mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Weight-based dosing at 20 mg/kg (for patients whose weight falls to <30 kg during the study) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (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(w/v). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Do not co-administer other drugs through the same infusion line.

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. Table 9 summarizes time allowances and temperatures.

Table 9 MEDI4736 temperature and infusion time allowances

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

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

All details can be found in the Drug Handling Instructions.

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; it has a pH of 5.5. The nominal fill volume is 20 mL. IP 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 IP 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 75 mg (for patients ≥30 kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline, with a final tremelimumab concentration ranging from 0.1 to 10 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Remove 3.8 mL of IV solution from the IV bag prior to addition of tremelimumab. Next, 3.8 mL of tremelimumab (ie, 75 mg of tremelimumab) is then added to the IV bag such that the final concentration is within 0.1 to 10 mg/mL (IV bag volumes of 50 to 500 mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Weight-based dosing at 1 mg/kg (for patients whose weight falls to < 30 kg during the study) will be administered using an IV bag containing 0.9% (w/v) saline, 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.

Do not co-administer other drugs through the same infusion line.

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. Table 10 summarizes time allowances and temperatures.

Table 10 Tremelimumab temperature and infusion time allowances

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

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

All details can be found in the Drug Handling Instructions.

7.1.3 Standard of Care treatment

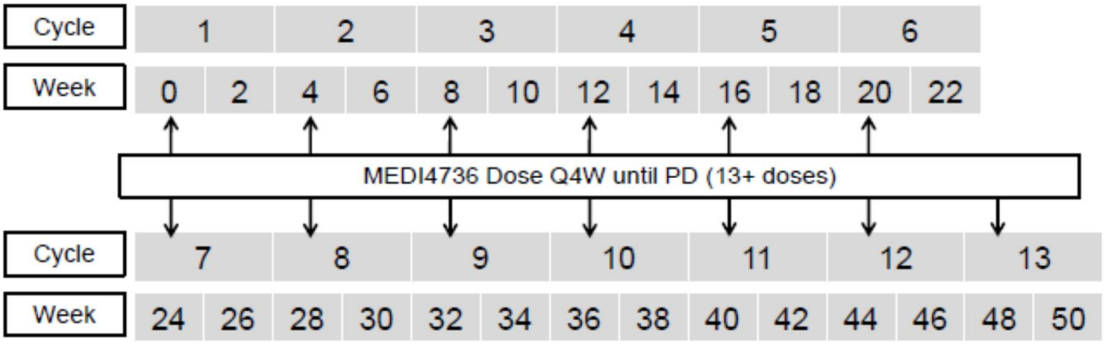
Each SoC agent will be sourced as commercially available material/locally sourced, prescribed according to local regulations, and will be administered according to prescribing information or treatment guidance in general use by the Investigating site. Under certain circumstances when local sourcing is not feasible, a SoC agent will be supplied centrally by AstraZeneca. This will be labeled with local language translated text in accordance with regulatory guidelines.

7.2 Dose and treatment regimens

7.2.1 Treatment regimens

MEDI4736 monotherapy: Patients enrolled on the MEDI4736 monotherapy arm of this study will receive 1500 mg MEDI4736 q4w via IV infusion beginning on Day 1 until PD (see Figure 4). (N.B. If a patient's weight falls below 30 kg during the study, the patient should receive weight-based dosing equivalent to 20 mg/kg of MEDI4736 Q4W until the weight improves to ≥30 kg, at which point the patient should start receiving the fixed dosing of MEDI4736 (1500 mg Q4W.)

Figure 4 Dosing scheme - MEDI4736 monotherapy



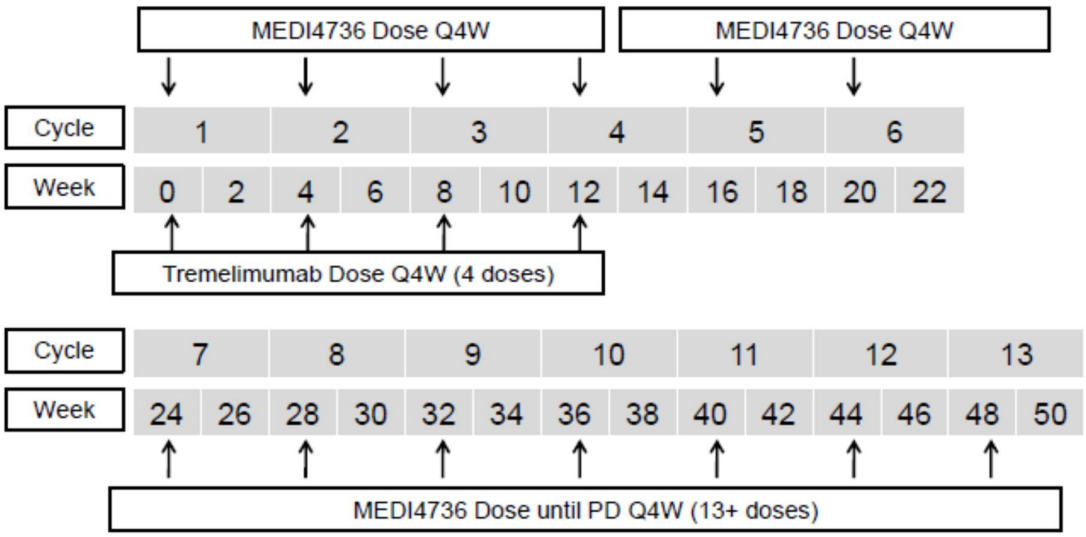
Q4W Every 4 weeks.

MEDI4736 + tremelimumab combination therapy:

Patients enrolled on the MEDI4736 + tremelimumab combination therapy arm of this study will receive 75 mg tremelimumab via IV infusion q4w for 4 doses beginning on Day 1 and 1500 mg MEDI4736 via IV infusion q4w until PD (see Figure 5). (N.B. If a patient's weight falls to below 30 kg during the study, the patient should receive weight-based dosing equivalent to 20 mg/kg MEDI4736 Q4W and 1 mg/kg tremelimumab Q4W until the weight improves to ≥30 kg, at which point the patient should start receiving the fixed dosing of MEDI4736 (1500 mg) plus tremelimumab (75 mg) Q4W.)

During the first infusion of the combination regimen, tremelimumab will be administered first; the MEDI4736 infusion will start approximately 1 hour (maximum 2 hours) after the end of the tremelimumab infusion. If there are no clinically significant infusion reactions with the first cycle, then for all other cycles, the MEDI4736 infusion can begin immediately after the tremelimumab infusion has finished.

Figure 5 Dosing scheme - MEDI4736 + tremelimumab combination therapy



Q4W Every 4 weeks.

SoC (EXTREME): Patients in the SoC treatment arm will receive the EXTREME regimen consisting of a maximum of six 3-week cycles of cetuximab, a platinum, and 5FU, with continuation of cetuximab. Patients in this arm will receive either cisplatin (at a dose of 100 mg/m^2 of body surface area on Day 1) or carboplatin (at an AUC of 5 mg/mL/min on Day 1), at the discretion of the Investigator and an infusion of 5FU (at a dose of 1000 mg/m^2/day on Days 1 through 4 of every 3-week cycle). Cetuximab will be administered at an initial dose of 400 mg/m^2 on Cycle 1 Day 1, followed by subsequent weekly doses of 250 mg/m^2. Weekly monotherapy with cetuximab should continue after the completion of up to 6 cycles of chemotherapy in patients who achieve SD or better. Any drug within the triplet regimen (cetuximab, a platinum, and 5FU) can be discontinued at any time due to toxicity at the discretion of the Principal Investigator.

Patients will be treated with MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, or SoC until confirmed PD (unless, in the Investigator's opinion, the patient continues to receive benefit from the treatment and after discussion with the Sponsor), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or another treatment discontinuation criterion is met (see Section 3.9). Patients with PD in target lesions after objective response are not eligible to continue treatment.

Disease progression requires confirmation for patients receiving IMT. All scans showing PD by RECIST 1.1 should be confirmed, preferably at the next scheduled visit and no earlier than 4 weeks after the preceding assessment of PD in the absence of clinical deterioration. Disease progression in patients in the SoC arm should be confirmed by a scan obtained no earlier than 4 weeks after the initial assessment of PD and preferably at the next scheduled imaging visit, if clinically feasible. Treatment in all arms will continue between the assessment of progression and its confirmation. If progression is not confirmed, then the patient should continue receiving study treatment and participating in study assessments. If progression is confirmed and the patient continues to receive some clinical benefit, treatment may be continued at the Investigator's discretion. Patients with clinical evidence of progression who do not meet PD criteria by RECIST 1.1 should have radiographic documentation of PD.

Patients who have discontinued treatment due to toxicity or symptomatic deterioration, or who have commenced subsequent anticancer therapy, will be followed up until confirmed disease progression and for survival (see Table 4). Patients with confirmed progression in any arm cannot continue therapy if the progression occurs in a target lesion that has previously shown an objective response.

7.2.2 Duration of treatment

All treatment in all arms will be administered beginning on Day 1 until confirmed PD, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met (at the Investigator's discretion), as described below. Patients in all arms with a symptomatic solitary lesion, a brain lesion, or a lesion of clinical importance (eg, impending fracture, etc) may be treated with radiation after approval from the Sponsor. Non-irradiated lesions need to continue to be measurable by RECIST. The time interval between the last systemic treatment and radiation should be 10 days, and systemic treatment can be resumed 1 week post radiation.

Treatment through progression is permitted in all arms if, in the Investigator's opinion, the patient continues to receive benefit from the treatment. Treatment through progression is at the Investigator's discretion, and 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. The Investigator should ensure that patients will 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:

- 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.

- Absence of clinical symptoms or signs indicating clinically significant disease progression and no decline in WHO/ECOG performance status to >1.
- 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.

Patients who the Sponsor and Investigator determine may not continue treatment after confirmed PD will enter follow-up. Patients who have discontinued treatment due to toxicity or symptomatic deterioration, or who have commenced subsequent anticancer therapy, will be followed for confirmed disease progression and survival.

Post final Data Cut Off (DCO)

Patients who continue to receive benefit from their assigned treatment at the final 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 durvalumab 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 durvalumab in order to manage AEs in accordance with the durvalumab toxicity management guidelines (as referenced in Section 6.7.2).

In the event that a roll-over or safety extension study is available after final analysis, patients currently receiving treatment with durvalumab may be transitioned to such a study, and the current study would reach its end. The roll-over or safety extension study would ensure treatment continuation with visits assessment per its protocol. Any patient that would be proposed to move to such study would be given a new Informed Consent.

7.2.3 Criteria for Retreatment for Patients in the MEDI4736 + tremelimumab arm

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, including the same dose and frequency of treatments, and a similar schedule of assessments (see Table 2).

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:

1. Patients who complete the 4 dosing cycles of the MEDI4736 + tremelimumab combination therapy portion of the regimen (with clinical benefit per Investigator's judgment) 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).

For patients in the MEDI4736 + tremelimumab combination therapy arm, before a patient restarts treatment, the Investigator should ensure that the patient:

1. Does not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient
2. Still fulfills the eligibility criteria for this study, including re-consenting to restart MEDI4736 + tremelimumab combination therapy
3. Has not have received an intervening systemic anticancer therapy after their assigned treatment discontinuation
4. Has had a baseline tumor assessment within 28 days prior to restarting their assigned treatment; all further scans should occur with the same frequency as during the initial treatment (relative to the date of restarting treatment) until study treatment is stopped
5. Undergoes a tumor biopsy as described in Section 5.5.1

During the retreatment period, patients in the MEDI4736 + tremelimumab combination therapy arm will resume 75mg of tremelimumab q4w for 4 doses and MEDI4736 dosing at 1500 mg q4w until PD.

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.

Treatment compliance will be assured by reconciliation of site drug accountability logs.

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:**
Additional investigational anticancer therapy concurrent with those under investigation in this study	Should not be given whilst the patient is on IP treatment (including SoC)
mAbs against CTLA-4, PD-1, or PD-L1	Should not be given whilst the patient is on IP treatment (including SoC).
Any concurrent chemotherapy, local therapy (except palliative therapy for non-target lesions, eg, radiotherapy, surgery, radiofrequency ablation), biologic therapy, or hormonal therapy for cancer treatment	Should not be given whilst the patient is on IP treatment (including SoC). (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. A symptomatic solitary lesion, a brain lesion, or a lesion of clinical importance (eg, impending fracture, etc) may be treated with radiation after approval from the Sponsor.)
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 whilst the patient is on IP treatment (including SoC). (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. Use of steroids as pre-medication for either hypersensitivity reactions (eg, CT scan pre-medication) or as anti-emetic prior to administration of SoC treatment is permitted.) Short term use of immunosuppressive medications, including corticosteroids, for the acute management of non-IP-related emergencies (eg, COPD, asthma, etc) is permitted.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC) during the study

AE Adverse event; CT Computed tomography; CTLA-4 Cytotoxic T-lymphocyte-associated antigen 4; IP Investigational product; mAb monoclonal antibody; PD-1 Programmed cell death 1; PD-L1 Programmed cell death ligand 1; SoC Standard of Care; 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
BSC (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

BSC Best supportive care.

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 efficacy analysis, AstraZeneca will continue to supply open-label drug to patients receiving MEDI4736 + tremelimumab combination therapy or MEDI4736 monotherapy up to clinical disease progression (Section 7.2).

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 primary aim of the study is to compare the efficacy and safety of MEDI4736 monotherapy to SoC.

8.2 Sample size estimate

The study will enroll approximately 1016 patients in order to randomize 760 eligible patients in a 2:1:1 ratio (380:190:190 patients) to MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, or SoC. The study was originally sized to characterize the OS benefit of MEDI4736 + tremelimumab combination therapy versus SoC in the all-comers population. The sizing assumes a 3-month delay in separation of the OS curves between each arm, hence the use of average HRs.

The primary analysis of OS will be performed when approximately 147 death events have occurred in approximately 172 patients (85% maturity) across the MEDI4736 monotherapy and SoC treatment groups in the PD-L1 TC/IC high subgroup, assuming that

45% of the patients randomized are within this subgroup. No interim efficacy analyses will be performed in this study.

If OS at 24 months in the PD-L1 TC/IC high subgroup was 30% with MEDI4736 monotherapy and 12% with SoC (with a 10.1-month median OS), and assuming the true average OS HR is 0.59, the trial will have approximately 90% power to demonstrate statistical significance at the 5% level (using a 2-sided test) for the comparison of MEDI4736 monotherapy versus SoC in the PD-L1 TC/IC high subgroup, with the smallest treatment difference that could be statistically significant being an average HR of 0.72. With a 17-month recruitment period and a minimum follow-up period of 23.6 months from "last patient in" assumed, it is anticipated that the analysis will be performed approximately 40.6 months after the first patient has been recruited.

Table 11 provides a summary of the statistical assumptions for the first two levels of the MTP.

Table 11 Summary of statistical assumptions

	N ratio	Overall HR	Landmarks at 24 months	Events (maturity)	Power	Critical values HR (landmarks)
Primary objective						
OS: Mono versus SoC; PD-L1 TC/IC high subgroup	86:86	0.59	30% vs 12%	147 (85%)	90%	0.72 (22%)
Secondary objectives:						
OS: Mono versus SoC; low risk of EM subgroup	152:152	0.70	24% vs 12%	254 (84%)	81%	0.78 (19%)

Note: The sample size estimates in the PD-L1 TC/IC high subgroup comparisons assume that 45% of the patients randomized are within this subgroup; The sample size estimate in the low risk of EM subgroup assume that 80% of the patients randomized are within this subgroup.
EM Early mortality; HR Hazard ratio; IC tumor-associated immune cells; Mono MEDI4736 monotherapy; OS Overall survival; SoC Standard of Care (EXTREME); TC tumor cells.

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	Populations
Efficacy Data	
OS, PFS, ORR, APF6, APF12, OS12, OS18, OS24,	PD-L1 TC/IC analysis set, low risk of EM analysis set, ctDNA TMB analysis set and all-comers (FAS)
DoR, BoR, TTR, TFST, TSST, PFS2, PROs, and symptom endpoints	PD-L1 TC/IC analysis set and all-comers (FAS)
Demography	PD-L1 TC/IC analysis set, and FAS (ITT population)
PK data	PK Analysis Set
Safety Data	
Exposure	Safety Analysis Set
AEs	Safety Analysis Set
Laboratory measurements	Safety Analysis Set
Vital Signs	Safety Analysis Set

AE Adverse event; APF12 Proportion of patients alive and progression free at 12 months; BoR Best objective response; DoR Duration of response; EM Early mortality; FAS Full analysis set; IC tumor-associated immune cells; ITT Intent-to-Treat; ORR Objective response rate; OS Overall survival; OS12 Proportion of patients alive at 12 months; OS18 Proportion of patients alive at 18 months; OS24 Proportion of patients alive at 24 months after randomization; PD-L1 Programmed cell death ligand 1; PFS Progression-free survival; PFS2 Second progression; PK Pharmacokinetic; PRO Patient-reported outcome; TMB Tumor Mutation Burden (The ctDNA TMB cutpoint of 16mut/Mb for MEDI4736+tremelimumab and MEDI4736 monotherapy was derived from the EAGLE study (Li et al 2020)).; TC tumor cells; TTR Time to response.

8.3.1 Full Analysis Set

The full analysis set (FAS) will include all randomized patients (all-comers). 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 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 for the all-comers (FAS), the PD-L1 TC/IC high subgroup and the low risk of EM subgroup according to the treatment received, that is, erroneously treated patients (eg, those randomized to treatment A but actually given treatment B) will be summarized according to the treatment they actually received.

8.3.3 PD-L1 TC/IC Analysis Set

The PD-L1 TC/IC analysis set will include the subset of patients in the FAS with PD-L1 evaluable samples and available results as determined by the analytically validated

VENTANA PD-L1 (SP263) Assay. Subgroups are defined as PD-L1 high, low and unknown.

PD-L1 high is defined as either ≥ 50% of the tumor cells (TC) or ≥ 25% of the immune cells (IC) staining for PD-L1 at any intensity if >1% of the tumor area contains IC, or ≥ 50% of TC or 100% of IC staining for PD-L1 at any intensity if 1% of the tumor area contains IC. PD-L1 low is defined as not meeting any of the criteria for PD-L1 high.

The scoring algorithm was derived from data from two phase 2 studies, D4193C00001 (HAWK, DCO September 2016) and D4193C00003 (CONDOR, DCO March 2017).

8.3.4 PK Analysis Set

All patients who receive at least 1 dose of IP per the protocol for whom any post-dose PK data are available.

8.3.5 ctDNA TMB Analysis Set

The ctDNA TMB analysis set will include the subset of patients in the FAS with ctDNA TMB evaluable samples and available result. Subgroups are defined as ctDNA TMB high (≥16 mut/Mb), low (<16 mut/Mb).

ctDNA TMB outputs will also incorporate the non-evaluable data set: Failed, Not Done, Not Provided, and No Call/not evaluable.

8.3.6 Low Risk of Early Mortality (EM) Analysis Set

The low risk of EM analysis set consists of patients who are at low risk of early mortality CCI [redacted] based on laboratory values according to a specific prognostic model CCI [redacted]. Further details will be provided in the SAP.

8.4 Outcome measures for analyses

8.4.1 Calculation or derivation of efficacy variables

8.4.1.1 Primary and secondary endpoint (OS)

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 data cut-off for the analysis (these contacts should generally occur within 7 days of the data cut-off). If patients are confirmed to be alive or if the death date is post the data cut-off date, these patients will be censored at the date of data cut-off. Death dates may be found by checking publicly available death registries.

8.4.1.2 RECIST 1.1-based endpoints

The analysis of the other secondary endpoints, PFS, ORR, DoR, BoR, TTR, APF6 and APF12, will be based on the investigator assessments using RECIST 1.1. In addition, PFS2 will be defined by local clinical practice.

Investigator RECIST 1.1-based assessments

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

At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, or PD depending on the status of their disease compared with baseline and previous assessments. Baseline will be assessed within the 28 days prior to enrollment. If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE; unless there is evidence of progression in which case the response will be assigned as PD).

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

BICR-based assessments

A BICR of radiological imaging data will be conducted according to RECIST 1.1 and used for a sensitivity analysis for the secondary objective of PFS. All radiological scans for all patients (including those at unscheduled visits or outside visit windows) obtained prior to version 8 of the clinical study protocol (dated 13 Feb 2018) will be provided to the BICR. Prior radiotherapy will also be provided to the BICR to allow the selection of appropriate target lesions.

The imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1 and will be adjudicated, if required. For each patient, the BICR will define the overall visit response data (CR, PR, SD, PD, or NE) and the relevant scan dates for each time point (ie, for visits where response or progression is/is not identified). If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of NE (unless there is evidence of progression, in which case the response will be assigned as PD). Sensitivity analysis of PFS will be derived from the overall visit response date and the scan dates.

CCI [redacted]

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

8.4.1.3 Secondary endpoints

Progresson Free Survival

PFS (per RECIST 1.1 as assessed by the 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 discontinues 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 and not visit dates.

RECIST 1.1 assessments/scans contributing toward 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 progression.
- For BICR assessments, date of progression will be determined based on the earliest of the dates of the component that triggered the progression on the first set of scans that indicates progression for the adjudicated reviewer selecting PD, or of either reviewer where both reviewers select PD as a timepoint response, and there is no adjudication for central review (BICR) data.
- 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.

A sensitivity analysis of PFS will be performed using BICR assessments according to RECIST 1.1.

CCI [redacted]

Objective response rate

ORR (per RECIST 1.1 using investigator assessments) is defined as the number (%) of patients with at least 1 visit response of CR or PR. 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.

Duration of response

DoR (per RECIST 1.1 using investigator assessments) 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 (ie, date of PFS event or censoring – date of first response + 1). The end of response should coincide with the date of progression or death from any cause used for the RECIST 1.1 PFS endpoint.

The time of the initial response will be defined as the latest of the dates contributing toward 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.

Time from randomization to second progression (PFS2)

PFS2 will be defined as the time from the date of randomization to the earliest of the progression event subsequent to that used for the PFS endpoint or death. The date of second progression will be recorded by the Investigator in the eCRF and defined according to local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression, or death. Second progression status will be reviewed (every 6 weeks for the first 48 weeks relative to the date of randomization and then every 8 weeks thereafter) following the progression event used for the primary variable PFS (the first progression) and status recorded. Patients alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without a second disease progression, that is, censored at the latest of the PFS or PFS2 assessment date if the patient has not had a second progression or death.

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.

Time from randomization to the second subsequent therapy or death

As a supportive summary to PFS2, time to second subsequent therapy (TSST) or death will be defined as the time from the date of randomization to the earlier of either the start date of the second subsequent anticancer therapy after discontinuation of first subsequent therapy, or the date of death. Any patient not known to have had a second subsequent anticancer therapy will be censored at the last date when the patient was known not to have received a second subsequent anticancer therapy. If a patient terminated the study for

reason other than death before second subsequent anticancer therapy, the patient will be censored at the earliest of the last known to be alive and termination dates.

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

The APF6 and APF12 will be defined as the Kaplan-Meier estimate of PFS (per RECIST 1.1 as assessed by the investigator) at 6 months and 12 months respectively.

Proportion of patients alive at 12, 18 and 24 months after randomization

The OS12, OS18 and OS24 will be defined as the Kaplan-Meier estimate of OS at 12, 18 and 24 months respectively after randomization.

Best objective response

Best objective response (BoR) is calculated based on the overall visit responses from each RECIST 1.1 assessment, as described in Appendix E. It is the best response a patient has had during their time in the study up until RECIST 1.1 progression or 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 all investigator assessments up until the first progression event. 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 ≤90 days (ie, 2 × (6 weeks ±3 days)) after randomization, then BoR will be assigned to the progression (PD) category. For patients who die with no evaluable RECIST 1.1 assessments, if the death occurs >90 days (ie, 2 × (6 weeks ±3 days)) after the date of randomization, then BoR will be assigned to the NE category.

Progression events that have been censored due to them being >90 days after the last evaluable assessment will not contribute to the BoR derivation.

Time to response

Time to response (per RECIST 1.1 as assessed by the investigator) is defined as the time from the date of randomization until the date of documented response. The date of documented response should coincide with that used for the RECIST 1.1 DoR endpoint.

8.4.2 Calculation or derivation of safety variables

8.4.2.1 Adverse events

Safety and tolerability will be assessed in terms of AEs (including SAEs), deaths, laboratory data, vital signs, ECGs, and exposure. These will be collected for all patients. Data from all cycles of treatment will be combined in the presentation of safety data. "On treatment" will be defined as assessments between date of start dose and 90 days following discontinuation of IP (ie, the last dose of MEDI4736 + tremelimumab combination therapy or MEDI4736 monotherapy). For AEs, on treatment (or treatment-emergent AEs) will be

defined as any AEs that started after dosing or prior to dosing and which worsens following exposure to the treatment.

SAS will be used for reporting of safety data.

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 examinations, the baseline value will be the latest result obtained prior to the start of study treatment.

QTcF will be derived during creation of the reporting database using the reported ECG values (RR and QT) using the following formula:

QTcF = QT/RR^ (1/3) where RR is in seconds

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

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

The denominator used in laboratory summaries will only include evaluable patients, ie, those who had sufficient data to have the possibility of an abnormality.

For example:

- If a CTCAE criterion involves a change from baseline, evaluable patients would have both a pre-dose and at least 1 post-dose value recorded.
- If a CTCAE criterion does not consider changes from baseline to be evaluable, the patient need only have 1 post-dose value recorded.

The denominator in vital signs data should include only those patients with recorded data.

8.4.3 Calculation or derivation of patient-reported outcome variables

PRO questionnaires will be assessed using the EORTC QLQ-C30 and EORTC QLQ-H&N35. All items/questionnaires will be scored according to published scoring guidelines. All PRO analyses will be based on the FAS.

8.4.3.1 EORTC QLQ-C30

The EORTC QLQ-C30 consists of 30 questions that can be combined to produce 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), and a global measure of health status. The EORTC QLQ-C30 will be scored according to the EORTC QLQ-C30 scoring manual (Fayers et al 1999). An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales, each of the functional scales, and the global health status scale in the EORTC QLQ-C30 according to the EORTC QLQ-C30 Scoring Manual. Higher scores on

the global health status and functioning scales indicate better health status/function, but higher scores on symptom scales represent greater symptom severity.

The change from baseline in 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 3.

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	≥+10	Deterioration
	≤-10	Improvement
	Otherwise	No change
EORTC QLQ-C30 functional scales	≥+10	Improvement
	≥-10	Deterioration
	Otherwise	No change

EORTC European Organisation for Research and Treatment of Cancer; QLQ-C30 30-item core quality of life questionnaire.

For each subscale, if <50% of the subscale items are missing, then the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscales (Fayers et al 1999). If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded. If there is evidence that the missing data are systematic, missing values will be handled to ensure that any possible bias is minimized.

Time to symptom deterioration

For each of the symptoms scales in the EORTC QLQ-C30, time to symptom deterioration will be defined as the time from randomization until the date of the first clinically meaningful symptom deterioration (an increase in the score from baseline of ≥10) or death

(by any cause) in the absence of a clinically meaningful symptom deterioration, regardless of whether the patient discontinues study treatment or receives another anticancer therapy prior to symptom deterioration. Death will be included as an event only if the death occurs within 2 visits of the last PRO assessment where the symptom change could be evaluated.

Patients whose symptoms (as measured by EORTC QLQ-C30) have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the symptom could be evaluated. Also, if symptoms deteriorate after 2 or more missed PRO assessment visits or the patient dies after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where the symptom could be evaluated. If a patient has no evaluable visits or does not have baseline data they will be censored at 0 days. The population for the analysis of time to symptom deterioration will include a subset of the FAS who have baseline scores of ≤90.

Time to 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 discontinues study treatment or receives another anticancer therapy prior to QoL/function deterioration. Death will be included as an event only if the death occurs within 2 visits of the last PRO assessment where the QoL/function change could be evaluated.

Patients whose QoL (as measured by EORTC QLQ-C30) have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the QoL/function could be evaluated. Also, if QoL deteriorates after 2 or more missed PRO assessment visits or the patient dies after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where QoL/function could be evaluated. If a patient has no evaluable visits or does not have baseline data they will be censored at 0 days. The population for the analysis of time to QoL/function deterioration will include a subset of the FAS who have baseline scores of ≥10.

Symptom improvement rate

The symptom improvement rate will be defined as the number (%) of patients with 2 consecutive assessments at least 14 days apart that show a clinically meaningful improvement (a decrease from baseline score ≥10 for EORTC QLQ-C30 symptom scales) in that symptom from baseline. The denominator will consist of a subset of the FAS who have a baseline symptom score ≥10.

QoL/function improvement rate

The QoL/function improvement rate will be defined as the number (%) of patients with 2 consecutive assessments at least 14 days apart that show a clinically meaningful improvement (an increase from baseline score ≥10 for EORTC QLQ-C30 functional scales and global health status/QoL) in that scale from baseline. The denominator will consist of a subset of the FAS who have a baseline QoL/function score ≥10.

8.4.3.2 EORTC QLQ-H&N35

The QLQ-H&N35 is a head and neck cancer-specific module from the EORTC comprising 35 questions to assess head and neck cancer symptoms. The head and neck cancer module includes 11 single items and 7 multi-item scales that assess pain, swallowing, senses (taste and smell), speech, social eating, social contact, and sexuality. For all items and scales, high scores indicate increased symptomatology/more problems.

The scoring approach for the QLQ-H&N35 is identical in principle to that for the symptom scales/single items of the EORTC QLQ-C30. As the wording is reversed on the QLQ-H&N35, higher scores represent greater symptom severity.

Definition of clinically meaningful changes

Changes in score compared with baseline will be evaluated. A minimum clinically meaningful change is defined as a change in the score from baseline of >10 for scales/items from QLQ-H&N35 (Bjordal et al 2000). For example, a clinically meaningful deterioration or worsening in dry mouth (as assessed by QLQ-H&N35) is defined as an increase in the score from baseline of ≥10. At each post-baseline assessment, the change in symptoms/functioning from baseline will be categorized as improved, no change, or deterioration, as shown in Table 14.

Table 14 Visit response for HRQoL and disease-related symptoms

Score	Change from baseline	Visit response
QLQ-H&N35 symptom scales and items	≥+10	Deterioration
	≤-10	Improved
	Otherwise	No change

HRQoL Health-related quality of life; QLQ-H&N35 35-item head and neck quality of life questionnaire.

Time to symptom deterioration

For each of the symptom scales/items in the QLQ-H&N35, time to symptom deterioration will be defined as the time from the date of the first dose until the date of the first clinically meaningful symptom deterioration (an increase in the score from baseline of ≥10) or death (by any cause) in the absence of a clinically meaningful symptom deterioration, regardless of whether the patient discontinues study treatment or receives another anticancer therapy prior to symptom deterioration. Death will be included as an event only if the death occurs within 2 visits of the last PRO assessment where the symptom change could be evaluated.

Patients whose symptoms (as measured by the QLQ-H&N35) have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the symptom could be evaluated. Also, if symptoms progress after 2 or more missed PRO assessment visits or the patient dies after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where the symptom could be evaluated. If a patient has no evaluable visits or does not have baseline data, they will be censored at 0 days.

Symptom improvement rate

The symptom improvement rate will be defined as the number (%) of patients with 2 consecutive assessments at least 14 days apart that show a clinically meaningful improvement (a decrease from baseline score >10 for QLQ-H&N35 scales/items) in that symptom from baseline.

8.4.3.3 CCI [redacted]

[redacted]

8.4.4 Calculation or derivation of pharmacokinetic variables

8.4.4.1 Population pharmacokinetics and exposure-response/safety analysis

A population PK model may be developed using a non-linear mixed-effects modeling approach for MEDI4736 monotherapy and for MEDI4736 in combination with tremelimumab. The impact of physiologically-relevant patient characteristics (covariates) and disease on PK of both agents may be evaluated. The relationship between MEDI4736 PK exposure or tremelimumab PK exposure and the effect on safety and efficacy end points may be evaluated. The results of such analyses will be reported outside of the CSR.

8.4.4.2 Pharmacokinetic analysis

Pharmacokinetic data analyses of MEDI4736 and tremelimumab will be performed by the MedImmune Global Pharmacokinetics Pharmacodynamics (PK-PD) & Bioanalysis group or designee. No formal non-compartmental (NCA) PK analysis will be conducted due to the sparse PK sampling scheme for MEDI4736 and tremelimumab, which does not allow for meaningful determination of PK parameters. MEDI4736 and tremelimumab concentration data and summary statistics will be tabulated by treatment arm and visit. PK parameters, such as peak and trough concentration of MEDI4736 and tremelimumab, will be derived from raw data measurements as data allow.

8.4.4.3 Immunogenicity analysis

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable ADAs against MEDI4736. The same analysis will be conducted for ADAs against tremelimumab. The immunogenicity titer will be reported for samples confirmed positive for the presence of ADAs. The effect of

immunogenicity on PK, pharmacodynamics, efficacy, and safety may be evaluated as data allow.

8.5 Methods for statistical analyses

The formal statistical analysis will be performed to test the main hypotheses:

- H_0: No difference between MEDI4736 monotherapy and SoC
- H_1: Difference between MEDI4736 monotherapy and SoC

The primary objective is OS in the PD-L1 TC/IC high subgroup.

The analysis of OS will be performed when approximately 147 death events have occurred in approximately 172 patients (85% maturity) across the MEDI4736 monotherapy and SoC treatment groups in the PD-L1 TC/IC high subgroup. All other endpoints will be analysed at this time. No interim analyses will be performed for any efficacy endpoint.

Descriptive statistics will be used for all variables, as appropriate, and will be presented by treatment arm. 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.

PK data will be summarized and analyzed based on the PK Analysis Set. Safety data will be summarized on the safety analysis set.

Results of all statistical analyses will be presented using approximately-sized 95% CIs and 2-sided p-values, unless otherwise stated.

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

Endpoints Analyzed	Notes
OS	Stratified log-rank tests and Cox proportional method for: Primary objectives MEDI4736 monotherapy versus SoC in the PD-L1 TC/IC high subgroup (stratified by PD-L1 status, tumor location and smoking history) Secondary objectives – MEDI4736 monotherapy versus SoC in the low risk of EM subgroup (stratified by PD-L1 status, tumor location and smoking history) – MEDI4736 monotherapy versus SoC in ctDNA TMB high subgroup (≥ 16mut/Mb) – MEDI4736 monotherapy versus SoC in all-comers population – MEDI4736 + tremelimumab combination therapy versus SoC in the PD-L1 TC/IC high subgroup (stratified by PD-L1 status, tumor location and smoking history) – MEDI4736 + tremelimumab combination therapy versus SoC in the low risk of EM subgroup (stratified by PD-L1 status, tumor location, and smoking history) – MEDI4736 + tremelimumab combination therapy versus SoC in ctDNA TMB high (≥16 mut/Mb) subgroup – MEDI4736 + tremelimumab combination therapy versus SoC in all-comers (stratified by PD-L1 status, tumor location, and smoking history) – MEDI4736 + tremelimumab combination therapy versus MEDI4736 monotherapy (PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high (≥16 mut/Mb) and all-comers); stratified by PD-L1 status, tumor location and smoking history) Sensitivity Analyses: Sensitivity analysis using the Max-combo test

Endpoints Analyzed	Notes
PFS	Stratified log-rank tests and Cox proportional method for: – Secondary objectives using investigator assessments (RECIST 1.1): MEDI4736 monotherapy versus SoC (PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high (≥16 mut/Mb) subgroup and all-comers); stratified by PD-L1 status, tumor location and smoking history – MEDI4736 + tremelimumab combination therapy versus SoC (PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high (≥16 mut/Mb) subgroup and all-comers); stratified by PD-L1 status, tumor location and smoking history – MEDI4736 + tremelimumab combination therapy versus MEDI4736 monotherapy (PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high (≥16 mut/Mb) subgroup and all-comers); stratified by PD-L1 status, tumor location and smoking history Sensitivity analyses – Sensitivity analysis using BICR assessments (RECIST 1.1) – Sensitivity analysis based on RECIST 1.1 modified for confirmation of progression using site Investigator assessments Exploratory analyses – CCI [redacted]
OS12, OS18 and OS24	OS rates using the Kaplan-Meier estimates at 12, 18 and 24 months for the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high (≥16 mut/Mb) subgroup and all-comers
ORR	Logistic regression for: Secondary objectives – Secondary analysis for the, PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high (≥16 mut/Mb) subgroup and all-comers using investigator RECIST 1.1 assessments Exploratory analyses – CCI [redacted]
DoR	Descriptive statistics and Kaplan-Meier plot for the PD-L1 TC/IC high subgroup and all-comers
BoR	Descriptive statistics N (%) for the PD-L1 TC/IC high subgroup and all-comers
TTR	Descriptive statistics N (%) for the PD-L1 TC/IC high subgroup and all-comers
TFST	Stratified log-rank test for the PD-L1 TC/IC high subgroup and all-comers
TSST	Stratified log-rank test for the PD-L1 TC/IC high subgroup and all-comers
APF6 and APF12	PFS rates using the Kaplan-Meier estimates of PFS at 6 and 12 months for the low risk of EM subgroup, ctDNA TMB high (≥16 mut/Mb), PD-L1 TC/IC high subgroup and all-comers
Time from randomization to second progression	Stratified log-rank test for the PD-L1 TC/IC high subgroup and all-comers

Endpoints Analyzed	Notes
Time to symptom deterioration (EORTC QLQ-C30 and EORTC QLQ-H&N35 endpoints)	Stratified log-rank test for the PD-L1 TC/IC high subgroup, and all-comers
Improvement rate (EORTC QLQ-C30 and EORTC QLQ-H&N35 endpoints)	Logistic regression For all-comers and the PD-L1 TC/IC high subgroup populations
Average change from baseline (EORTC QLQ-C30 and EORTC QLQ-H&N35 endpoints)	Mixed effect model repeated measurement (MMRM) analysis. Descriptive statistics including change from baseline for all-comers and the PD-L1 TC/IC high subgroup populations.

APF12 Proportion of patients alive and progression free at 12 months; BICR Blinded Independent Central Review; BoR Best objective response; ctDNA circulating tumor DNA; DCR Disease control rate; DoR Duration of response; EM Early mortality; EORTC European Organisation for Research and Treatment of Cancer; HR Hazard ratio; IC tumor-associated immune cells; irRECIST 1.1 Immune-related response criteria updated for RECIST 1.1; ITT Intent-to-Treat; ORR Objective response rate; OS Overall survival; OS12 Proportion of patients alive at 12 months after randomization; OS18 Proportion of patients alive at 18 months after randomization; OS24 Proportion of patients alive at 24 months after randomization; PD-L1 Programmed death ligand 1; PFS Progression-free survival; 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; TC tumor cells; TFST Time to first subsequent therapy; TMB Tumor Mutation Burden; TTR Time to response; TSST Time to second subsequent therapy.

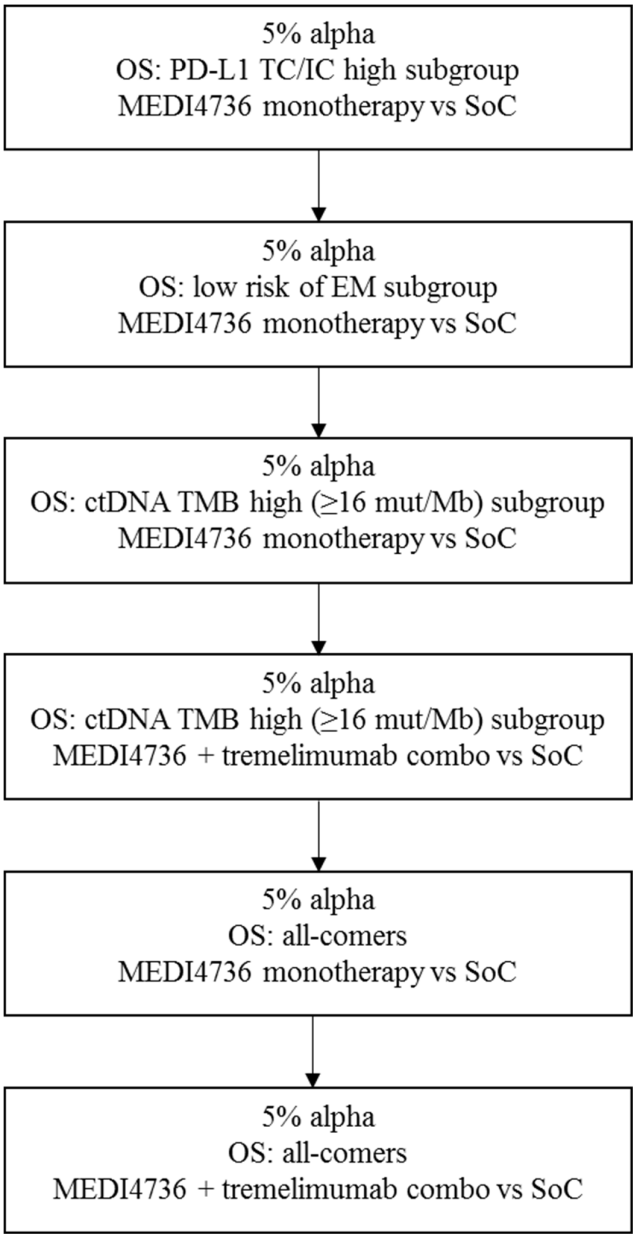
Multiple testing procedure (MTP)

In order to strongly control the type I error at 5% (2-sided), the MTP shown in Figure 6 will be used across the primary endpoint (OS), treatment comparisons (MEDI4736 monotherapy versus SoC and MEDI4736 + tremelimumab combination therapy versus SoC), and across the analysis populations (PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high (≥16 mut/Mb) subgroup, and all-comers). If the highest level hypothesis in the MTP is statistically significant then the next hypothesis in the hierarchy will then be tested, and so on through the hierarchy until a hypothesis is not-statistically significant. Implementation of this pre-defined ordered testing procedure will strongly control type I error at 5% (2-sided) among all key hypotheses.

Of note, the comparison of MEDI4736 + tremelimumab combination therapy versus MEDI4736 monotherapy and the comparison of MEDI4736 + tremelimumab combination therapy versus SoC (in the PD-L1 TC/IC high subgroup, and low risk of EM subgroup will not be included in the MTP, and therefore will not be conducted under strict alpha control.

The OS analysis will be performed when approximately 147 death events from the PD-L1 TC/IC high subgroup have occurred in approximately 172 patients (85% maturity) across the MEDI4736 monotherapy and SoC treatment groups. All other endpoints will be analysed at this time. No interim analyses will be performed for any efficacy endpoint.

Figure 6 Multiple testing procedure for controlling the overall type 1 error rate



Combo MEDI4736 + tremelimumab combination therapy; ctDNA circulating tumor DNA; EM Early mortality; IC tumor-associated immune cells; OS Overall survival; PD-L1 Programmed death ligand 1; SoC Standard of Care; TC tumor cells; TMB Tumor Mutation Burden

8.5.1 Analysis of the primary endpoint

8.5.1.1 Overall survival

The analysis of OS will be done using a stratified log-rank test stratified by PD-L1 status (positive versus negative), tumor location (OPC versus non-OPC, with a subsequent adjustment for HPV status in patients with OPC), and smoking history (>10 versus ≤10 pack-years) as entered in the IVRS system. Refer to Figure 6 for the multiple testing procedure (MTP) with the primary objective at the first row of the testing sequence.

The effect of treatment will be estimated by the HR together with its corresponding 95% CI and p-value, using a stratified Cox propotional hazards model.

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 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 modeling will be employed to assess the effect of covariates on the HR estimate. Details will be presented in the SAP.

Impact of switching (crossover outside of this study) to immunotherapies (or other potentially active investigational agents) on OS analyses

CCI [redacted]

8.5.1.2 Subgroup analysis of OS

Subgroup analyses will be conducted comparing OS between MEDI4736 + tremelimumab combination therapy versus SoC, MEDI4736 monotherapy versus SoC and MEDI4736 + tremelimumab combination therapy versus MEDI4736 monotherapy in the PD-L1 TC/IC high subgroup, ctDNA TMB high subgroup (≥16 mut/Mb), low risk of EM subgroup and the FAS (all-comers):

- Sex (male, female)
- Age at randomization (<65, ≥65-<75, ≥75 years of age)
- PD-L1 TC≥25 status for stratification (positive, negative)
- PD-L1 TC/IC expression (TC≥50 or IC≥25 (High), TC<50 and IC<25 (Low))
- CCI [redacted]
- Tumor location/HPV (OPC/Positive, OPC/Negative, non-OPC/Any HPV)
- Primary tumor site (oropharynx, oral cavity, hypopharynx, larynx)
- Smoking history (>10, ≤10 pack-years)
- Race (Asian, non-Asian)

- ECOG Performance status (0, 1)
- Extent of Disease (only locoregionally recurrent, metastatic with or without locoregional recurrence)

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.

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 the 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.

A forest plot will be presented for the subgroups showing the comparison of MEDI4736 +/- tremelimumab therapy versus SoC in the PD-L1 TC/IC subgroup, low risk of EM subgroup, all-comers and the ctDNA TMB (≥16 mut/Mb) subgroup.

8.5.2 Analysis of the secondary variable(s)

8.5.2.1 Progression-free survival

The PFS analysis will be based on the programmatically derived RECIST 1.1 using the investigator assessments. The analysis will be performed with the, PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high (≥16 mut/Mb) subgroup and all-comers using a stratified log-rank test stratified by PD-L1 status (positive versus negative), tumor location (OPC versus non-OPC, with a subsequent adjustment for HPV status in patients with OPC), and smoking history (>10 versus ≤10 pack-years) as entered in the IVRS system.

The effect of MEDI4736 monotherapy versus SoC treatment will be estimated by the HR together with its corresponding 95% CI and p-value. The stratification factors will be based on the values entered into IVRS at randomization even if it is subsequently discovered that these values were incorrect.

The hazard ratio (HR) of PFS, along with 95% confidence interval (using the same strata information as above) will be estimated using a stratified Cox model with treatment as the only covariate.

A PFS analysis will also be performed to compare MEDI4736 + tremelimumab combination therapy versus SoC as well as to compare MEDI4736 + tremelimumab combination therapy versus MEDI4736 monotherapy for the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high (≥16 mut/Mb) subgroup, and all-comers. These analyses will be performed using the same methodology as described above.

Kaplan-Meier plots of PFS will be presented by treatment arm in the low risk of EM subgroup, all-comers, PD-L1 TC/IC high subgroup and ctDNA TMB high (≥16 mut/Mb) subgroup where appropriate.

A sensitivity analysis will be performed by analyzing the BICR assessments. The stratified log-rank test will be repeated on these data. The HR and CI will be presented. The methodology will be documented in the SAP.

CCI [redacted]

8.5.2.2 Objective response rate

The ORR will be based on the programmatically derived RECIST 1.1 using investigator assessment data. The ORR will be compared between MEDI4736 monotherapy versus SoC, MEDI4736 + tremelimumab versus SoC, and MEDI4736 + tremelimumab versus MEDI4736 monotherapy using logistic regression models adjusting for the same factors as the primary endpoint (PD-L1 status, tumor location, and smoking history). 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). This analysis will be performed on the PD-L1 TC/IC high subgroup, low risk of EM subgroup and all-comers. The ORR will again be compared between MEDI4736 +/- tremelimumab versus SoC using logistic regression models for the ctDNA TMB high (≥16 mut/Mb) subgroup.

CCI [redacted]

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

8.5.2.3 Duration of response

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).

8.5.2.4 Best objective response

BoR based on site investigator data (RECIST 1.1), for each treatment arm, BoR will be summarized by n (%) for each category (CR, PR, SD, PD and NE). No formal statistical analysis are planned for BoR.

8.5.2.5 Time to response

The TTR, based upon the site investigator assessment of RECIST 1.1, will be summarised (ie, number of patients [%] based upon the number of responders) by the scheduled assessment timepoint that the response was first observed. Additionally, descriptive summary statistics (ie, minimum, maximum, median, Q1 and Q3) will also be presented.

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

The APF6 and APF12 will be summarized (using the Kaplan-Meier estimate) and presented by treatment arm. APF6 and APF12 will be compared between MEDI4736 monotherapy versus SoC and MEDI4736 + tremelimumab combination therapy versus SoC, PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high (≥16 mut/Mb) subgroup and all-comers by using the Kaplan-Meier estimate of PFS at 6 and 12 months for each treatment.

8.5.2.7 Time from randomization to PFS2

PFS2 is defined as the time from the date of randomization to the earliest of the progression event subsequent to that used for the PFS endpoint. PFS2 will be analyzed using a stratified log-rank tests, using the same methodology as described for the primary PFS endpoint. The effect of MEDI4736 monotherapy versus SoC and MEDI4736 + tremelimumab combination therapy versus SoC for the PD-L1 TC/IC high subgroup and all-comers will be estimated by the HR together with its corresponding CI and p-value. Kaplan-Meier plots will be presented by treatment arm. 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.

8.5.2.8 Time from randomization to first and second subsequent therapy or death

For supportive purposes, the time to the start of the first and the second subsequent therapy or death will be analyzed for the PD-L1 TC/IC high subgroup and all-comers using the same methodology and model as that used for the analysis of PFS. 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 the first and the second subsequent therapy will be presented by treatment arm, and the time between progression and start of the first and the second subsequent therapy will be assessed. This interval will be summarized per treatment arm, but no formal comparisons will be made.

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

The number of patients prematurely censored will also be summarized.

8.5.2.9 Proportion of OS12, OS18 and OS24

OS12, OS18 and OS24 will be summarized (using the Kaplan-Meier estimate) and presented by treatment arm for the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high (≥16 mut/Mb) and all-comers.

8.5.3 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.

8.5.3.1 EORTC QLQ-C30

Time to symptom deterioration in the PD-L1 TC/IC high subgroup and all-comers will be analyzed for each of the 3 symptom scales (fatigue, pain, and nausea/vomiting). Time to HRQoL/function deterioration in all-comers 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), using the same methodology as described for the primary PFS endpoint.

The effect of MEDI4736 monotherapy versus SoC 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 arm. 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 scales/items (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, and each functional domain will be reported by visit for each treatment arm. Graphical presentations may also be produced as appropriate.

Analysis of HRQoL or symptom will also be carried out by comparing mean change from baseline in the global health status/QoL, functions (physical, role, cognitive, social and emotional) scores (from the EORTC QLQ-C30 questionnaire).

Change from baseline will be derived using a MMRM analysis of all the post-baseline scores for each visit. The model will include treatment, visit, and treatment by visit interaction as explanatory variables and the baseline score as a covariate. Adjusted mean estimates per treatment group and corresponding 95% CIs will be presented along with an overall estimate of the treatment difference, 95% CI and p-value. An overall adjusted mean estimate will be derived that will estimate the average treatment effect over visits giving each visit equal weight using least squares means.

8.5.3.2 EORTC QLQ-H&N35

Time to symptom deterioration in the PD-L1 TC/IC high subgroup and all-comers 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 effect of MEDI4736 monotherapy versus SoC 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 plot. Summaries of the number and percentage of patients experiencing a clinically meaningful deterioration or death, and the median time to deterioration, will also be provided for each treatment group.

A summary of the symptom improvement rate 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 for each of the 7 symptom scales/items (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.

The assessment of symptoms comparing mean change from baseline using the MMRM as described for EORTC QLQ-C30 will be repeated for pain, swallowing, senses, and speech of the EORTC QLQ-H&N35. All assumptions and outputs as described for the EORTC QLQ-C30 are applicable and the same approach from EORTC QLQ-C30 will be applied.

8.5.3.3 Exploratory patient-reported outcomes

CCI [redacted]

8.5.4 Safety data

Safety and tolerability data will be presented by treatment arm, for patients in the PD-L1 TC/IC high subgroup, low risk of EM subgroup and all-comers, using the safety analysis set.

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. 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 + tremelimumab 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 + tremelimumab combination therapy, MEDI4736 monotherapy, and SoC will be summarized. Time on study, MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, and SoC dose delays 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.

8.5.5 Pharmacokinetic data

PK concentration data of MEDI4736 and tremelimumab will be listed for each patient and each dosing day with a matching PK sample, and a summary will be provided for all evaluable patients.

8.5.6 Immunogenicity data

Immunogenicity results will be listed by patient, and a summary will be provided by the number and percentage of patients who develop detectable anti-MEDI4736 and anti-tremelimumab antibodies. The immunogenicity titer and neutralizing ADA data will be listed for samples confirmed positive for the presence of anti-MEDI4736 and anti-tremelimumab antibodies.

The effect of immunogenicity as well as the effect of its neutralizing properties on PK, pharmacodynamics, efficacy, and safety may be evaluated as data allow.

8.5.7 Biomarker data

CCI [redacted]

Subgroup analysis by HPV/EBV status may be performed, if data are available.

8.5.8 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.

No interim analyses will be performed for any efficacy endpoint.

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 (CSP) and related documents

with the investigational staff and train them in any study-specific procedures and IVRS/IWRS, WBDC, and any ePRO systems to be utilized.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

9.2 Monitoring of the study

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

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

9.2.2 Study agreements

The Principal Investigator at each center should comply with all the terms, conditions, and obligations of the CSA for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP 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.

9.2.3 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 Q4 2015 and end by Q3 2019.

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

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.

Data management of genotype data

Any genotype data generated in this study will be stored in the AstraZeneca genotyping database or other appropriate secure system within AstraZeneca and/or a third party contracted to work with AstraZeneca to analyze samples. The results from this genetic research may be reported in the CSR for the main study or in a separate report, as appropriate.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Data associated with human biological samples

Data associated with human biological samples will be transferred from laboratories internal or external to AstraZeneca.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH)/GCP, applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

The 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)/Institutional Review Board (IRB) should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable EC/IRB and to the study site staff.

The opinion of the EC/IRB should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrollment 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 enrollment of any patient into the study, the final study protocol, including the final version of the ICF, should be approved by the national regulatory authority or a notification to the national regulatory authority should be approved, 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 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 he or she is 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.

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 CSP).

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.

For sites in Japan only

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca. If it is necessary for the study protocol to be amended, the amendment should be submitted to the Head of the Study Site and be approved by its IRB. If applicable, AstraZeneca should submit a notification to the regulatory authority before it is implemented. If a protocol amendment requires a change to a particular center's ICF, then AstraZeneca and the center's IRB should be notified by the Principal Investigator. Approval of the revised ICF by AstraZeneca and IRB is required before the revised form is used. If an administrative change is required, such a change should be notified to or approved by each IRB according to local requirements.

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.

11. LIST OF REFERENCES

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Appendix A Signatures

Electronically approved.

Appendix B 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 adverse event (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.

- Angioedema not severe enough to require intubation but requiring intravenous 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

When making an assessment of causality, consider the following factors when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the 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?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, or other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of "related" is made if, following a review of the relevant data, there is evidence for a "reasonable possibility" of a causal relationship for the individual case. The expression "reasonable possibility" of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as "not related."

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Creatinine Calculation

Cockcroft-Gault equation

Males:

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

Females:

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

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 C IATA 6.2 Guidance Document

Labeling and Shipment of Biohazard Samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. 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
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D Actions Required in Cases of Combined Increases in Liver Biochemistry and Evaluation of Hy's Law

Introduction

This appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on the managing liver abnormalities can be found in Sections 5.2.1 and 6.7.2 of the protocol.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3 × Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥2 × ULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥3 × ULN **together with** TBL ≥2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3 × ULN
- AST ≥3 × ULN
- TBL ≥2 × ULN

If a central laboratory is used

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Definitions of this appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

If a local laboratory is used

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Determine whether the patient meets PHL criteria (see Definitions of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

Follow-up

Potential Hy's Law criteria not met

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

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

Potential Hy's Law criteria met

If the patient does meet PHL criteria the Investigator will:

- 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. If a central laboratory is used, this includes deciding which the tests available in the Hy's law lab kit should be used.
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

Review and Assessment of Potential Hy's Law Cases

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

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment

This section is applicable to patients with liver metastases who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met[#]
  - If there is no significant change no action is required
  - If there is a significant change notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Potential Hy's Law criteria met of this Appendix

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g. chronic or progressing malignant disease, severe infection or liver disease, or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment?

If No: follow the process described in Potential Hy's Law criteria met of this appendix

If Yes:

Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Potential Hy's Law criteria met of this appendix

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Appendix E Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors)

Introduction

This appendix details the implementation of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines (Eisenhauer et al 2009) for the D419LC00001 study with regards to Investigator assessment of tumor burden including protocol-specific requirements for this study.

Definition of Measurable, Non-measurable, Target and Non-target Lesions

Only patients with measurable disease at baseline should be included in the study. Measurable disease is defined by the presence of at least 1 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[1]) with computed tomography (CT) or magnetic resonance imaging (MRI) and that 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, or abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Previously irradiated lesions that have not demonstrated progression[2]
- Brain metastasis

[1] Nodes with <10 mm short axis are considered non-pathological and should not be recorded or followed as non-target lesions (NTLs). The short axis is defined at the longest axis perpendicular to the long axis of the tumour.
[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.

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.

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.

Table16 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}F-Fluoro-deoxyglucose positron emission tomography; MRI Magnetic resonance imaging.

CT and MRI

CT and MRI (both preferably with IV contrast) 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 D419LC00001 study, the methods of assessment of tumor burden used at baseline and follow-up visits are contrast-enhanced CT/MRI of the neck, chest, and abdomen (including liver and adrenal glands). Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients. CT examination with intravenous contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For brain lesion assessment, MRI is the preferred method.

Clinical examination

In the D419LC00001 study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as TLs if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

X-ray

Plain X-ray

In the D419LC00001 study plain X-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

Ultrasound

In the D419LC00001 study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumor size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

Endoscopy and laparoscopy

In the D419LC00001 study, endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor assessment.

Tumor markers

In the D419LC00001 study, tumor markers will not be used for tumor response assessments as per RECIST 1.1.

Cytology and histology

In the D419LC00001 study histology will not be used as part of the tumor response assessment as per RECIST 1.1.

Isotopic bone scan

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

In the D419LC00001 study, isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and X-ray is recommended where bone scan findings are equivocal.

FDG-PET scan

In the D419LC00001 study, ^{18}F-Fluoro-deoxyglucose positron emission tomography (FDG-PET) scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive ^{18}F-Fluoro-deoxyglucose uptake[3] not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

Tumor Response Evaluation

Schedule of evaluation

RECIST 1.1 assessments will be performed using contrast-enhanced CT/MRI assessments of chest, abdomen, and pelvis. 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 randomization, and ideally should be performed as close as possible prior to the start of study treatment (see Table 2, Table 3, and Table 4 of the Clinical Study Protocol). Follow-up assessments will be performed every 6 weeks ±1 week for the first 24 weeks relative to the date of randomization and then every 8 weeks ±1 week thereafter until confirmed objective disease progression as defined by RECIST 1.1 (irrespective of the reason for stopping treatment or subsequent therapy).

Additional assessments will be performed post confirmed objective disease progression for patients remaining on assigned 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.

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

Target lesions

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. Although a visit response of PD will be assigned in the vast majority of these cases, a case should be flagged and reviewed by the Study Physician in a blinded fashion if use of the estimated size in the calculation of TL would not give an overall visit response of PD.
- 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.

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 TLs, 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 and an absolute increase of at least 5 mm, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study).
Not Evaluable (NE)	Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. Note: if the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response.

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

Non-target lesions

Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit (see Table 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 with no evidence of progression.
Progression (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: for patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

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

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

New lesions

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

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

The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor.

If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

Symptomatic deterioration

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

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

Evaluation of overall visit response

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

Table 19 Overall visit response

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

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

Confirmation of Progression

Disease progression in the immunomodulatory therapy arms 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. Disease progression in patients in the Standard of Care arm should be confirmed by a scan obtained no earlier than 4 weeks after the initial assessment of PD and preferably at the next scheduled imaging visit, if clinically feasible.

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

- ≥20% increase in the sum diameters of TLs compared with the nadir at 2 consecutive scan timepoints with an absolute increase of 5mm* *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 timepoint are considered non-target lesions at the confirmatory scan timepoint), *and/or*
- Additional new unequivocal lesions at the confirmatory scan time-point.

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

If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression, then the patient should still continue to be followed until confirmed objective disease progression.

Central Review

The imaging Contract Research Organization (iCRO) appointed by AstraZeneca to perform the collection, QC, and storage of images from the Investigator sites for this study will provide guidelines for image acquisition, image anonymization, image storage at the investigative site as source data, and image transfer to the iCRO. The decision to perform a BICR by the iCRO is at the discretion of AstraZeneca. If a BICR is performed, assessments will be performed by the central radiologists according to RECIST 1.1, and irRECIST 1.1 (Nishino et al 2013). The management of patients will be based solely upon the local assessments conducted by the Investigator.

Further details of the Blinded Independent Central Review will be documented in the Independent Review Charter (also referred to as 'Imaging Charter').

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.

Nishino et al 2013
Nishino M Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH, Hodi FS. Developing a common language for tumor response to immunotherapy: Immune-related response criteria using unidimensional measurements. Clin Cancer Res, 2013;19(14):3936-43.

Appendix F Patient-Reported Outcomes

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____
Your birthdate (Day, Month, Year): ____
Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

ENGLISH

EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Have you had pain in your mouth?	1	2	3	4
32.	Have you had pain in your jaw?	1	2	3	4
33.	Have you had soreness in your mouth?	1	2	3	4
34.	Have you had a painful throat?	1	2	3	4
35.	Have you had problems swallowing liquids?	1	2	3	4
36.	Have you had problems swallowing pureed food?	1	2	3	4
37.	Have you had problems swallowing solid food?	1	2	3	4
38.	Have you choked when swallowing?	1	2	3	4
39.	Have you had problems with your teeth?	1	2	3	4
40.	Have you had problems opening your mouth wide?	1	2	3	4
41.	Have you had a dry mouth?	1	2	3	4
42.	Have you had sticky saliva?	1	2	3	4
43.	Have you had problems with your sense of smell?	1	2	3	4
44.	Have you had problems with your sense of taste?	1	2	3	4
45.	Have you coughed?	1	2	3	4
46.	Have you been hoarse?	1	2	3	4
47.	Have you felt ill?	1	2	3	4
48.	Has your appearance bothered you?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:		Not at all	A little	Quite a bit	Very much
49.	Have you had trouble eating?	1	2	3	4
50.	Have you had trouble eating in front of your family?	1	2	3	4
51.	Have you had trouble eating in front of other people?	1	2	3	4
52.	Have you had trouble enjoying your meals?	1	2	3	4
53.	Have you had trouble talking to other people?	1	2	3	4
54.	Have you had trouble talking on the telephone?	1	2	3	4
55.	Have you had trouble having social contact with your family?	1	2	3	4
56.	Have you had trouble having social contact with friends?	1	2	3	4
57.	Have you had trouble going out in public?	1	2	3	4
58.	Have you had trouble having physical contact with family or friends?	1	2	3	4
59.	Have you felt less interest in sex?	1	2	3	4
60.	Have you felt less sexual enjoyment?	1	2	3	4

During the past week:		No	Yes
61.	Have you used pain-killers?	1	2
62.	Have you taken any nutritional supplements (excluding vitamins)?	1	2
63.	Have you used a feeding tube?	1	2
64.	Have you lost weight?	1	2
65.	Have you gained weight?	1	2

CCI

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Document Title:	D419LC00001 Clinical Study Protocol version 12	
Document ID:	Doc ID-003967645	
Version Label:	4.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
30-Jun-2020 12:27 UTC	PPD	Content Approval
30-Jun-2020 12:09 UTC	PPD	Content Approval
30-Jun-2020 03:15 UTC	PPD	Content Approval
29-Jun-2020 22:56 UTC	PPD	Author Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.