Clinical Study Protocol	
Study Intervention	Monalizumab and cetuximab
Study Code	D7310C00001
Version	2.0
Date	07 July 2021

A Phase 3 Randomized, Double-blind, Multicenter, Global Study of Monalizumab or Placebo in Combination With Cetuximab in Participants With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck Previously Treated With an Immune Checkpoint Inhibitor

Sponsor Name:	**AstraZeneca AB**
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Regulatory Agency Identifier Number(s):	**IND number 145482**
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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 Number: D7310C00001

Amendment Number: 1

Study Intervention: Monalizumab (IPH2201) and cetuximab

Study Phase: 3

Short Title: Study of Monalizumab Given With Cetuximab or Placebo Given with Cetuximab in Participants With Recurrent or Metastatic Head and Neck Cancer

Acronym: INTERLINK-1

Study Clinical Lead Name and Contact Information will be provided separately

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	07 July 2021
Original Protocol	10 February 2020

Amendment 1 (07 July 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the EU.

Overall Rationale for the Amendment

The protocol was updated to change the primary population of interest for the primary endpoint from the FAS to the HPV-unrelated Analysis Set (randomized participants who are either OPC HPV negative or non-OPC regardless of HPV status). To allow for the change in population assessed for the primary endpoint, the planned number of participants was increased and the hierarchical testing procedure was updated. A futility analysis for OS was added as a new interim analysis for the HPV-unrelated Analysis Set . Guidance relating to the COVID-19 pandemic was added.

In addition, a number of non-substantial changes were made and errors were corrected.

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Protocol Amendment Summary of Changes Table	Section “Protocol Amendment Summary of Changes Table” was added.	To describe changes in Amendment 1	Non-substantial
Section 1.1 Synopsis, Rationale	Text updated in line with changes to protocol body.	See below	See below
Section 1.1 Synopsis, Objectives and Endpoints	Text updated in line with changes to protocol body.	See below	See below
Section 1.1 Synopsis, Overall Design	Text updated in line with changes to protocol body. In addition, the number of sites was increased from 175 to 190.	See below	See below
Section 1.1 Synopsis, Number of Participants	Text updated in line with changes to protocol body.	See below	See below

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.1 Synopsis, Statistical Methods	Text updated in line with changes to protocol body.	See below	See below
Section 1.3 Schedule of Activities	**Table 1** Added collection of PD-L1 results at screening, if available. Clarification added (Footnote "d") that the most recent PD-L1 results should be provided and if PD-L1 results were not collected at screening, they will be collected retrospectively.	As part of the biomarker evaluation	Non-substantial
	Table 1 Added separate line for assessment of Coagulation parameters and footnote 'j' as mentioned in Section 8.2.4.	For clarification	Non-substantial
	Table 1 CCI	Based on PK advice	Non-substantial
	Table 1 CCI	Based on PK advice	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Table 1 and Table 2 Order of T3 and T4 changed to T4 followed by T3 in Table 1 and footnote "k" of Table 1 and in Table 2 and footnote "c" of Table 2; footnote "k" (Table 1)/footnote "c" (Table 2) changed from "Free T3 and free T4" to "Free T4 or/and free T3 (per local standard clinical practice)".	To correct an error	Non-substantial
Section 2.2 Background	Updated to reflect most recent NCCN guidelines.	To present most recent guidelines	Non-substantial
Section 3 Objectives and Endpoints	Population used for analysis of the primary objective was changed from the FAS to the HPV-unrelated Analysis Set (randomized participants who are either OPC HPV negative or non-OPC regardless of HPV status).	Primary population was updated to reflect the updated primary population of interest (HPV-unrelated participants)	Substantial
	The previous primary objective (to compare the effect of monalizumab and cetuximab (Arm A) relative to placebo and cetuximab (Arm B) by assessment of OS in all participants [ie, in the FAS]) was moved to a secondary objective. The population was confirmed as all randomized patients.	To allow for the primary objective to be assessed in the HPV-unrelated Analysis Set	Substantial
	For the secondary objective "To compare the effect of monalizumab and cetuximab (Arm A) relative to placebo and cetuximab (Arm B) by assessment of PFS, ORR, and DoR", the populations to be analyzed were changed to "participants who are HPV-unrelated" and "all randomized participants".	To clarify that the HPV-unrelated Analysis Set will also be used for this analysis	Substantial
	Text added to the following objectives to clarify they will be analyzed in the HPV-unrelated population and in all randomized participants: "To assess disease-related symptoms, functioning, and HRQoL in participants treated with monalizumab and cetuximab (Arm A) compared to placebo and	To clarify that these objectives will be analyzed in the HPV-unrelated Analysis Set and in all	Substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	cetuximab (Arm B) using the EORTC QLQ-C30 and the EORTC QLQ-H&N35 questionnaires” CCI	randomized participants	
Section 4.1 Overall Design	CCI	To allow for the change in planned sample size given the primary population has been changed to HPV-unrelated population	Substantial
	Now states that the IDMC will review data for both IAs (previously there was only one IA).	For clarity	Non-substantial
	Text added to describe a cap on the number of OPC HPV-positive participants of approximately 20%.	To ensure sufficient sample size for HPV-unrelated participants	Substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis	New section to provide instructions in the case of civil crisis, natural disaster, or public health crisis.	In response to COVID-19 pandemic, to reflect current AstraZeneca processes	Substantial
Section 4.2.1 Rationale for Study Design and Participant Population	Added clarification that unblinded pharmacists and 'unblinded Study Monitors' will be used in order to maintain the blind.	For clarification	Non-substantial
	Text added to give rationale for testing in the HPV-unrelated population.	To align with the change to the primary population	Non-substantial
Section 5.1 Inclusion Criterion 7	Added clarification that tumor tissue beyond the 3-month window and up to 6 months old may be considered, provided that no intervening systemic regimen was ongoing at the time of sample collection. A reference to the Laboratory Manual was also added.	For clarification	Non-substantial
Section 5.2 Exclusion Criterion 13	Triplicate ECG timings replaced with a cross reference to Section 8.2.3.	For clarity	Non-substantial
Section 6.1.1 Investigational Medicinal Products	**Table 5** CCI [redacted]	Updated to align with CSP template	Non-substantial
	CCI [redacted]	For clarification	Non-substantial
	CCI [redacted]	For clarification	Non-substantial
	Clarified that cetuximab will be supplied by AstraZeneca, but if locally sourced the approved commercial product should be used.	For clarification	Non-substantial
Section 6.1.2 Dosing Instructions	**Dosing regimen**	For clarification	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Now states that the total infusion duration for both interventions must not exceed 8 hours. Also states the iv line will be flushed according to local practices to ensure the full dose is administered, and the infusion time does not include the final flush time.		
Section 6.2 Preparation/Handling/ Storage/Accountability of Interventions	Clarified that IMP *must* be kept in original packaging.	For clarification	Non-substantial
Section 6.2.1.1 Monalizumab	Removed the text stating that monalizumab should be protected from direct sunlight during preparation and handling. Clarified that the reconstitution and administration time of monalizumab *must* not exceed values stated. CCI [redacted]	For clarification	Non-substantial
	CCI [redacted]	CCI [redacted]	Non-substantial
Section 6.2.1.3 Placebo	Revised text to state an CCI [redacted] CCI [redacted] Clarified that the total infusion time *must* not exceed 8 hours at room temperature.	For clarification	Non-substantial
6.3.1 Participant Enrollment and Randomization	Text added to describe a cap on the number of OPC HPV-positive participants of approximately 20%.	To ensure sufficient sample size for HPV-unrelated participants	Substantial
	Amended to state all screening laboratory and imaging results must be obtained within 28 days of randomization (was "within 28 days of randomization/the first dose of study intervention").	For consistency with tumor assessment timings in	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
		Inclusion Criterion 6	
	Amended to state a tumor tissue sample *should* be submitted to the central laboratory.	To ensure samples are submitted for analysis	Non-substantial
Section 6.5 Concomitant Therapy	**Table 7** Text amended to state permitted vaccines are limited to non-live attenuated preparations. A reference to Appendix C was also added for details about vaccination against COVID-19.	To align with current AstraZeneca template	Non-substantial
Section 6.5.3 Rescue Medication	Removed the need to record the time of rescue medication administration.	Removed as this is not necessary	Non-substantial
Section 6.6 Dose Modification	Added reference for managing dose delays due to treatment-related toxicity.	To reflect current AstraZeneca processes	Non-substantial
	Added reference to the new COVID-19 Appendix C.	To reflect current AstraZeneca processes	Substantial
	Replaced the term “IMP” with the specified study treatment.	For clarity	Non-substantial
Section 8.1.1 Imaging Tumor Assessments	Clarified that screening/baseline imaging should be performed no more than 28 days before randomization (not 28 days before start of study intervention).	For clarification	Non-substantial
Section 8.1.4.7 Administration of Electronic PRO Questionnaires	Clarified that if technical or other device-related issues prohibit completion of the questionnaires on the device, an appropriate backup option may be considered.	For clarification	Non-substantial
	Clarified that relatives, friends, or clinic staff should not help participants decide on answers to the questionnaires.	For clarification	Non-substantial
	Clarified that if a participant *needs* (rather than *uses*) visual aids for reading and they do not have them when attending clinic, they will be exempted from completing the ePROs at that visit.	For clarification	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Clarified reasons for exemption from completing the ePROs, and added the need to contact AstraZeneca to determine if the participant is exempt.	For clarification	Non-substantial
	Wording regarding language of the questionnaires updated; questions must not be translated from an available language in the device into the language the participant speaks.	For clarification	Non-substantial
	Clarified (in relation to ePRO reporting) that Cycle 1 Day 1 is baseline.	For clarification	Non-substantial
	Removed "REVPRDI" as the eCRF onto which completion status is to be recorded.	For clarification	Non-substantial
	Text added to describe process regarding participant compliance.	For clarification	Non-substantial
Section 8.1.4.8 WHO/ECOG PS	Numbering of WHO/ECOG classification corrected.	To correct an error	Non-substantial
	Sentence added to state the ECOG status collected at screening must be reported in IRT and not re-assessed.	For clarification	Non-substantial
Section 8.2.2 Vital Signs	Added the approximate time window for collection of vital signs before cetuximab dosing	For clarification	Non-substantial
Section 8.2.3 Electrocardiograms	Resting ECG description changed to "semi-recumbent or supine".	To correct an error	Non-substantial
Section 8.2.4 Clinical Safety Laboratory Assessments	Timing of sampling for coagulation parameters aligned with Table 8: "baseline on Day 1 (unless all screening laboratory hematology assessments are performed within 3 days prior to Day 1), and then as clinically indicated"	For clarification	Non-substantial
	Table 8 Order of T3 and T4 changed to T4 followed by T3 in Table 8; footnote "h" amended to "Free T4 or/and free T3 (per local standard clinical practice)…".	To correct an error	Non-substantial
	Table 8 Footnote c clarified that absolute neutrophil counts must be recorded at screening ie, they must not be recorded as percentages.	For clarification	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	The calculation of absolute counts from percentages was removed as this is not currently achievable.		
	Table 8 Coagulation was moved from the clinical chemistry column to the hematology/hemostasis column.	To correct an error	Non-substantial
Section 8.3 Adverse Events and Serious Adverse Events	Cross reference to new COVID-19 Appendix C added.	To reflect current AstraZeneca processes	Substantial
Section 8.3.13.1 Maternal Exposure	"Congenital abnormalities/abnormality" changed to "congenital anomalies/anomaly".	This change is in line with regulatory requirements	Non-substantial
Section 8.3.13.2 Paternal Exposure	"Congenital abnormality" changed to "congenital anomaly".	This change is in line with regulatory requirements	Non-substantial
Section 8.3.14 Medication Error	Clarified that medication error information should be reported on the specific medication error eCRF.	Updated in line with new AstraZeneca requirements	Non-substantial
Section 8.3.15.2 Cetuximab	Management of AEs with cetuximab text amended to refer to local label (details of actions to take have been removed).	To avoid possible mis-alignment with future changes to prescribing information	Substantial
Section 8.6.1 Collection of Mandatory Samples for Biomarker Analysis	Added clarification that tumor tissue beyond the 3-month window and up to 6 months old may be considered, provided that no intervening systemic regimen was ongoing at the time of sample collection. A reference to the Laboratory Manual was also added.	For clarification	Non-substantial
	Added clarification that fresh tumor biopsy should not be collected from lesions in proximity to structures that would make the collection procedure high risk.	Per USA FDA request	Non-substantial
Section 9.2 Sample Size Determination	Number of randomized participants increased from 600 to 624.	To align with the changes in	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
		Section 4 Study Design	
	Text amended to reflect change in population analyzed for the primary endpoint.	To reflect the change in the primary population	Substantial
	Futility analysis for OS added for the HPV-unrelated Analysis Set.	Futility analysis was added for risk mitigation	Substantial
	Statistical methods for the primary endpoint were updated to reflect that analysis will be performed on HPV-unrelated participants.	To reflect the change in the primary population	Substantial
	Text added to describe a cap on the number of OPC HPV-positive participants of approximately 20%.	To ensure sufficient sample size for HPV-unrelated participants	Substantial
	Hypothesis text split to reflect hypotheses at each analysis (IA2 and final analysis).	For clarification	Substantial
Section 9.3 Populations for Analyses	**Table 9** HPV-unrelated Analysis Set added to analysis of OS, PFS, ORR, DoR, PRO endpoints, demography and other baseline characteristics, and biomarkers.	To allow analysis for the updated primary population	Substantial
	Table 9 Footnotes added to clarify definitions of ORR and PRO.	For clarification	Non-substantial
Section 9.3.1 HPV-unrelated Analysis Set	New section added to describe new analysis set.	To allow analysis for the updated primary population	Substantial
Section 9.3.2 Full Analysis Set	Amended to state FAS will be used for summarizing baseline characteristics, all efficacy endpoints (including PROs) and biomarker analyses as secondary analyses.	The HPV-unrelated Analysis Set is the primary analysis set	Substantial
	"Analysis for ORR will be based on participants in the FAS who had measurable disease at baseline. Analysis of DoR will be based on participants in the	It is more appropriate to include the description of the subset used for ORR and	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	FAS who achieved objective response" was removed.	DoR analyses in the sections for ORR and DoR	
Section 9.3.3 Safety Analysis Set	Clarified that all participants who received any amount of study treatment (not at least 1 dose) will be included in the Safety Analysis Set.	For clarification	Non-substantial
Section 9.4.1 General Considerations	Hypothesis text split to reflect hypotheses at each analysis (IA2 and final analysis).	For clarification	Substantial
	Number of OS events and % maturity updated to reflect change in primary analysis population to HPV-unrelated Analysis Set.	To reflect the change in the primary population	Substantial
	Text changed to reflect that the efficacy and PRO analyses will be performed on the HPV-unrelated population and repeated for the FAS as a secondary analysis.	Updated so that the PRO analysis is performed for both the primary and secondary populations	Substantial
	Table 10 Added populations analyzed and amended stratification factors for each endpoint to reflect populations analyzed. Added OS in FAS as a secondary endpoint.	To reflect the change in the primary population	Substantial
	Table 10 OS: KM plot of time to censoring removed from the sensitivity and supplemental analysis.	Removed as it is not considered necessary	Non-substantial
	Table 10 OS: Cox proportional hazards models removed from the sensitivity and supplemental analysis.	For consistency with the SAP that has changed during development	Non-substantial
Section 9.4.1.1 Methods for Multiplicity Control	Text was added to more fully describe the hierarchical testing procedure.	For clarification	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Number of OS events updated to reflect change in primary analysis population to HPV-unrelated Analysis Set; new figure added to describe multiplicity testing procedure.	To allow updated sample size justification with the change in the primary population. To allow clarification in the multiple testing procedure of OS and PFS with the primary population (HPV-unrelated Analysis Set) and the secondary population (FAS)	Substantial
	Statement that PFS will be formally tested only if OS is statistically positive replaced by statement that each statistical test will be performed only if the preceding test is positive.	To allow clarification in the multiple testing procedure of OS and PFS with the primary population (HPV-unrelated Analysis Set) and the secondary population (FAS)	Substantial
Section 9.4.2.1 Primary Endpoint	**Primary analysis** Analysis set changed from FAS to HPV-unrelated Analysis Set. As the population studied is now the HPV-unrelated Analysis Set, adjustment for HPV status was removed.	To allow analysis for the updated primary population and adjust the sensitivity analyses accordingly	Substantial
	Sensitivity analysis	Added max-combo test as it is	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Details added regarding the stratified max-combo test that will be used as a sensitivity analysis. Removal of KM plot for the time to censoring (attrition bias).	recommended by the Cross-Pharma Non-proportional Hazard Working Group in the presence of non-proportional hazards. Removed KM plot of time to censoring as it is not as informational.	
	Cox proportional hazards models removed from the sensitivity and supplemental analysis.	For consistency with the SAP that has changed during development	Non-substantial
	Analysis of OS in FAS New section to describe analysis of OS in the FAS.	To describe analysis of secondary endpoint	Substantial
	Subgroup analysis Clarified that subgroup analyses will be performed on HPV-unrelated Analysis Set and FAS, where applicable.	To allow analysis for the updated primary population	Substantial
	"Race" changed to "Race/ethnicity data" for clarification.	For clarification	Non-substantial
9.4.2.2.1 Progression-free Survival	**Analysis of PFS** Text amended to state PFS will be analyzed in the HPV-unrelated Analysis Set as well as the FAS.	To allow analysis in the primary population	Substantial
9.4.2.2.2 Objective Response Rate	**Analysis of ORR**	To allow analysis in the	Substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Text amended to state ORR will be analyzed in the HPV-unrelated Analysis Set as well as the FAS.	primary population	
Section 9.4.2.2.4 Patient-reported Outcome: EORTC QLQ-C30	Detailed information about PRO definitions were removed as the information will be included in the SAP. The number of analyses of PROs was reduced.	Information will be detailed in the SAP	Non-substantial
	Text amended to state analyses will be performed on the HPV-unrelated Analysis Set as well as the FAS.	To allow analysis in the primary population	Substantial
Section 9.4.2.2.5 Patient-reported Outcome: EORTC QLQ-H&N35	Detailed information about PRO definitions were removed as the information will be included in the SAP.	Information will be detailed in the SAP	Non-substantial
	Analysis methods Text amended to state the analyses will be performed for the HPV-unrelated Analysis Set as well as the FAS. The number of analyses of PROs was reduced.	To allow analysis in the primary population	Substantial
Section 9.4.2.3.1 Time from Randomization to Second Progression or Death	Removal of KM plot for the time to censoring (attrition bias).	Removed as it is not considered necessary	Non-substantial
CCI [redacted]			
Section 9.7 Impact of COVID-19 on Data	New section added to acknowledge possible impact of COVID-19 on the data: reference to SAP (where details will be supplied) included.	In response to COVID-19 pandemic, to reflect current AstraZeneca processes	Substantial
Appendix B 2 Definitions of Serious Adverse Event	"Congenital abnormality" changed to "congenital anomaly.	This change is in line with	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
		regulatory requirements	
Appendix C Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis, including COVID-19 Outbreak	New appendix added to describe study conduct details pertaining to COVID-19 outbreak. All subsequent appendices renumbered.	In response to COVID-19 pandemic, to reflect current AstraZeneca processes	Substantial
Appendix E 8 Laboratory Tests (now Appendix F 8)	Table of Hy's law laboratory tests: footnote "a" removed from HBV DNA as it is not applicable for HBV DNA; footnote "c" removed since the study is not expected to be conducted in China.	Amendment of error and clarification	Non-substantial
Throughout	The terms "Medical Monitor" and "Study Physician" were changed to "Study Clinical Lead".	In line with latest AstraZeneca template	Non-substantial

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3 Randomized, Double-blind, Multicenter, Global Study of Monalizumab or Placebo in Combination With Cetuximab in Participants With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck Previously Treated With an Immune Checkpoint Inhibitor

Short Title: Study of Monalizumab Given With Cetuximab or Placebo Given with Cetuximab in Participants With Recurrent or Metastatic Head and Neck Cancer

Rationale: The aim of this study is to assess the efficacy and safety of monalizumab and cetuximab compared to placebo and cetuximab in participants with R/M SCCHN after receiving an ICI and platinum-based chemotherapy, regardless of the sequence of these therapies. Monalizumab is a first-in-class ICI that blocks the inhibitory CD94/NKG2A receptor resulting in the stimulation of NK cell and CD8+ T cell cytolytic activity. Additionally, monalizumab enhances human NK-cell ADCC mediated by cetuximab. While monalizumab monotherapy has shown limited clinical activity, encouraging antitumor results have been observed following monalizumab and cetuximab combination therapy in patients with R/M SCCHN who have received prior platinum-based chemotherapy, including patients who have also received prior therapy with an ICI. This dual targeting could therefore provide greater antitumor activity than cetuximab alone. The combination of monalizumab and cetuximab could be a key option to improve clinical outcomes in patients with R/M SCCHN, regardless of HPV status, after receiving an ICI.

Objectives and Endpoints

Objective	Estimand [a] Description/Endpoint
Primary	
To compare the effect of monalizumab and cetuximab (Arm A) relative to placebo and cetuximab (Arm B) by assessment of OS in HPV-unrelated participants	• Population: The HPV-unrelated Analysis Set which will include all randomized participants who are either OPC HPV negative or non-OPC regardless of HPV status • Endpoint: OS, which is defined as time from randomization until the date of death due to any cause • Intercurrent events: If a participant is lost to follow-up or withdraws consent, OS will be censored based on the last recorded date on which the participant was known to be alive • Summary measure: p-value of treatment comparison using a stratified log rank test and hazard ratio of Arm A relative to Arm B with its confidence interval using a stratified Cox Proportional Hazards model
Secondary	
To compare the effect of monalizumab and cetuximab (Arm A) relative to placebo and cetuximab (Arm B) by assessment of OS in all randomized participants	• Population: The FAS which will include all randomized participants • Endpoint: OS, which is defined as time from randomization until the date of death due to any cause • Intercurrent events: If a participant is lost to follow-up or withdraws consent, OS will be censored based on the last recorded date on which the participant was known to be alive • Summary measure: p-value of treatment comparison using a stratified log rank test and hazard ratio of Arm A relative to Arm B with its confidence interval using a stratified Cox Proportional Hazards model
To compare the effect of monalizumab and cetuximab (Arm A) relative to placebo and cetuximab (Arm B) by assessment of PFS, ORR, and DoR in participants who are HPV-unrelated and in all randomized participants	• PFS is defined as time from randomization until disease progression, per RECIST 1.1 as assessed by the investigator at local site or death due to any cause, whichever occurs first. • ORR is defined as the proportion of participants with measurable disease who have a confirmed CR or PR, as determined by the investigator at local site per RECIST 1.1. • DoR is defined as the time from the date of first documented response until date of documented disease progression or death in the absence of disease progression.
To assess disease-related symptoms, functioning, and HRQoL in participants treated with monalizumab and cetuximab (Arm A) compared to placebo and	Symptoms, functioning, and global health status/QoL scale/item scores of the EORTC QLQ-C30 & EORTC QLQ-H&N35

Objective	Estimand [a] Description/Endpoint
cetuximab (Arm B) using the EORTC QLQ-C30 and the EORTC QLQ-H&N35 questionnaires in participants who are HPV-unrelated and in all randomized participants	• Change from baseline scores across visits • Time to clinically meaningful deterioration in scores
To assess the PK of monalizumab	Concentration of monalizumab in blood and PK parameters (such as C_{max}, C_{trough}, as data allow; sparse sampling)
To investigate the immunogenicity of monalizumab	Presence of ADAs for monalizumab (confirmatory results: positive or negative, titers)
To characterize the association between clinical outcome and protein expression in the tumor microenvironment in participants treated with monalizumab and cetuximab (Arm A) or placebo and cetuximab (Arm B) in participants who are HPV-unrelated and in all randomized participants	HLA-E and NKp46+ expression in pre-treatment and post-treatment tumor biopsies
Secondary safety	
To assess the safety and tolerability of monalizumab and cetuximab (Arm A) compared to placebo and cetuximab (Arm B) in participants with R/M SCCHN previously treated with ICI	AEs, vital signs, clinical laboratory results, ECGs

[a] Estimand is the target of estimation to address the scientific question of interest posed by the primary objective. Attributes of an estimand include the population of interest, the variable (or endpoint) of interest, the specification of how intercurrent events are reflected in the scientific question of interest, and the population-level summary for the variable.

ADA = antidrug antibodies; AE = adverse event; C_{max} = maximum serum concentration; CR = complete response; C_{trough} = trough serum concentration; DoR = duration of response; ECG = electrocardiogram; EORTC = European Organisation for Research and Treatment of Cancer; FAS = full analysis set; HLA-E = human leukocyte antigen E; HPV = human papillomavirus; HRQoL = health-related quality of life; NK = natural killer; OPC = oropharyngeal cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic(s); PR = partial response; QLQ-C30 = 30-item Core Quality of Life Questionnaire; QLQ-H&N35 = Quality of Life Questionnaire Head and Neck Module; RECIST 1.1 = Response Evaluation Criteria for Solid Tumors version 1.1; R/M = recurrent or metastatic; SCCHN = squamous cell carcinoma of the head and neck.

For exploratory objectives, see Section 3 of the protocol.

Overall Design

Study D7310C00001 is a Phase 3, randomized, double-blind, multicenter, global study assessing the safety and efficacy of monalizumab or placebo in combination with cetuximab in participants with R/M SCCHN not amenable to curative treatment previously treated with platinum-based chemotherapy and an ICI, regardless of the sequence of these therapies. Approximately 190 sites globally will participate in this study.

Following a 28-day screening period, eligible participants will be randomized on Day 1 in a

2:1 ratio to one of the following treatment arms: (1) Arm A: monalizumab and cetuximab or (2) Arm B: placebo and cetuximab. Participants will be stratified by:

- Human papillomavirus status: (i) OPC HPV positive or (ii) HPV-unrelated,
  - The number of OPC HPV-positive participants will be closely monitored throughout the study and is planned to be capped at approximately 20% of the total sample size.
- World Health Organization/ECOG PS (0 or 1), and
- Number of prior lines of therapy in the R/M setting (1 or 2)
  - The number of participants in each stratum (1 or 2 prior lines of therapy in the R/M setting) will be closely monitored throughout the study. If a disproportionate number of participants are enrolled in a single stratum (eg, > 75% of the total sample size), the Sponsor may elect to close further recruitment into that stratum.

Participants will receive study intervention until disease progression, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. An IDMC will review safety data regularly and make recommendations regarding further study conduct.

Disclosure Statement: This is a parallel group treatment study with 2 arms that is participant and investigator blinded.

Number of Participants:

Approximately 832 participants will be enrolled to achieve approximately 624 participants randomly assigned to study intervention while ensuring at least 498 participants who are either OPC HPV negative or non-OPC regardless of the HPV status (HPV-unrelated participants). This includes approximately 416 participants randomized to Arm A (monalizumab and cetuximab) and 208 participants randomized to Arm B (placebo and cetuximab) in the overall population; while for the HPV-unrelated population, this includes approximately 332 participants randomized to Arm A and 166 participants randomized to Arm B.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study but are not randomly assigned in the study are considered "screen failures".

Intervention Groups and Duration:

Participants will be randomized in a 2:1 ratio to Arm A or Arm B.

- Arm A: monalizumab and cetuximab
  Monalizumab CCI and cetuximab 400 mg/m^2 iv initial dose followed by 250 mg/m^2 iv Q1W

- Arm B: placebo and cetuximab
  Placebo iv Q2W and cetuximab 400 mg/m^2 iv initial dose followed by 250 mg/m^2 iv Q1W

Study intervention will continue until RECIST 1.1-defined radiological disease progression per investigator, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Crossover between treatment arms will not be permitted.

Follow-up of participants post discontinuation of study intervention

After discontinuation of study intervention, all participants will have safety assessment follow-up for 3 months after their last dose of study intervention.

Participants who have discontinued study intervention in the absence of RECIST 1.1-defined radiological disease progression per investigator will continue with scheduled tumor assessments until RECIST 1.1-defined disease progression or death regardless of whether the participant started a subsequent anticancer therapy, unless they have withdrawn all consent to study-related assessments.

Additionally, after study intervention discontinuation, all participants will be followed for survival status, subsequent anticancer therapy, and time to disease progression occurring during or after subsequent therapy (as determined per local standard clinical practice) until death, withdrawal of consent, or the end of the study.

Data Monitoring Committee: Yes

Statistical Methods

The primary objective of the study is to compare the effect of monalizumab and cetuximab (Arm A) relative to placebo and cetuximab (Arm B) in terms of OS in HPV-unrelated participants.

The primary endpoint OS is defined as the time from the date of randomization until death due to any cause. Secondary efficacy endpoints include PFS, ORR, DoR, and PROs.

The primary population is the HPV-unrelated Analysis Set which will include all randomized participants who are either OPC HPV negative or non-OPC regardless of the HPV status. The HPV status will be determined by HPV status in the eCRF and not the IVRS value. The HPV-unrelated Analysis Set and FAS (all randomized participants) will be used for summarizing baseline characteristics, all efficacy analyses, including PROs, and biomarker analyses. Treatment arms will be compared on the basis of randomized study intervention, regardless of the intervention actually received. Participants who were randomized but did not subsequently go on to receive study intervention are included in the analysis in the treatment arm to which they were randomized.

The primary analysis of OS in the HPV-unrelated Analysis Set will be performed using a stratified log-rank test, adjusting for WHO/ECOG PS (0 or 1) and number of prior lines of therapy in the R/M setting (1 or 2). The HR and its CI will be estimated from a stratified Cox Proportional Hazards model. The analysis of OS in the FAS will be additionally stratified by HPV status (OPC HPV-positive or HPV-unrelated). These stratification factors will be determined based on the randomization.

There will be two planned IAs and one FA for the study.

Interim Analysis 1 (IA1): Futility in OS will be evaluated when approximately 99 OS events have occurred across Arm A and Arm B in HPV-unrelated participants (25% information fraction) in participants randomized at least 2 months before the DCO for the futility analysis (ie, with a minimum follow-up of 2 months).

Interim Analysis 2 (IA2): A hypothesis of monalizumab plus cetuximab (Arm A) prolongs OS compared to placebo plus cetuximab (Arm B) will be tested at IA2 when approximately 278 OS events have occurred across Arm A and Arm B in HPV-unrelated participants (approximately 70% information fraction, 56% maturity).

Final Analysis (FA): A hypothesis of improved OS will be tested at the final analysis when approximately 397 OS events have occurred across Arm A and Arm B in HPV-unrelated participants (approximately 80% maturity).

If the true OS HR is 0.72, corresponding to an approximate 3-month improvement in median OS compared to Arm B of 7.7 months, approximately 397 OS events in HPV-unrelated participants will provide approximately 86.5% power to demonstrate statistical significance at the 5% level (using a 2-sided test) for the FA. The 5% (2-sided) alpha for the OS analysis will be controlled at the IA2 and FA time points by using the Lan-DeMets (Lan and DeMets 1983) spending function that approximates the O'Brien-Fleming approach, where the significance level applied depends upon the proportion of information (ie, information fraction) available at the time of IA2. For example, if the information fraction for OS at IA2 is 70% then the two-sided significance levels of 1.48% and 4.55% will be applied to IA2 and FA for OS, respectively. The smallest detectable treatment difference in HR, ie, critical value, that could be statistically significant at the FA is 0.81. With a planned recruitment period of 30 months, it is expected that a total of 498 HPV-unrelated participants are needed in order to achieve 397 OS events with a follow-up period of approximately 12 months. The 278 OS events for the IA2 are expected to be reached approximately 30.5 months after the randomization of the first participant.

The number of OPC HPV-positive participants will be closely monitored throughout the study and is planned to be capped at approximately 20% of the total sample size. With the assumption that 20% of participants will be OPC HPV positive, approximately

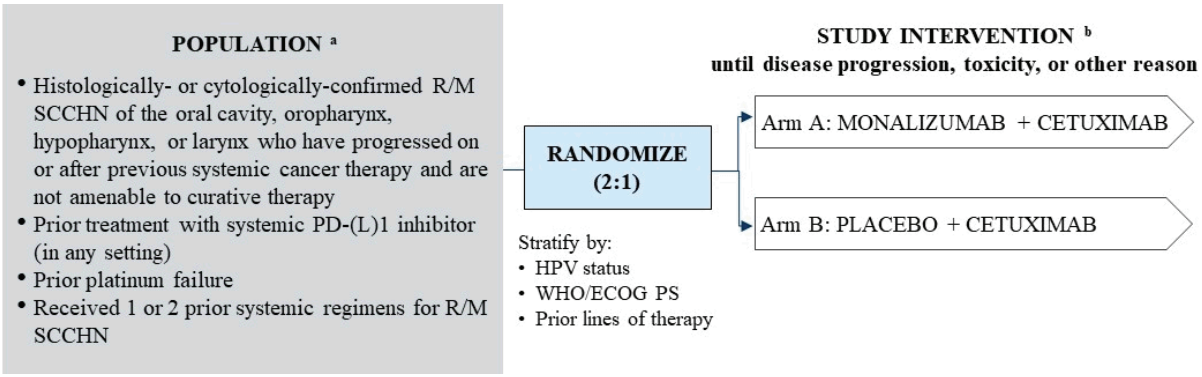
624 randomized participants will be needed in the overall population. Under the same assumption of effect size in HR and median OS stated above, approximately 498 OS events are expected in all participants which will provide approximately 93.0% power to demonstrate statistical significance at the 5% level (using a 2-sided test) for the FA.

Strong control of the FWER at 5% level (2 sided) across the testing of OS and PFS endpoints will be achieved through a combined approach of alpha allocation to the OS analyses (IA2 and the FA) via alpha spending function as previously mentioned and a hierarchical testing procedure; that is, OS in FAS will be tested only if OS in HPV-unrelated analysis set met significance at IA2 or FA; PFS will be tested only if OS met statistical significance at IA2 or FA and PFS in FAS will be tested only if PFS in HPV-unrelated analysis set met statistical significance at IA2 or FA (Glimm et al 2010).

1.2 Schema

The general study design is summarized in Figure 1.

Figure 1 Study Design



[a] Prior platinum failure is defined as either: (i) disease progression during or after treatment with a platinum-containing regimen for R/M disease or (ii) recurrence/progression during or within 6 months of the last dose of platinum as part of multimodal therapy for LA disease.
Eligible participants must not have received prior cetuximab, unless administered in the LA setting with radiotherapy and no disease progression for at least 6 months following the last cetuximab dose.

[b] Study intervention regimens: monalizumab [redacted]; cetuximab, 400 mg/m^2 iv initial dose then 250 mg/m^2 iv Q1W.

WHO/ECOG PS = World Health Organization/Eastern Cooperative Oncology Group performance status; iv = intravenous; HPV = human papillomavirus; LA = locally advanced; PD-(L)1 = programmed cell death-1 or programmed cell death ligand-1; [redacted]; [redacted] R/M = recurrent/metastatic; SCCHN = squamous cell carcinoma of the head and neck.

1.3 Schedule of Activities

The SoA are presented in Table 1 for the screening and intervention periods and Table 2 for the follow-up period.

Table 1 Schedule of Activities – Screening Period and Intervention Period

CCI

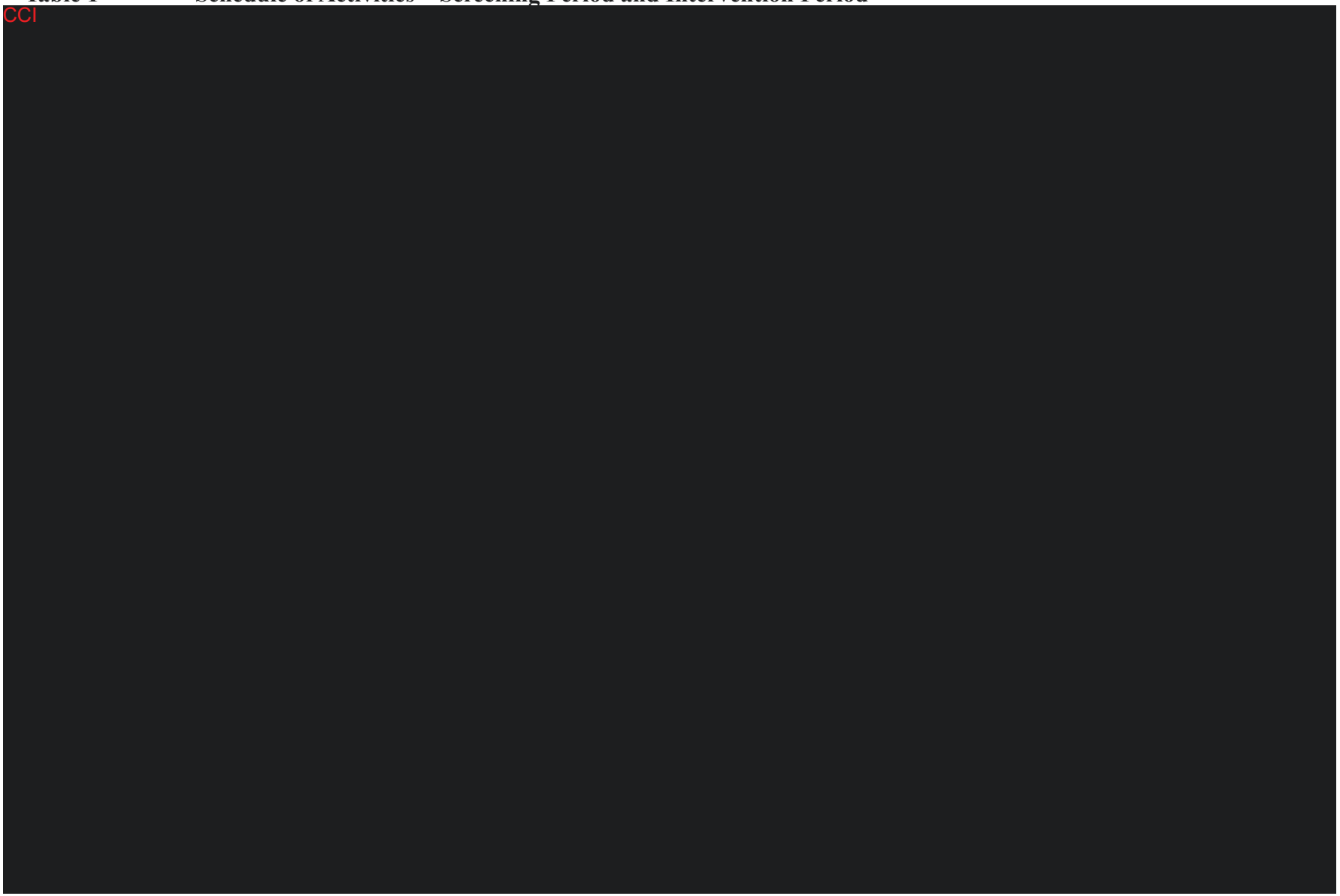


Table 1 Schedule of Activities – Screening Period and Intervention Period

CCI

Table 1 Schedule of Activities – Screening Period and Intervention Period

CCI

Table 1 Schedule of Activities – Screening Period and Intervention Period

Procedure	Screening	Intervention period (1 cycle = 14 days)														For details see Section
		C1		C2		C3		C4		C5		C6		C7+		
		C1 D1	C1 D8	C2 D1	C2 D8	C3 D1	C3 D8	C4 D1	C4 D8	C5 D1	C5 D8	C6 D1	C6 D8	C7 D1	C7 D8	
Week	**-4 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13+**	**14+**	
Day	**-28 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85+**	**D92+**	
Window (days) [a]	**NA**	**+2**	**±1**	**+2**	**±1**	**+2**	**±1**	**+2**	**±1**	**+2**	**±1**	**+2**	**±1**	**+2**	**±1**	
Biomarker sampling																
CCI	X							X (optional)								
Tumor biopsy at time of progression (optional)			X													
CCI																

Table 1 Schedule of Activities – Screening Period and Intervention Period

Procedure	Screening	Intervention period (1 cycle = 14 days)														For details see Section
		C1		C2		C3		C4		C5		C6		C7+		
		C1 D1	C1 D8	C2 D1	C2 D8	C3 D1	C3 D8	C4 D1	C4 D8	C5 D1	C5 D8	C6 D1	C6 D8	C7 D1	C7 D8	
Week	-4 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13+	14+	
Day	-28 to -1	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85+	D92+	
Window (days) [a]	NA	+2	±1	+2	±1	+2	±1	+2	±1	+2	±1	+2	±1	+2	±1	
CCI																
Pharmacokinetic measurements																
CCI																

Table 1 Schedule of Activities – Screening Period and Intervention Period

Procedure	Screening	Intervention period (1 cycle = 14 days)														For details see Section
		C1		C2		C3		C4		C5		C6		C7+		
		C1 D1	C1 D8	C2 D1	C2 D8	C3 D1	C3 D8	C4 D1	C4 D8	C5 D1	C5 D8	C6 D1	C6 D8	C7 D1	C7 D8	
Week	-4 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13+	14+	
Day	-28 to -1	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85+	D92+	
Window (days) [a]	NA	+2	±1	+2	±1	+2	±1	+2	±1	+2	±1	+2	±1	+2	±1	
CCI																
Immunogenicity measurements																
CCI																

Table 1 Schedule of Activities – Screening Period and Intervention Period

Procedure	Screening	Intervention period (1 cycle = 14 days)														For details see Section
		C1		C2		C3		C4		C5		C6		C7+		
		C1 D1	C1 D8	C2 D1	C2 D8	C3 D1	C3 D8	C4 D1	C4 D8	C5 D1	C5 D8	C6 D1	C6 D8	C7 D1	C7 D8	
Week	**-4 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13+**	**14+**	
Day	**-28 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85+**	**D92+**	
Window (days) [a]	**NA**	**+2**	**±1**	**+2**	**±1**	**+2**	**±1**	**+2**	**±1**	**+2**	**±1**	**+2**	**±1**	**+2**	**±1**	
CCI																
Efficacy measurements																
Tumor imaging (RECIST 1.1)	X	Intravenous contrast-enhanced CT or MRI of the neck, chest, and abdomen (includes entire liver) Q8W (± 1 week) for the first 48 weeks after randomization and then Q12W (±1 week) thereafter (relative to randomization), until RECIST 1.1-defined radiological disease progression; plus at least 1 additional follow-up scan. This schedule MUST be followed regardless of any delays in dosing.														8.1.1, Appendix G

Table 1 Schedule of Activities – Screening Period and Intervention Period

Procedure	Screening	Intervention period (1 cycle = 14 days)														For details see Section
		C1		C2		C3		C4		C5		C6		C7+		
		C1 D1	C1 D8	C2 D1	C2 D8	C3 D1	C3 D8	C4 D1	C4 D8	C5 D1	C5 D8	C6 D1	C6 D8	C7 D1	C7 D8	
Week	**-4 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13+**	**14+**	
Day	**-28 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85+**	**D92+**	
Window (days) [a]	**NA**	**+2**	**±1**	**+2**	**±1**	**+2**	**±1**	**+2**	**±1**	**+2**	**±1**	**+2**	**±1**	**+2**	**±1**	
PRO (e-device) and health economic measurements																
Allocate ePRO device	X															8.1.4.7
ePRO device training	X															
EORTC QLQ-C30		X				X				X				X then Q4W		8.1.4.1
EORTC QLQ-H&N35		X				X				X				X then Q4W		8.1.4.2
CCI																

Table 1 Schedule of Activities – Screening Period and Intervention Period

Procedure	Screening	Intervention period (1 cycle = 14 days)														For details see Section
		C1		C2		C3		C4		C5		C6		C7+		
		C1 D1	C1 D8	C2 D1	C2 D8	C3 D1	C3 D8	C4 D1	C4 D8	C5 D1	C5 D8	C6 D1	C6 D8	C7 D1	C7 D8	
Week	-4 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13+	14+	
Day	-28 to -1	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85+	D92+	
Window (days) [a]	NA	+2	±1	+2	±1	+2	±1	+2	±1	+2	±1	+2	±1	+2	±1	
CCI																
Other assessment																
CCI																
Study intervention administration																
CCI																

[a] Unless noted otherwise.
The interval between monalizumab/placebo and cetuximab interventions should be at least 14 days for monalizumab/placebo and at least 7 days for cetuximab. If either intervention is delayed > 2 weeks then consult the Sponsor. See Section 6.6 for action in case of a dose delay.

[b] May be obtained prior to 28-day screening window to permit tumor biopsy sample acquisition and analysis.

[c] As clinically indicated.

[d] The most recent PD-L1 results should be provided. If PD-L1 results were not collected at screening, they will be collected retrospectively.

[e] For AEs/SAEs reported during screening, additional information such as medical history and concomitant medications may be needed.

[f] Screening laboratory assessments must be obtained within 7 days prior to Day 1.

[g] Pregnancy test may occur on Day 1, but results must be reviewed by the treating physician/investigator prior to dosing.

Table 1 Schedule of Activities – Screening Period and Intervention Period

Procedure	Screening	Intervention period (1 cycle = 14 days)														For details see Section
		C1		C2		C3		C4		C5		C6		C7+		
		C1 D1	C1 D8	C2 D1	C2 D8	C3 D1	C3 D8	C4 D1	C4 D8	C5 D1	C5 D8	C6 D1	C6 D8	C7 D1	C7 D8	
Week	-4 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13+	14+	
Day	-28 to -1	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85+	D92+	
Window (days) [a]	NA	+2	±1	+2	±1	+2	±1	+2	±1	+2	±1	+2	±1	+2	±1	

[h] Results for urea and electrolytes, full blood count, and liver function tests must be available before commencing study intervention (samples must have been obtained within 3 days prior to initiating study intervention).
During the intervention period, clinical chemistry and hematology assessments may be performed more frequently if clinically indicated.

[i] If screening clinical chemistry and hematology assessments are performed within 3 days prior to Day 1, they do not need to be repeated on Day 1 if the participant's condition has not changed.

[j] Coagulation parameters are to be assessed at baseline on Day 1 (unless all screening laboratory hematology assessments are performed within 3 days prior to Day 1), and then as clinically indicated.

[k] If TSH is measured within 14 days prior to Day 1, it does not need to be repeated at Day 1. Free T4 or/and free T3 (per local standard clinical practice) will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

[l] No premedication is required prior to monalizumab administration. However, from Cycle 2, premedication with acetaminophen or an antihistamine might be prescribed, at the investigator's discretion, if the participant experienced any Grade 1 to 3 infusion-related AE at the previous cycle.

[m] Participants should be premedicated per US PI or local label (where available). Premedication may also be based on institutional guidance for management of infusion-related reactions.

ADA = antidrug antibody; AE = adverse event; C = cycle; CT = computed tomography; CCI D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; ePRO = electronic patient-reported outcome; CCI HIV = human immunodeficiency virus; CCI IHC = immunohistochemistry; IMP = investigational medicinal product; iv = intravenous; mos = months; MRI = magnetic resonance imaging; OPC = oropharyngeal cancer; PBMC = peripheral blood mononuclear cells; PD = progressive disease; PD-L1 = programmed cell death ligand-1; CCI CCI PK = pharmacokinetic; CCI PS = performance status; Q4W = every 4 weeks; Q6W = every 6 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; QLQ-C30 = 30-item Core Quality of Life Questionnaire; QLQ-H&N35= Quality of Life Questionnaire Head and Neck Module; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; SAE = serious adverse event; CCI ; SPFQ = Study Participant Feedback Questionnaire; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; US PI = United States Package Insert; W = week; WHO = World Health Organization; WOCBP = women of childbearing potential.

Table 2 Schedule of Activities – Follow-up Period for Participants Who Discontinued Study Intervention Due to Disease Progression or Other Reason

Procedure	End of treatment	Follow-up period						For details see Section
Month (post last dose IMP)	**1**	**2**	**3**	**4**	**6**	**9**	**12+**	
Window	**± 1 week**	**± 1 week**	**± 1 week**	**± 1 week**	**± 1 week**	**± 1 week**	**± 1 week**	
Clinical procedures								
Full physical examination	X							8.2.1
WHO/ECOG PS [a]	X	X	X					8.1.4.8
Vital signs	X							8.2.2
Weight	X							8.2.1
12-lead ECG (triplicate)	X							8.2.3
Concomitant medications	X	X	X					6.5
Subsequent anticancer therapy [b]	X	X	X	X	X	X	X then Q6M (± 2 weeks)	8.1.2
CCI [redacted]								
Safety measurements								
Adverse events	X	X	X					8.3
Pregnancy test; serum or urine (WOCBP only)	X	X (as clinically indicated)						8.2.4
Clinical chemistry	X	X	X					
Hematology	X	X	X					
TSH (and reflex free T4 or/and free T3) [c]	X		X					

Table 2 Schedule of Activities – Follow-up Period for Participants Who Discontinued Study Intervention Due to Disease Progression or Other Reason

Procedure	End of treatment	Follow-up period						For details see Section
Month (post last dose IMP)	**1**	**2**	**3**	**4**	**6**	**9**	**12+**	
Window	**± 1 week**	**± 1 week**	**± 1 week**	**± 1 week**	**± 1 week**	**± 1 week**	**± 1 week**	
Biomarker sampling								
Tumor biopsy at time of progression (optional)	X							
CCI								
Pharmacokinetic measurements								
CCI								
Immunogenicity measurements								
CCI								
Efficacy measurements								
Tumor imaging (RECIST 1.1)	Participants who discontinued study intervention due to reason other than disease progression or death (regardless of whether started subsequent anticancer therapy): intravenous contrast-enhanced CT or MRI of the neck, chest, and abdomen (includes entire liver) Q8W (± 1 week) for the first 48 weeks after randomization and then Q12W (±1 week) thereafter (relative to randomization), until RECIST 1.1-defined radiological disease progression; plus at least 1 additional follow-up scan..							8.1.1, Appendix G
Survival status: phone call for participants who refuse to return for evaluations and agree to be contacted [d]		X	X	X	X	X	X then Q2M (± 2 weeks)	7.1.1.3

Table 2 Schedule of Activities – Follow-up Period for Participants Who Discontinued Study Intervention Due to Disease Progression or Other Reason

Procedure	End of treatment	Follow-up period						For details see Section
Month (post last dose IMP)	**1**	**2**	**3**	**4**	**6**	**9**	**12+**	
Window	**± 1 week**	**± 1 week**	**± 1 week**	**± 1 week**	**± 1 week**	**± 1 week**	**± 1 week**	
PRO (e-device) and health economic measurements								
EORTC QLQ-C30	X	X	X	Every visit until RECIST 1.1-defined radiological disease progression (for participants who discontinued due to other reason) or start of subsequent anticancer therapy (whichever occurs first)				8.1.4.1
EORTC H&N35	X	X	X					8.1.4.2
CCI [redacted]								
Other assessment								
SPFQ (optional)	X							8.9

Table 2 Schedule of Activities – Follow-up Period for Participants Who Discontinued Study Intervention Due to Disease Progression or Other Reason

Procedure	End of treatment	Follow-up period						For details see Section
Month (post last dose IMP)	1	2	3	4	6	9	12+	
Window	± 1 week	± 1 week	± 1 week	± 1 week	± 1 week	± 1 week	± 1 week	

[a] WHO/ECOG PS should also be collected at other site visits, if appropriate site staff are available. In addition, WHO/ECOG performance status should be provided when subsequent anticancer therapy information is collected, where possible.

[b] Details of any treatment for SCCHN (including surgery) post the last dose of study intervention must be recorded in the eCRF. At minimum, collect the start date and description of the subsequent anticancer therapy.

[c] Free T4 or/and free T3 (per local standard clinical practice) will only be measured if TSH is abnormal or if there is clinical suspicion of an adverse event related to the endocrine system.

[d] Participants may be contacted in the week following data cutoffs to confirm survival status. Details of any treatment for SCCHN (including surgery) post the last dose of study intervention must be recorded in the eCRF.

ADA = antidrug antibody; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EORTC = European Organisation for Research and Treatment of Cancer; CCI iv = intravenous; MRI = magnetic resonance imaging; CCI CCI CCI PK = pharmacokinetic; CCI PS = performance status; Q2M = every 2 months; Q6M = every 6 months; QLQ-C30 = 30-item Core Quality of Life Questionnaire; QLQ-H&N35= Quality of Life Questionnaire Head and Neck Module; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; SAE = serious adverse event; SCCHN = squamous cell carcinoma of the head and neck; SPFQ = Study Participant Feedback Questionnaire; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WHO = World Health Organization; wk = week; WOCBP = women of childbearing potential.

2 INTRODUCTION

Monalizumab is a first-in-class ICI targeting NKG2A. It is a non-depleting humanized IgG4 mAb that binds with high affinity and specificity to, and blocks the inhibitory activity of the CD94/NKG2A receptor resulting in the stimulation of the cytolytic activity of CD94/NKG2A-expressing NK cells and CD8+ T cells. Monalizumab is being developed for the treatment of various cancers, including solid tumors and hematologic malignancies either as monotherapy or in combination.

2.1 Study Rationale

The aim of the study is to assess the efficacy and safety of monalizumab and cetuximab, compared to placebo and cetuximab in participants with R/M SCCHN after receiving an ICI.

In addition to blocking the CD94/NKG2A receptor, monalizumab enhances human NK cell ADCC mediated by cetuximab. While monalizumab monotherapy has shown limited clinical activity, encouraging antitumor results have been observed following monalizumab and cetuximab combination therapy in patients with R/M SCCHN who have received prior platinum-based chemotherapy, including patients who have also received prior therapy with an ICI. This dual targeting could therefore provide greater antitumor activity than cetuximab alone. The combination of monalizumab and cetuximab could be a key option to improve clinical outcomes in patients with R/M SCCHN after receiving an ICI.

2.2 Background

Overall, outcomes in patients with R/M SCCHN remain poor and most patients will ultimately experience disease progression and eventually die of the disease.

For 1L treatment of R/M SCCHN, the combination therapy of cetuximab plus platinum (either cisplatin or carboplatin) and 5-FU followed by cetuximab until progression or intolerance (EXTREME regimen) has been the standard of care in the European Union and the USA per the ESMO and NCCN guidelines, respectively (Gregoire et al 2010, NCCN 2021). In clinical practice, other single agents or doublet combinations, such as a taxane or cisplatin plus cetuximab, are also sometimes used as 1L treatment for R/M SCCHN when patients are not fit enough for the EXTREME regimen (Argiris et al 2017).

Squamous cell carcinoma of the head and neck tumors, like many other malignancies, create a highly immunosuppressive environment and are amenable to therapeutic intervention with immune-modulating agents (Curry et al 2014, Moy et al 2017). Recently, the PD-1 inhibitor pembrolizumab (KEYTRUDA®) received US FDA approval as: (i) a single agent for the 1L treatment of patients with metastatic or with unresectable, recurrent SCCHN whose tumors express PD-L1 (combined positive score ≥ 1, as determined by a US FDA-approved test) or (ii) in combination with platinum and 5-FU for the 1L treatment of patients with metastatic or

with unresectable, recurrent SCCHN (Keytruda 2021). The NCCN recommend pembrolizumab as a category 1 of evidence and consensus in the 1L R/M setting (NCCN 2021).

Patients who progress or are intolerant to 1L therapy are typically treated with single-agent cetuximab, single-agent chemotherapy (eg, taxanes, methotrexate), or since recently with PD-1 inhibitors. Cetuximab was approved by the US FDA in 2006 and for a decade remained the only drug indicated for the treatment of patients with R/M SCCHN progressing after platinum-based therapy (Erbitux PI 2021). Cetuximab continues as one of the recommended treatment options in the NCCN guideline (NCCN 2021); the ESMO guideline notes that single-agent cetuximab has activity comparable to single-agent methotrexate with a favorable safety profile (Gregoire et al 2010). In 2016, the US FDA granted approval to pembrolizumab (under accelerated approval) and another PD-1 inhibitor nivolumab (OPDIVO®) in patients with R/M SCCHN with disease progression on or after platinum therapy (Keytruda 2021, Opdivo 2021).

Treatment for patients with R/M SCCHN who progress after receiving a PD-1 inhibitor, such as pembrolizumab/nivolumab monotherapy or pembrolizumab in combination with platinum-based chemotherapy, in the 1L or second-line setting is not clearly defined. A re-challenge with PD-(L)1 inhibitors is not currently recommended. As no treatment strategies in the immunotherapy-refractory disease setting are currently approved or uniformly adopted by the medical community, a suggested approach is to enroll a patient with R/M SCCHN into a clinical study assessing combination immunotherapy (Cohen et al 2019a).

Human leukocyte antigen E, a nonclassical major histocompatibility complex class I molecule, is expressed on tumor cells in 78% to 86% of patients with SCCHN (Andre et al 2018, Nasman et al 2013, Silva et al 2011). Human leukocyte antigen E is the ligand of the inhibitory CD94/NKG2A receptors that are found on NK cells and intratumoral CD8+ T cells in a variety of tumor types, including SCCHN (Braud et al 1998, Gooden et al 2011, Katou et al 2007, Lee et al 1998). The interaction of HLA-E with CD94/NKG2A receptor results in the inhibition of NK cell and cytotoxic T lymphocyte-dependent tumor lysis and may represent a significant immune-escape mechanism by tumor cells (Borrego et al 1998, Braud et al 1998, van Montfoort et al 2018). Monalizumab is a humanized mAb of the IgG4 subtype that specifically binds and blocks the function of CD94/NKG2A.

Cetuximab is a chimeric monoclonal IgG1 antibody that is specifically directed against the EGFR. The EGFR is an important regulator of cell growth and differentiation. Upon ligand binding, EGFR homodimerizes or interacts with other HER members, ie, HER2 and HER3, to form heterodimers. This results in activation of downstream signaling cascades such as the RAS ERK pathway and PI3K/Akt pathway, thereby controlling many biological processes. These pathways play a pivotal role in multiple tumor types, including head and neck cancers,

and are frequently dysregulated via overexpression or autocrine stimulation. Targeting EGFR, eg, with an anti-EGFR mAb like cetuximab, is an important treatment modality for head and neck cancers. Several studies have suggested that ADCC activity is important for cetuximab clinical efficacy and is dependent on tumor cell surface EGFR expression (Kol et al 2017).

It has been previously demonstrated in nonclinical studies that high expression of HLA-E and CD94/NKG2A on tumor cells and effector lymphocytes, respectively, impaired ADCC activity and reduced cetuximab clinical efficacy (Levy et al 2009). NKG2A blockade with monalizumab has been shown to increase cetuximab-dependent ADCC activity, which may translate into increased clinical benefit for the use of cetuximab. Additionally, nonclinical studies have shown increased cetuximab-dependent NK cell-mediated ADCC in SCCHN cell lines expressing HLA-E and EGFR when exposed to monalizumab (Andre et al 2018). As CD94/NKG2A inhibits the effector function of NK cells in the presence of HLA-E, it is expected that blocking of this inhibitory signaling pathway with monalizumab will increase cetuximab-dependent NK cell-mediated ADCC activity, which could subsequently lead to increased clinical benefit.

A detailed description of the chemistry, pharmacology, mechanism of action, efficacy, and safety of monalizumab and cetuximab is provided in the Monalizumab IB and cetuximab (ERBITUX®) current US PI or local label (where available).

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of monalizumab and cetuximab may be found in the Monalizumab IB and current cetuximab US PI or local label (where available).

2.3.1 Risk Assessment

Potential risks for monalizumab are related to hypersensitivity, including anaphylaxis, serious allergic reactions, and immune complex disease. Administration of any therapeutic immunoglobulin antibody/protein is associated with the potential to induce infusion-related and/or hypersensitivity reactions. Infusion-related reaction is an identified risk with monalizumab. Immune-mediated adverse events are considered important potential risks for monalizumab. Activation of NK cells and subsets of T cells through blockade of inhibitory receptors may potentially lead to imAEs.

For cetuximab, skin reactions, hypomagnesemia, and infusion-related reactions are listed as very common (frequency of ≥ 10%) in the US PI or EU SmPC. Skin reaction is the most frequent side effect of cetuximab and may develop in more than 80% of patients.

Current data suggest no change to the safety profile of either product when monalizumab is given in combination with cetuximab.

Monalizumab monotherapy

Study IND.221 (NCT0259301) is a completed Phase 1/2 externally-sponsored, open-label, dose-ranging, cohort-expansion, single-agent, multicenter study of monalizumab in adult participants with R/M gynecologic malignancies who had received prior platinum-based therapy. In the dose-ranging part, up to 18 participants (6/dose level) were to be randomized to receive monalizumab 1.0, 4.0, or 10 mg/kg iv Q2W. In the cohort-expansion part, up to 40 participants were to receive monalizumab 10 mg/kg iv Q2W.

Study EORTC-1159 (NCT03088059/EudraCT 2017-000086-74) is an ongoing externally-sponsored, biomarker-driven platform study in participants with R/M SCCHN who progressed after 1L platinum-based chemotherapy. In the closed immunotherapy cohort 1, participants were to receive monalizumab 10 mg/kg iv Q2W.

In Study IND.221, Grade 3 monalizumab-related AEs were reported for Study IND.221 in 3/18 participants in the Phase 1b dose-ranging part: Grade 3 nausea, vomiting, dehydration (one participant each), and fatigue (2 participants); and in 2/40 participants in the cohort-expansion part: Grade 3 anorexia, nausea, dyspnea (one participant), and proctitis (one participant). No treatment-related Grade 4 AEs were reported. In Study EORTC-1159, none of the participants in immunotherapy cohort 1 had a Grade 3 or 4 monalizumab-related AE.

Monalizumab in combination with cetuximab

CCI

CCI

2.3.2 Benefit Assessment

While monalizumab monotherapy has shown limited clinical activity in participants with R/M SCCHN or gynecological malignancies (Tinker et al 2019a, 2019b), encouraging antitumor results have been observed following monalizumab and cetuximab combination therapy in participants with R/M SCCHN who have received prior platinum-based chemotherapy, including participants who have also received prior therapy with an ICI.

The combination of monalizumab and cetuximab demonstrated preliminary efficacy in participants with R/M SCCHN who had received prior platinum therapy (Cohen et al 2019c) (Table 3). In Cohorts 1 and 2 of Study 203 (see Section 2.3.1), participants may have received up to 2 prior systemic therapies, including platinum-based chemotherapy. Additionally, subjects in Cohort 2 were to have received prior anti-PD-(L)1 therapy. As of the DCO date of 30 April 2019, Cohort 1 completed enrollment of 40 participants with a median duration of 17 months follow-up. Of these participants, 53% were considered resistant to platinum therapy (ie, progressive disease on treatment or within 6 months after end of treatment), 53% had received more than one prior systemic regimen, and 43% had received prior PD-(L)1 inhibitor therapy (PD-[L]1 pretreated). The overall ORR per RECIST 1.1 was 27.5% (11/40 participants; 95% CI: 16%, 43%), with one CR. This represents an approximate doubling of the ORR of cetuximab monotherapy reported as 13% in participants with R/M SCCHN participants who had progressed on 2 to 6 cycles of platinum therapy (Erbitux PI 2021, Vermorken et al 2007). Median OS was 8.5 months. In PD-(L)1-pretreated participants, the ORR per RECIST 1.1 was 16.7% (3/18 participants with partial response [PR]; 95% CI: 6%, 39%), with a median OS of 14.1 months. In participants who had not received prior therapy with a PD-(L)1 inhibitor (PD-[L]1 naive), the ORR was 36.4% (8/22 participants; 95% CI: 20%, 57%), with one CR, and a median OS of 7.8 months. Preliminary data based on a recent data snapshot of 04 September 2019 from ongoing Cohort 2 in participants who had received prior platinum and prior PD-(L)1 therapy, showed an ORR of 24% (5/21 participants with PR; 95% CI: 11%, 45%). These results are consistent with the response rate seen in Cohort 1 PD-(L)1-pretreated participants.

Table 3 Preliminary Efficacy, Cohort 1 - Expansion Phase (Monalizumab + Cetuximab), All Subjects Treated (Study IPH2201-203)

Parameter	Total (N = 40)	PD-(L)1 pre-treated (N = 18)	PD-(L)1 naive (N = 22)
ORR, % (95% CI)	27.5 (16, 43)	16.7 (6, 39)	36.4 (20, 57)
Complete response	1 (2.5)	0	1 (4.5)
Partial response	10 (25.0)	3 (16.7)	7 (31.8)
Median PFS	4.5 (3.5, 5.8)	5.1 (3.5, 8.8)	3.9 (3.5, 6.9)
Median OS	8.5 (7.5, 16.4)	14.1 (8.0, NR)	7.8 (6.9, 15.8)

Participants received monalizumab 10 mg/kg iv Q2W + cetuximab at the approved dosage of 400 mg/m^2 iv initial dose followed by subsequent weekly doses of 250 mg/m^2 iv.
CI = confidence interval; NR = not reached; ORR = objective response rate; OS = overall survival; PD-(L)1 = programmed cell death-1 or programmed cell death ligand-1; PFS = progression-free survival; Q2W = every 2 weeks; iv = intravenous.
Based on a data snapshot date of 30 April 2019.

With regards to cetuximab, single-agent cetuximab is active in the treatment of participants with R/M SCCHN who progressed on platinum therapy with an ORR of approximately 13% (Vermorken et al 2007), and is listed as a recommended treatment option for SCCHN patients in the R/M setting in the latest NCCN and ESMO guidelines (Gregoire et al 2010, NCCN 2021) and SITC recommendations (Cohen et al 2019a). In the USA, the use of single-agent cetuximab is approved for R/M SCCHN progressing after platinum-based therapy (Erbitux PI 2021).

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures to minimize risk to participants in this study, the potential risks identified in association with monalizumab and cetuximab are justified by the anticipated benefits to participants with R/M SCCHN who have been previously treated with platinum-based chemotherapy and an ICI.

3 OBJECTIVES AND ENDPOINTS

Table 4 Objectives and Endpoints

Objective	Estimand [a] Description/Endpoint
Primary	
To compare the effect of monalizumab and cetuximab (Arm A) relative to placebo and cetuximab (Arm B) by assessment of OS in HPV-unrelated participants	• Population: The HPV-unrelated Analysis Set which will include all randomized participants who are either OPC HPV negative or non-OPC regardless of HPV status • Endpoint: OS, which is defined as time from randomization until the date of death due to any cause • Intercurrent events: If a participant is lost to follow-up or withdraws consent, OS will be censored based on the last recorded date on which the participant was known to be alive • Summary measure: p-value of treatment comparison using a stratified log rank test and hazard ratio of Arm A relative to Arm B with its confidence interval using a stratified Cox Proportional Hazards model
Secondary	
To compare the effect of monalizumab and cetuximab (Arm A) relative to placebo and cetuximab (Arm B) by assessment of OS in all randomized participants	• Population: The FAS which will include all randomized participants • Endpoint: OS, which is defined as time from randomization until the date of death due to any cause • Intercurrent events: If a participant is lost to follow-up or withdraws consent, OS will be censored based on the last recorded date on which the participant was known to be alive • Summary measure: p-value of treatment comparison using a stratified log rank test and hazard ratio of Arm A relative to Arm B with its confidence interval using a stratified Cox Proportional Hazards model
To compare the effect of monalizumab and cetuximab (Arm A) relative to placebo and cetuximab (Arm B) by assessment of PFS, ORR, and DoR in participants who are HPV-unrelated and in all randomized participants	• PFS is defined as time from randomization until disease progression, per RECIST 1.1 as assessed by the investigator at local site or death due to any cause, whichever occurs first. • ORR is defined as the proportion of participants with measurable disease who have a confirmed CR or PR, as determined by the investigator at local site per RECIST 1.1. • DoR is defined as the time from the date of first documented response until date of documented disease progression or death in the absence of disease progression.

Table 4 Objectives and Endpoints

Objective	Estimand [a] Description/Endpoint
To assess disease-related symptoms, functioning, and HRQoL in participants treated with monalizumab and cetuximab (Arm A) compared to placebo and cetuximab (Arm B) using the EORTC QLQ-C30 and the EORTC QLQ-H&N35 questionnaires in participants who are HPV-unrelated and in all randomized participants	Symptoms, functioning, and global health status/QoL scale/item scores of the EORTC QLQ-C30 & EORTC QLQ-H&N35 • Change from baseline scores across visits • Time to clinically meaningful deterioration in scores
To assess the PK of monalizumab	Concentration of monalizumab in blood and PK parameters (such as C_{max}, C_{trough}, as data allow; sparse sampling)
To investigate the immunogenicity of monalizumab	Presence of ADAs for monalizumab (confirmatory results: positive or negative, titers)
To characterize the association between clinical outcome and protein expression in the tumor microenvironment in participants treated with monalizumab and cetuximab (Arm A) or placebo and cetuximab (Arm B) in participants who are HPV-unrelated and in all randomized participants	HLA-E and NKp46+ expression in pre-treatment and post-treatment tumor biopsies
Secondary safety	
To assess the safety and tolerability of monalizumab and cetuximab (Arm A) compared to placebo and cetuximab (Arm B) in participants with R/M SCCHN previously treated with ICI	AEs, vital signs, clinical laboratory results, ECGs
Exploratory	
CCI	

Table 4 Objectives and Endpoints

Objective	Estimand [a] Description/Endpoint
CCI	

[a] Estimand is the target of estimation to address the scientific question of interest posed by the primary objective. Attributes of an estimand include the population of interest, the variable (or endpoint) of interest, the specification of how intercurrent events are reflected in the scientific question of interest, and the population-level summary for the variable.

ADA = antidrug antibodies; AE = adverse event; C_{max} = maximum serum concentration; CR = complete response; CCI C_{trough} = trough serum concentration; DoR = duration of response; ECG = electrocardiogram; EORTC = European Organisation for Research and Treatment of Cancer; CCI FAS = full analysis set; HLA-E = human leukocyte antigen E; CCI HRQoL = health-related quality of life; ICI = immune checkpoint inhibitor; NK = natural killer; OPC = oropharyngeal cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; CCI CCI CCI PK = pharmacokinetic(s); PR = partial response; CCI QLQ-C30 = 30-item Core Quality of Life Questionnaire; QLQ-H&N35 = Quality of Life Questionnaire Head and Neck Module; RECIST 1.1 = Response Evaluation Criteria for Solid Tumors version 1.1; R/M = recurrent or metastatic; SCCHN = squamous cell carcinoma of the head and neck; CCI .

4 STUDY DESIGN

4.1 Overall Design

Study D7310C00001 is a Phase 3, randomized, double-blind, multicenter, global study assessing efficacy and safety of monalizumab and cetuximab compared to placebo and cetuximab in participants with R/M SCCHN previously treated with platinum-based

chemotherapy and an ICI, regardless of the sequence of these therapies.

Approximately 624 eligible participants will be randomized in a 2:1 ratio to one of the following treatment arms.

- Arm A (n = 416): monalizumab and cetuximab
  Monalizumab [redacted] and cetuximab 400 mg/m^2 iv initial dose followed by 250 mg/m^2 iv Q1W, as per label
- Arm B (n = 208): placebo and cetuximab
  Placebo iv Q2W and cetuximab 400 mg/m^2 iv initial dose followed by 250 mg/m^2 iv Q1W, as per label

Participants will be stratified by the following (see Section 6.3.1 for more detail):

- Human papillomavirus status (OPC HPV positive or HPV-unrelated),
  - The number of OPC HPV-positive participants will be closely monitored throughout the study and is planned to be capped at approximately 20% of the total sample size.
- World Health Organization/ECOG PS (0 or 1), and
- Number of prior lines of therapy in the R/M setting (1 or 2)
  - The number of participants in each stratum (1 or 2 prior lines of therapy in the R/M setting) will be closely monitored throughout the study. If a disproportionate number of participants are enrolled in a single stratum (eg, > 75% of the total sample size), the Sponsor may elect to close further recruitment into that stratum.

Participants will be treated until RECIST1.1-defined radiological disease progression per investigator, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Crossover between treatment arms will not be permitted.

An IDMC will review safety data regularly and make recommendations regarding further study conduct (see Appendix A 5). For both IAs, the IDMC will review unblinded interim data and inform the Sponsor whether the interim boundaries specified in Section 9.5 are met.

After discontinuation of study intervention, all participants will have a 3-month safety follow-up (see Section 7.1.1). Participants who have discontinued study intervention in the absence of RECIST 1.1-defined radiological disease progression per investigator will continue with scheduled tumor assessments until RECIST 1.1-defined disease progression or death. Additionally, all participants will be followed for survival status, subsequent anticancer therapy, and [redacted], withdrawal of consent, or the end of the study.

An overview of the study design is presented in Figure 1. Details on the efficacy and safety

endpoints are provided in Section 3.

Section 6.7 presents treatment options after the final DCO and database closure.

4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with GCP, and minimize risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent/re-consent for the mitigation procedures (note, in the case of verbal consent/re-consent, the ICF should be signed at the participant's next contact with the study site).
- Rescreening: additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The investigator should confirm this with the designated Study Clinical Lead.
- Telemedicine or Remote visit (where applicable): remote contact with the participants using telecommunications technology including phone calls and virtual or video visits.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix C.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Study Design and Participant Population

The primary aim of this study is to assess the efficacy of monalizumab and cetuximab compared to cetuximab and placebo in terms of OS. It is a double-blind, randomized study CCI [redacted]; unblinded Pharmacists and unblinded Study Monitors will be used in order to maintain the blind.

Preliminary data show that the combination monalizumab and cetuximab is well tolerated (Cohen et al 2017, Cohen et al 2018a, Cohen et al 2018b) and has promising activity. As the estimated percentage of patients with cancer eligible for ICI (including but not limited to anti-PD-(L)1 antibodies) in the course of their disease is increasing, it is crucial to confirm the activity seen with monalizumab administered in combination with cetuximab in population of patients who have previously received ICI.

Participants enrolled in this study will have R/M SCCHN arising in the oropharynx regardless of HPV status, hypopharynx, larynx (supraglottis, glottis, and subglottis) or oral cavity; must have progressed on or after previous systemic cancer therapy (up 2 prior systemic regimens in the R/M setting); are not amenable to further therapy having curative intent; and must have received prior treatment with platinum-based chemotherapy and a systemic PD-(L)1 inhibitor in any setting, regardless of the sequence of these therapies (see inclusion criteria in Section 5.1).

Since HPV-positive OPC represents a biologically distinct disease (Taberna et al 2017), the study design proposed is considered the best approach to evaluate the contribution of monalizumab to cetuximab because the combination therapy will be compared directly to single-agent cetuximab in HPV-unrelated participants. Cetuximab is a valid treatment option for the study population per the revised NCCN and current ESMO guidelines (Gregoire et al 2010, NCCN 2021) and SITC recommendations (Cohen et al 2019a).

4.2.2 Rationale of Study Endpoints

Rationale for primary endpoint and other efficacy endpoints

The primary endpoint of the proposed study will be OS, defined as the time from the date of randomization until death due to any cause. Overall survival is considered the most reliable cancer endpoint supported by the US FDA and EMA guidelines (EMA 2017, FDA 2018a).

Rationale for other efficacy endpoints

The secondary efficacy endpoints will include PFS, ORR, DoR, and PRO measures. All tumor-related endpoints will be assessed by the investigator according to RECIST 1.1.

Target engagement of monalizumab will be assessed through HLA-E and NKp46+ expression in the TME and association with the participant's radiologic response.

In addition to assessing OS and other clinical endpoints in oncology studies, it is important to assess the impact of the disease and its treatment on cancer symptoms, functioning, and HRQoL of the patient, to aid understanding of how clinical benefit relates to patient wellbeing, and for consideration in making risk-benefit evaluations. Moreover, PROs assist in the documentation of symptoms and specifically what symptoms and impacts are most

important to patients and how these relate to clinical outcomes. In this study, general cancer symptoms, functioning and HRQoL will be assessed with the EORTC QLQ-C30 while SCCHN-specific symptoms will be evaluated using the EORTC QLQ-H&N35. CCI [redacted] CCI The rationale for selecting the EORTC QLQ-C30 and QLQ-H&N35 and other PRO instruments is primarily because they have good coverage of the symptoms and impacts most important to SCCHN patients (Degboe et al 2018). These PRO questionnaires are also well established in oncology clinical studies for directly assessing patients' experience of cancer as well as the treatment impact.

4.3 Justification for Dose

4.3.1 Rationale for Monalizumab Dose

Existing PK and pharmacodynamic data, modeling and simulation, and clinical data have been utilized to guide the regimen selection for the combination of monalizumab CCI plus cetuximab at 400 mg/m^2 initial dose followed by 250 mg/m^2 Q1W. See the Monalizumab IB for more detail on monalizumab PK, pharmacodynamics, immunogenicity, and clinical activity.

Available PK/pharmacodynamic data were analyzed from ongoing Phase 1/2 Study D419NC00001 for monalizumab doses ranging from CCI to CCI or CCI in combination with durvalumab 1500 mg Q4W. An approximate dose-proportional increase in PK exposure (C_{max} and area under the serum drug concentration-time curve from time 0 to Day 28 post-dose) was observed with increasing doses of monalizumab (CCI and CCI). Full suppression of the target on NK cell in the periphery was observed over the dose range studied, consistent with engagement of monalizumab with NKG2a.

Pharmacokinetic data from the dose-escalation cohort in ongoing Phase 1b/2 Study IPH2201-203 (Study 203) of monalizumab CC to CCI in combination with cetuximab 400 mg/m^2 initial dose followed by 250 mg/m^2 Q1W showed an approximate dose-proportional increase in monalizumab C_{max} over the dose range for the first dosing cycle. These data were consistent with the predicted monotherapy PK data (5th, 50th, and 95th percentiles) for a Q2W regimen.

Antidrug antibody analyses of serum samples from treated participants in Study D419NC00001 and Study 203, showed a low ADA signal, close to the screening cut point, for all ADA-positive samples, suggesting either false positive result or low ADA concentration. PK profiles for participants with ADA-positive samples were not modified, indicating that ADA did not impact monalizumab exposure.

Clinical data

A tolerable safety profile was observed for participants in Study 203 Cohorts 1 and 2 treated with monalizumab [redacted] or [redacted] respectively, plus cetuximab 400 mg/m^2 initial dose followed by 250 mg/m^2 Q1W. Promising clinical activity was observed in Cohort 1, with consistent preliminary results from ongoing Cohort 2.

Based on these data, the combination of monalizumab [redacted] plus cetuximab 400 mg/m^2 initial dose followed by 250 mg/m^2 Q1W was selected for further development. This dose is expected to achieve complete target saturation in the majority of participants and account for anticipated variability in PK, pharmacodynamics, and clinical activity in SCCHN populations.

Rationale for fixed-dose of monalizumab

Current ongoing studies with the combination of monalizumab and cetuximab administer monalizumab using either weight-based dosing (ie, monalizumab [redacted]; Study 203 Cohort 1) or [redacted] dosing (ie, monalizumab [redacted] Study 203 Cohort 2 and Study D419NC00001).

Comparison of the observed monalizumab exposure between [redacted] and [redacted] showed similar preliminary PK exposure (C_{max} and C_{trough}) after the first monalizumab dose for the [redacted] dosage (monalizumab in combination with cetuximab, Study 203 Cohort 1) and the [redacted] dosage (monalizumab in combination with durvalumab, Study D419NC00001). The observed PK of monalizumab when administered in combination with cetuximab is within the range of monalizumab monotherapy PK.

A population PK model was developed for monalizumab using PK data from Study 203 and Study D419NC00001 in participants with solid tumors, including SCCHN, microsatellite-stable colorectal cancer, ovarian cancer, endometrial cancer, non-small cell lung cancer, cervical cancer, or pancreatic cancer. At the time of analysis, a total of 95 evaluable participants treated with monalizumab [redacted] or [redacted] in combination with cetuximab (N = 30; Study 203) or monalizumab [redacted], or [redacted] or [redacted] [redacted] in combination with durvalumab (N = 65; Study D419NC00001) were used for building the preliminary population PK model. To determine the impact of body weight-based ([redacted]) or [redacted] dosing ([redacted]) on monalizumab PK exposure, simulations were conducted (N = 500 participants/cohort with a body-weight distribution of 40 to 120 kg) and predicted steady state concentrations were compared. A [redacted] dose of [redacted] was selected to approximate [redacted] based on the median body weight of 75 kg. Simulation results demonstrated that body weight-based and [redacted]-dosing regimens yield similar steady-state PK concentrations with similar overall between-participant variability. The predicted similarity of exposure following either of the dosing regimen is consistent with literature showing that an

exponent of the covariate model for body weight of approximately 0.5 is expected to yield similar median PK profiles without following either [redacted] or body weight-based dosing (Wang et al 2009). Therefore, based on an average body weight of 75 kg, a [redacted] dose of [redacted] monalizumab is equivalent to [redacted] respectively.

The proposed Phase 3 study of monalizumab in combination with cetuximab, will use the [redacted] dose of monalizumab [redacted] This dosing regimen is aligned with the standard flat dosing of monalizumab [redacted] being investigated in the multiple ongoing monalizumab clinical studies (see Monalizumab IB).

4.3.2 Rationale for Cetuximab Dose

The dose regimen for cetuximab in this study (400 mg/m^2 initial dose followed by 250 mg/m^2 Q1W starting on Day 8) is per the cetuximab US PI (Erbitux PI 2021).

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the SoA (Section 1.3). Participants will be followed for survival status until death, withdrawal of consent, or the end of the study.

The end of the study is defined as the date of the last visit of the last participant in the study globally.

The study may be stopped if, in the judgment of the Sponsor, participants are placed at undue risk because of clinically significant findings.

See Section 6.7 for details on participant management following the final DCO as well as following study completion.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1 Participant must be ≥ 18 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 Histologically or cytologically confirmed R/M SCCHN of the oral cavity, oropharynx, hypopharynx, or larynx who have progressed on or after previous systemic cancer therapy and are not amenable to curative therapy

3 Must have received prior treatment with a systemic PD-(L)1 inhibitor (in any setting)

4 Prior platinum failure as defined by either:

- Disease progression during or after treatment with a platinum-containing regimen for R/M disease or
- Recurrence/progression within 6 months of the last dose of platinum as part of multimodal therapy for LA disease

5 Received 1 or 2 prior systemic regimens for R/M SCCHN (see Section 6.3.1 for additional detail on prior lines of therapy)

6 At least one lesion that qualifies as a RECIST 1.1 TL at baseline (see Appendix G). Tumor assessment by CT scan or MRI must be performed within 28 days prior to randomization.

7 Provide fresh or recently acquired tumor tissue (≤ 3 months prior to screening) for the purpose of biomarker testing. Tumor tissue collected when previous treatments were still ongoing is not acceptable.

- Tumor tissue beyond the 3-month window and up to 6 months old may be considered with Sponsor consultation provided that no intervening systemic regimen was ongoing at the time of sample collection (see Laboratory Manual for more information).

8 For participants with OPC only: known HPV status prior to randomization (see Section 6.3.1)

9 WHO/ECOG PS of 0 or 1 at enrollment

10 Adequate organ function, defined as:

(a) Hemoglobin ≥ 9.0 g/dL

(b) Absolute neutrophil count ≥ 1500/mm^3

(c) Platelets ≥ 75,000/mm^3

(d) Total bilirubin ≤ 1.5 × institutional ULN. This will not apply to participants with confirmed Gilbert's syndrome, who will be allowed in consultation with their physician.

(e) Aspartate aminotransferase and ALT ≤ 2.5 × institutional ULN; for participants with hepatic metastases, ALT and AST ≤ 5 × ULN

(f) Measured CrCL ≥ 30 mL/min or calculated CrCL ≥ 30 mL/min as determined by Cockcroft-Gault (using actual body weight)

- Males:
  $$\text{CrCL(mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$
- Females:
  $$\text{CrCL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age}) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

11 Minimum life expectancy of 12 weeks

Weight

12 Body weight > 30 kg

Sex

13 Male and/or female

Reproduction

14 Negative pregnancy test ("highly effective" urine or serum test) for female participants of childbearing potential.

15 Female participants must be one year post-menopausal, surgically sterile, or using an acceptable method of contraception (see Appendix H) for the duration of the study (from the time they sign consent) and for 4 months after the last dose of study intervention to prevent pregnancy.

16 Male participants must be surgically sterile or using an acceptable method of contraception (see Appendix H) for the duration of the study (from the time they sign consent) and for 4 months after the last dose of study intervention to prevent pregnancy in a female partner. Male participants must not donate or bank sperm during the same time period.

Informed Consent

17 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this protocol

18 Provision of signed and dated, written ICF prior to any mandatory study specific procedures, sampling, and analyses

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5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

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 participants with squamous cell carcinoma of unknown primary or non-squamous histologies (eg, nasopharynx or salivary gland)

2 Prior cetuximab therapy (unless it was administered in curative LA setting with radiotherapy and no disease progression for at least 6 months following the last cetuximab dose)

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

   – Participants with irreversible toxicity not reasonably expected to be exacerbated by treatment with monalizumab and cetuximab may be included only after consultation with the Study Clinical Lead.

4 Has carcinomatous meningitis and/or untreated central nervous system metastases identified either on the baseline brain imaging (see Appendix G) obtained during the screening period or identified prior to signing the ICF. Participants with a history of brain metastases or with suspected brain metastases at screening must have an MRI (preferred) or CT each preferably with iv contrast of the brain prior to study entry. Participants whose brain metastases have been treated may participate provided they show radiographic stability (defined as 2 brain images, both of which are obtained after treatment to the brain metastases. These imaging scans should both be obtained at least 4 weeks apart and show no evidence of intracranial progression). In addition, any neurologic symptoms that developed either as a result of the brain metastases or their treatment must have resolved or be stable either, without the use of steroids, or are stable on a steroid dose of ≤ 10 mg/day of prednisone or its equivalent and anticonvulsants for at least 14 days prior to the start of treatment. Brain metastases will not be recorded as RECIST 1.1 TL at baseline.

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

6 History of allogeneic organ transplantation

7 History of allergic reactions or hypersensitivity attributed to compounds of similar chemical or biologic composition to cetuximab and monalizumab or any of their excipients

8 History of active primary immunodeficiency

9 Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:
   - Participants with vitiligo or alopecia
   - Participants with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement
   - Any chronic skin condition that does not require systemic therapy
   - Participants without active disease in the last 5 years may be included but only after consultation with the Study Clinical Lead
   - Participants with celiac disease controlled by diet alone

10 Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), **hepatitis B** (known positive HBV surface antigen [HBsAg] result), **hepatitis C** (HCV), or **human immunodeficiency virus** (positive HIV 1/2 antibodies). Participants with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Participants positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

11 Uncontrolled intercurrent illness, including but not limited to: ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, uncontrolled cardiac arrhythmia, active interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the participant to give written informed consent

12 History of another primary malignancy except for:
   - Malignancy treated with curative intent and with no known active disease ≥ 5 years before the first dose of study treatment and of low potential risk for recurrence
   - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
   - Adequately treated carcinoma in situ without evidence of disease

- Participants with a history of prostate cancer (tumor/node/metastasis stage) of Stage ≤ T2cN0M0 without biochemical recurrence or progression and who in the opinion of the investigator are not deemed to require active intervention

13 Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥ 500 ms calculated from 3 ECGs (see Section 8.2.3)

Prior/Concomitant Therapy

14 Any concurrent anticancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is allowed.

15 Receipt of the last dose of anticancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, mAbs, or investigational agents) or radiotherapy with curative intent (to more than 30% of the bone marrow or with a wide field of radiation) ≤ 28 days prior to the first dose of study intervention. If sufficient wash-out time has not occurred due to the schedule or PK properties of an anticancer agent, a longer wash-out period will be required, as agreed by the Sponsor and the investigator.

16 Current or prior use of immunosuppressive medication within 14 days before the first dose of study intervention. The following are exceptions to this criterion (see also Table 6):

- 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 premedication for hypersensitivity reactions (eg, CT scan premedication)

17 Receipt of live attenuated vaccine within 30 days prior to the first dose of study intervention.
Note: Participants, if enrolled, should not receive live vaccine whilst receiving study intervention and up to 30 days after the last dose of study intervention.

Prior/Concurrent Clinical Study Experience

18 Participation in another clinical study with an investigational product administered in the last 28 days prior to randomization or concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study

19 Prior treatment with monalizumab

Other Exclusions

20 Involvement in the planning and/or conduct of the study (applies to both Sponsor staff and/or staff at the study site).

21 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions and requirements.

22 Previous study intervention assignment in the present study.

23 For women only - currently pregnant (confirmed with positive pregnancy test) or breast-feeding.

24 Genetics research study (optional):

Exclusion criteria for participation in the optional (DNA) genetics research component of the study include:

- Previous allogeneic bone marrow transplant
- Transfusion of non-leukocyte-depleted blood or blood components within 120 days of genetic sample collection

5.3 Lifestyle Considerations

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

1 Participants must follow the contraception requirements outlined in Appendix H.

2 Participants should not donate blood or blood components while participating in this study and through 4 months after the last dose of study intervention.

3 Women must not breastfeed during the study, and for 4 months after the last dose of study intervention.

Restrictions relating to concomitant medications are described in Section 6.5.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but do not fulfill the eligibility criteria, and therefore must not be randomized. These participants should have the reason for study withdrawal recorded as “eligibility criteria not fulfilled” (ie, participant does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (ie, not randomized participants).

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE. If a pre-screened

tissue and/or whole blood/serum/plasma sample has already been procured prior to screen failure, a biomarker evaluation will be conducted if feasible (consistent with the ICF).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened a single time, but they may not be re-randomized. Rescreened participants should be assigned the same E-code as for the initial screening. Participants will reconfirm their consent to participate in the study by re-signing and dating their original ICF(s), next to their original signature and date, or according to local or site-specific procedures. All assessments must be repeated for rescreening unless they are within 28 days of randomization.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Interventions Administered

6.1.1 Investigational Medicinal Products

Table 5 Investigational Medicinal Products

Intervention name	Monalizumab	Cetuximab	Placebo
Type	Biologic	Biologic	Drug
Dose formulation	CCI	As sourced by AstraZeneca, cetuximab will be supplied as a liquid solution containing 5 mg/mL cetuximab, sodium chloride, glycine, polysorbate 80, citric acid monohydrate, sodium hydroxide, and WFI. If cetuximab is sourced locally it will be as the approved commercial product.	CCI
Unit dose strength(s)		500 mg (nominal) cetuximab per vial as sourced by AstraZeneca. Cetuximab will be locally	

Table 5 Investigational Medicinal Products

Intervention name	Monalizumab	Cetuximab	Placebo
		sourced as the approved commercial product.	
Dosage level(s)	CCI [redacted]	Initial dose: 400 mg/m2 Subsequent doses: 250 mg/m2 Q1W	CCI [redacted]
Route of administration		iv infusion	
Use	Experimental	Experimental/Active comparator	Placebo
IMP and NIMP	IMP	IMP	IMP
Sourcing	AstraZeneca	AstraZeneca source centrally or locally sourced where feasible	Sourced locally by site
Packaging and labelling	CCI [redacted]	Each vial will be labelled in accordance with GMP Annex 13 and per country regulatory requirement.	CCI [redacted]
Current/Former name(s) or alias(es)	IPH2201	Erbitux®	Not applicable

CCI [redacted] IMP = investigational medicinal product; NIMP = non-investigational medicinal product; CCI [redacted].

6.1.2 Dosing Instructions

A physician must be present at the site or immediately available to respond to emergencies during all administrations of IMP. Fully functional resuscitation facilities should be available. As with any mAb, allergic reactions to dose administration are possible. Therefore, 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. See Section 6.6 and Section 8.3.15 for dose modification and management of IMP-related toxicities, respectively.

Section 6.2.1 describes dose preparation and administration.

Permissible medications prior to administration of monalizumab or cetuximab are described in Section 6.5.1. No premedication is required prior to monalizumab administration, unless a

participant has experienced an infusion-related AE in the previous cycle. For cetuximab, participants should be premedicated per US PI (antihistamine iv 30 to 60 minutes prior to the first infusion or subsequent infusions of cetuximab as deemed necessary) or local label (where available). Premedication may also be based on institutional guidance for management of infusion-related reactions.

Dosing regimen

The dosing regimen for Arm A and Arm B is presented in Figure 2 (see also SoA Table 1).

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CCI

CCI

CCI

CCI

6.1.3 Duration of Treatment

All study intervention will be administered beginning on Day 1. Participants in Arm A or Arm B will remain on study intervention until RECIST 1.1-defined radiological disease progression (refer to Appendix G) unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. See Section 7.1 for information on discontinuation of study intervention for individual participants.

A follow-up scan is to be collected after the initial RECIST 1.1-defined disease progression, preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of disease progression (Eisenhauer et al 2009). This follow-up scan is evaluated using the Confirmation of Radiological Progression criteria outlined in Appendix G.

6.2 Preparation/Handling/Storage/Accountability of Interventions

1 The investigator or designee (eg, unblinded pharmacist) must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are to be reported and resolved before use of the study intervention.

2 Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

3 The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

4 Further guidance and information for the final disposition of unused study interventions will be provided to the sites.

All IMPs should be stored in a secure and dry place. Vials of IMP for parenteral administration should be stored at 2 °C to 8 °C (36 °F to 46 °F; refrigerated) and must not be frozen. IMP must be kept in original packaging until use to prevent prolonged light exposure.

Placebo will be locally sourced by the study site and cetuximab will either be locally sourced by the study site or centrally supplied by the Sponsor. When centrally supplied, cetuximab will be labeled with local language translated text in accordance with regulatory guidelines.

6.2.1 Dose Preparation and Administration

6.2.1.1 Monalizumab

The dose of monalizumab for administration must be prepared by the investigator's or site's designated IMP manager using aseptic technique. CCI [redacted]

CCI [redacted]

CCI [redacted]

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

The iv line will be flushed according to local practices to ensure the full dose is administered. Infusion time does not include the final flush time.

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

6.2.1.2 Cetuximab

The dose of cetuximab for administration must be prepared by the investigator's or site's designated IMP manager using aseptic technique. See the Pharmacy Manual for guidance on cetuximab storage conditions, dose preparation, and dose administration. See Section 6.1.2 for the cetuximab dosing regimen.

6.2.1.3 Placebo

CCI

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

The iv line will be flushed according to local practices to ensure the full dose is administered. Infusion time does not include the final flush time.

If either preparation time or infusion time exceeds the time limits, a new placebo dose must be prepared.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Participant Enrollment and Randomization

Participants will be randomized in a 2:1 ratio to Arm A or Arm B.

Randomization will be stratified by

- Human papillomavirus status (OPC HPV positive or HPV-unrelated),
  - The number of OPC HPV-positive participants will be closely monitored throughout the study and is planned to be capped at approximately 20% of the total sample size.
- World Health Organization/ECOG PS (0 or 1), and
- Number of prior lines of therapy in the R/M setting (1 or 2)
  - The number of participants in each stratum (1 or 2 prior lines of therapy in the R/M setting) will be closely monitored throughout the study. If a disproportionate number of participants are enrolled in a single stratum (eg, > 75% of the total sample size), the Sponsor may elect to close further recruitment into that stratum.

All participants will be centrally assigned to randomized study intervention using an IRT. Before the study is initiated, user guides, the log in information, and directions for the IRT will be provided to each site.

If participants withdraw from the study, then their randomization codes cannot be reused. Withdrawn participants will not be replaced.

Investigators should keep a record (ie, the participant screening log) of participants who entered screening.

At screening/baseline (Days -28 to -1), the investigators or suitably trained delegate will:

- Obtain signed informed consent before any study-specific procedures are performed. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the participants. However, all screening laboratory and imaging results must have been obtained within 28 days of randomization.
- Have participants identified to the IRT per country regulations. A unique 7-digit enrollment number (E-code) will be obtained, through the IRT in the following format (ECCNNXXX: CC being the country code, NN being the center number, and XXX being the participant enrollment code at the center). This number is the participant's unique identifier and is used to identify the participant on the eCRFs.
- Obtain a tumor tissue sample for determination of HLA-E and NKp46 expression (see Section 8.6.1).
- Determine participant eligibility (see Section 5.1 and Section 5.2).
- Determine HPV status (positive or negative) for participants with OPC for purposes of stratification. HPV status will be assessed using local testing by IHC analysis with CINtec® Histology p16 assay. Positive p16 IHC expression is defined as 70% or more of cytoplasmatic and nuclear staining of the tumor cells. Should the CINtec Histology assay not be available at a local institution, a tumor tissue sample should be submitted to the central laboratory for HPV assessment (details are provided in the Laboratory Manual).
- Determine WHO/ECOG PS (0 or 1)
- Determine the number of prior lines of therapy in the R/M setting (1 or 2) for stratification purposes.
  - For participants with LA disease previously treated with platinum (cisplatin/carboplatin) as part of multimodality therapy and progressed during or within 6 months after the last platinum dose, this will be considered as one line of therapy in the R/M setting.
- CCI [redacted]. Participants who decide CCI to sign CCI [redacted] the general study ICF, are eligible for study enrollment and all other study procedures.

At randomization, once the participant is confirmed to be eligible, the investigator or suitably

trained delegate will:

- Obtain a randomized treatment arm via the IRT. Randomization codes will be assigned strictly sequentially within each stratum and site/country/region as participant become eligible for randomization. The system will randomize the eligible participant to one of the 2 treatment arms.

If the participant is ineligible and not randomized, the IRT should be accessed to terminate the participant in the system.

Participants will begin treatment on Day 1. Every effort should be made to minimize the time between randomization and starting study intervention. It is strongly recommended that participants commence study intervention on the same day as randomization by IRT. If same-day treatment is not possible, then study intervention must occur within 2 days of randomization. Participants must not be randomized and treated unless all eligibility criteria have been met.

6.3.2 Procedures for Handling Incorrectly Enrolled or Randomized Participants

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

Where a participant does not meet all the eligibility criteria but is randomized in error, or incorrectly started on study treatment, the investigator should inform the Study Clinical Lead immediately, and a discussion should occur between the Study Clinical Lead and the investigator regarding whether to continue or discontinue the participant from study intervention. The Study Clinical Lead must ensure all decisions are appropriately documented and that the potential benefit/risk profile remains positive for the participant.

6.3.3 Methods for Assigning Treatment Arms

The actual treatment given to participants will be determined by the randomization scheme in the IRT. 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 randomization will be balanced within the IRT at the site/country/region/central level.

Randomization codes will be assigned strictly sequentially, within each stratum, as participants become eligible for randomization. The IRT will provide the kit identification

number for centrally supplied IMP to be allocated to the participant at the randomization visit and subsequent treatment visits.

6.3.4 Methods for Ensuring Blinding

The study will be conducted in a double-blind manner.

Monalizumab placebo CCI [redacted] will be prepared by the unblinded pharmacist. The participant, the investigator, and study center staff will be blinded to treatment arm allocation and will remain blinded to each participant's assigned study treatment throughout the course of the study. To maintain this blind, an otherwise uninvolved third party (ie, the unblinded pharmacist) will be unblinded to treatment allocation and will prepare monalizumab or placebo for a participant as specified by the randomization scheme and IRT (the unblinded pharmacist will be the only member of investigator site staff to know the randomization/treatment allocation details).

The IRT will provide to the investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit. Pharmacists will be given specific instructions for monalizumab/placebo preparation and will note if the double-blind conditions have been compromised or the blind has been broken. Lot numbers of monalizumab dispensed will be recorded by the pharmacist and monitored by an unblinded monitor. Other blinded study center staff and monitors will not be given access to lot number information. Blinded and unblinded access and notifications will be controlled using the IRT.

Routines for this will be described in the IRT user manual that will be provided to each center.

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization. The investigator documents and reports the action to the Sponsor, without revealing the treatment given to the participant to the Sponsor staff.

The Sponsor retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IMP and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

No member of the extended study team at the Sponsor, at the investigational centers, or any blinded CRO handling data will have access to the randomization scheme until the time of the final analysis or any IA data where a decision is made to unblind the study. At such time, the Sponsor and any CRO handling data will have access to the randomization scheme. Exceptions are relevant persons within the Pharmaceutical Development Supply Chain at AstraZeneca or their designee, where the information is needed to package the study

intervention; the drug safety departments at AstraZeneca; and the pharmacists required to dispense the study intervention at the study site. Investigators will be unblinded to treatment allocation only in cases of medical emergency. Additionally, at the request of the investigator, at progression of disease, the participant can be unblinded.

The treatment codes and results will be kept strictly within AstraZeneca to safeguard the integrity of the blind and hence to minimize any possible bias in data handling.

In the event that the treatment allocation for a participant becomes known to the investigator or other study staff involved in the management of study participants, or needs to be known to treat an individual participant for an AE, the Sponsor must be notified promptly by the investigator and, if possible, before unblinding.

The IRT will be programmed with blind-breaking instructions. The blind may be broken if, in the opinion of the investigator, it is in the participant's best interest for the investigator to know the study treatment assignment. The Sponsor must be notified before the blind is broken unless identification of the study intervention is required for a medical emergency in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition (eg, antidote available). In this case, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable. Study unblinding should occur after database lock, once all decisions on the evaluability of the data from each individual participant have been made and documented.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. This information, plus drug accountability for all study interventions at every visit, will be used to assess compliance. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Any change from the dosing schedule, dose delays/interruptions, and dose discontinuations should be recorded in the eCRF. Dose modifications for monalizumab/placebo and cetuximab are permitted per the guidelines described in Section 6.6.

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

The Investigator Product Storage Manager is responsible for managing the IMP from receipt by the study site until destruction of all unused IMP.

6.5 Concomitant Therapy

Any concomitant treatment, procedure, or medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the participant is receiving according to the schedule in the SoA (Section 1.3) must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Study Clinical Lead should be contacted if there are any questions regarding concomitant or prior therapy.

If any concomitant therapy is administered due to new or unresolved AE, it should be recorded.

Participants must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

Prohibited and permitted concomitant medications/therapies are described in Table 6 and Table 7, respectively. Refer also to the guidelines for management of IMP-related toxicities in Section 8.3.15. For cetuximab, refer to the local label (where available) with regard to warnings, precautions, and contraindications.

Table 6 Prohibited Concomitant Medication/Therapy

Type of medication/treatment	Timeline/Instructions
Any investigational therapy other than those under investigation in this study	Until end of study treatment.
Any concurrent chemotherapy, radiotherapy, immunotherapy (including other monoclonal antibodies), or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Until end of study treatment. Concurrent use of hormones for non-cancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable (eg, by local surgery or radiotherapy)

Table 6 Prohibited Concomitant Medication/Therapy

Type of medication/treatment	Timeline/Instructions
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly or used for premedication prior to the infusions of IMP. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IMP-related adverse events or infusion-related reactions • Short-term premedication for cetuximab where the local label requires the use of steroids • Short-term premedication for monalizumab/placebo following > Grade 2 infusion-related reaction at the previous cycle (see monalizumab TMG) • Use in participants with contrast allergies • Use of inhaled, topical, and intranasal corticosteroids A temporary period of steroid use will be permitted if clinically indicated and considered to be essential for the management of non-immunotherapy-related events experienced by the participant (eg, chronic obstructive pulmonary disease, radiation, nausea, etc).
Live attenuated vaccines	Within 30 days prior to the first dose of IMP, whilst receiving IMP and up to 30 days after the last dose of IMP.
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the Sponsor

IMP = investigational medicinal product.

Table 7 Permitted Concomitant Medication/Therapy

Type of medication/treatment	Timeline/Instructions
All necessary supportive care in the form of treatment or prophylaxis as clinically indicated eg, transfusion of blood products, antibiotics, anti-histamines, analgesics	Throughout the study
Vaccines limited to non-live attenuated preparations (eg, influenza vaccine) See Appendix C for vaccination against COVID-19	Throughout the study

COVID-19 = coronavirus disease 2019.

6.5.1 Permitted Medication Prior to Study Intervention

Monalizumab

No premedication is required prior to monalizumab administration. However, from Cycle 2, premedication with acetaminophen and/or an antihistamine drug might be prescribed, at the investigator's discretion, if the participant experienced any Grade 1 to 3 infusion-related AE at

the previous cycle (see monalizumab TMG provided as a supplement to the CSP).

Cetuximab

Participants should be premedicated per US PI (antihistamine iv 30 to 60 minutes prior to the first infusion or subsequent infusions of cetuximab as deemed necessary) or local label (where available). Premedication may also be based on institutional guidance for management of infusion-related reactions.

6.5.2 Drug-drug Interactions

No formal drug-drug interaction studies have been conducted with monalizumab. Monalizumab and cetuximab are immunoglobulins and the primary elimination pathways are protein catabolism via reticuloendothelial system or target mediated disposition. Therefore, there are no anticipated drug-drug interactions between monalizumab and cetuximab based on the elimination pathway when monalizumab and cetuximab are administered in combination. Moreover, monalizumab and cetuximab are not expected to induce or inhibit the major drug metabolizing cytochrome P450 pathways.

Based on available non-compartment analysis data, the observed PK of monalizumab when administered in combination with cetuximab is within the range of monalizumab monotherapy PK (see Monalizumab IB, Section 5.1 for further details).

6.5.3 Rescue Medication

Fully functional resuscitation facilities should be available at each site during infusion of the study interventions. Please see recommendations regarding rescue treatment (Section 6.1.2) and management of IMP-related toxicities (Section 8.3.15). The date of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.6 Dose Modification

It is important to keep the day on which monalizumab/placebo and cetuximab are administered as Day 1 of each 2-week cycle (except if one of the study interventions is permanently discontinued). If a participant does not meet monalizumab/placebo dosing criteria on Day 1 of any cycle, both monalizumab/placebo and cetuximab administration should be postponed for a week. If dosing criteria are not met after a week delay, suspension of study intervention will be extended for an additional week. In the absence of resolution after a 2-week delay, the investigator should contact the Sponsor for guidance on further dosing. If dosing delay is due to treatment-related toxicity, TMGs for monalizumab and local prescribing information for cetuximab should be followed (see Section 8.3.15).

For guidance on dose modification in relation to the novel coronavirus (COVID-19) outbreak,

see Appendix C.

Monalizumab/placebo

Dose delays are permitted for monalizumab/placebo (see management of monalizumab-related toxicities in Section 8.3.15.1). However, dose reduction is not permitted.

The duration between each monalizumab/placebo infusion should be at least 14 days (see Table 1 for administration schedule, including acceptable window).

In the event that monalizumab/placebo is discontinued due to monalizumab/placebo-related toxicity, treatment with cetuximab may continue at the investigator's discretion when toxicity resolves to ≤ Grade 1. Note: If the investigator determines that a participant is ready to restart treatment prior to the toxicity resolving to ≤ Grade 1, the Sponsor should be consulted for an exception to this rule.

Cetuximab

Cetuximab dose modification for the management of cetuximab-related toxicities should follow local standard clinical practice (see Section 8.3.15.2). For specific information, refer to the local label (where available) for cetuximab.

The duration between each cetuximab infusion should be at least 7 days (see Table 1 for administration schedule, including acceptable window). If dosing of cetuximab is delayed on Day 1 of a cycle (ie, when monalizumab/placebo is also due to be given) then dosing of monalizumab/placebo should also be delayed (see above). If cetuximab is delayed due to toxicity on Day 8 of a cycle (ie, when single-dose cetuximab is due to be given), the dose of cetuximab will be omitted and the next cycle can continue as usual.

In the event that cetuximab is discontinued due to cetuximab-related toxicity, treatment with monalizumab/placebo may continue at the investigator's discretion when the cetuximab-related toxicity resolves to ≤ Grade 2. Note: If the investigator determines that a participant is ready to restart treatment prior to the cetuximab-related toxicity resolving to ≤ Grade 2, the Sponsor should be consulted for an exception to this rule.

6.7 Intervention After the End of the Study

As described in Section 4.4, the study will remain open until all participants have discontinued study intervention and completed their last expected visit/contact.

After the final DCO and database closure, the Sponsor will supply open-label IMP to participants who are receiving benefit from their assigned treatment, for as long as they and their physician considers they are gaining clinical benefit. See Section 8 for a description of

the assessments to be conducted for these participants.

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, participants 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 visit assessments per its protocol. Any participant who would be proposed to move to such a study would be given a new ICF.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Participants will be discontinued from study intervention in the following situations.

- RECIST 1.1-defined radiological disease progression (refer to Section 6.1.3, Section 8.1.1, and Appendix G)
- Investigator determination that the participant is no longer benefiting from study intervention
- An AE that, in the opinion of the investigator or the Sponsor, contraindicates further dosing
- Any AE that meets criteria for discontinuation defined in the guidelines for management of IMP-related toxicities (see Section 8.3.15) or as defined in the local label (where available) for cetuximab
- Participant decision. The participant is at any time free to discontinue study intervention, without prejudice to further treatment. A participant who discontinues study intervention is normally expected to continue to participate in the study (eg, for safety and survival follow-up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 7.3).
- Severe non-compliance with the CSP as judged by the investigator or the Sponsor
- For females of childbearing potential, pregnancy or intent to become pregnant
- Initiation of subsequent anticancer therapy, including another investigational agent

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

See the SoA (Section 1.3) for data to be collected at the time of study intervention discontinuation and follow-up for safety and other assessments.

If a participant discontinues treatment with one of the combination agents due to toxicity, they may continue with monalizumab/placebo or cetuximab in monotherapy within the study as

long as they are continuing to show clinical benefit, as judged by the investigator and in the absence of discontinuation criteria.

7.1.1 Procedures for Discontinuation of Study Intervention

The EOT visit should be performed and conducted one month after the participant permanently discontinues from study intervention. The assessments to be conducted at the EOT visit are specified in the SoA (Table 2). The reason for discontinuation should be documented in the source document and the appropriate section of the eCRF.

Participants who have permanently discontinued from further receipt of study intervention will need to be discontinued from the IRT.

The date of last intake of study intervention should be documented in the eCRF. Discontinuation of study intervention, for any reason, does not impact on the participant's participation in the study. The participant should continue attending subsequent study visits and data collection should continue according to the study protocol. If the participant does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information including new AEs, follow-up on any ongoing AEs and concomitant medications, and subsequent anticancer therapy. This could be a telephone contact with the participant at one month (+ 3 days) after study intervention is discontinued, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A participant that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

The investigator should instruct the participant to contact the site before or at the time when study intervention is stopped. A participant that decides to discontinue study intervention will always be asked about the reason(s) and the presence of any AEs.

7.1.1.1 Tumor Assessment Post Discontinuation of Study Intervention

Participants who have discontinued study intervention prior to objective RECIST 1.1-defined radiological disease progression, regardless of whether they have commenced subsequent anticancer therapy will continue on their regular scan schedule (see SoA, Table 2) until RECIST 1.1-defined radiological disease progression or death, unless they have withdrawn all consent to study-related assessments.

7.1.1.2 CCI

CCI

CCI

CCI

7.1.1.3 Follow-up for Survival

Participants will be followed for survival status as indicated in the SoA (Table 2) until death, withdrawal of consent, or the end of the study. Survival information may be obtained via telephone contact with the participant or the participant's family, or by contact with the participant's current physician. Additional assessments to be performed at the time of survival follow-up are detailed in the SoA (Table 2).

Participants on treatment or in survival follow-up will be contacted following each DCO to provide complete survival data. These contacts should generally occur within 7 days after the DCO.

7.2 Participant Withdrawal From the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- Upon withdrawal from the study, an EOT visit should be conducted, if possible. See SoA (Section 1.3) for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she is still agrees for samples to be used (see Section A 3). He/she may request destruction of any samples taken, and the investigator must document this in the site study records.
- The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.
- The Sponsor or its delegate will request investigators to collect information on participants' vital status (dead or alive; date of death when applicable) during survival follow-up from publicly available sources, in accordance with local regulations. Knowledge of the vital status at study end in all participants is crucial for the integrity of the study.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site by the time the study is completed (see Section 4.4), such that there is insufficient information to determine the participant's status at that time.

Participants who decline to continue 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 participants throughout the study period. If contact with a missing participant is re-established, the participant should not be considered lost to follow-up and evaluations should resume according to the protocol.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant or next of kin by, eg, repeat telephone calls, certified letter to the participant's last known mailing address, or local equivalent methods. These contact attempts should be documented in the participant's medical record.
- Efforts to reach the participant should continue until the end of the study. Should the participant be unreachable at the end of the study, he/she will be considered lost to follow-up with unknown vital status at the end of the study and censored at latest follow-up contact.

In order to support key efficacy endpoints of OS, PFS, and CCI [redacted], the survival status of all participants in the FAS and the SAF should be re-checked; this includes those participants who withdrew consent or are classified as "lost to follow-up."

- Lost to follow-up – Site personnel should check hospital records and a publicly available death registry (if available), as well as checking with the participants' current physician, to obtain a current survival status. (The applicable eCRF modules will be updated.)
- In the event that the participant has actively withdrawn consent to the processing of their personal data, the survival status of the participant 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.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (see Section 1.3). Protocol waivers or exemptions are not allowed. Assessments following final DCO and database closure until the end of the study are described in Section 8.3.11.

- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Efficacy Assessments

8.1.1 Imaging Tumor Assessments

This study will evaluate a primary endpoint of OS and secondary endpoints of PFS, ORR, and DoR for Arm A vs Arm B. CCI
With the exclusion of OS, efficacy will be derived (by the Sponsor) using investigator RECIST 1.1 assessments.

Tumor assessments use images from iv contrast-enhanced CT (preferred) of the neck (including the base of skull), chest, and abdomen (including the entire liver) collected during screening/baseline and at regular (follow-up) intervals during study intervention. Any other areas of disease involvement should be additionally imaged at screening based on known metastasis sites or by the signs and symptoms of individual participants. MRI with iv contrast is acceptable if CT is contraindicated. The imaging modality (CT/MRI) used for baseline tumor assessments should be kept the same consistently at each subsequent follow-up assessment throughout the study if possible. It is important to follow the tumor assessment schedule as closely as possible (refer to the SoA [Section 1.3]) relative to randomization. Screening/baseline imaging should be performed no more than 28 days before randomization and ideally should be performed as close as possible to randomization. Scanning/tumor

assessments will continue throughout intervention until RECIST 1.1-defined radiological disease progression by investigator assessment (see Section 6.1.3). If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the participant has not progressed, every attempt should be made to perform the subsequent assessments at the next scheduled visit.

Tumor assessment by RECIST 1.1 guidelines are provided in Appendix G.

8.1.2 CCI

CCI

8.1.3 Overall Survival

Assessments for survival will be conducted according to the SoA (Table 2) following objective disease progression or treatment discontinuation. Survival information may be obtained via telephone contact with the participant, participant's family, by contact with the participant's current physician, or local death registries as described in Section 7.2.

8.1.4 Clinical Outcome Assessments

A COA is an assessment of a clinical outcome reported by a clinician, a patient, or a non-clinician observer, or through a performance-based assessment (FDA 2018b). A COA may be used in clinical studies to provide either direct or indirect evidence of treatment benefit. It is important to examine the impact of therapy on disease-related symptoms, physical function, and other HRQoL of the patient to aid understanding of how clinical benefit relates to patient well-being and for consideration in making benefit-risk evaluations. Patient-reported outcome is one type of clinical outcome assessment and is a general term referring to all outcomes and symptoms that are directly reported by the patient. Moreover, PROs assist in the documentation of symptoms and specifically what symptoms and impacts are most important to patients and how these relate to clinical outcomes. Patient-reported outcomes have become important in evaluating effectiveness of study treatments in clinical studies and will aid in understanding of the benefit-risk evaluation (Kluetz et al 2018). The following

PROs will be administered in this study: EORTC QLQ-C30, EORTC QLQ-H&N35, CCI [redacted]. See questionnaires in Appendix I. Patient-reported outcomes will be administered according to the SoA during the treatment and follow-up periods (see Section 1.3). Patient-reported outcomes will be translated into the language of the country being administere CCI [redacted].

8.1.4.1 EORTC QLQ-C30

The EORTC QLQ-C30 was developed by the EORTC Quality of Life Group 1993 (see Appendix I 1). It consists of 30 items and measures symptoms, functioning, and global health status/QoL (Aaronson et al 1993) for all cancer types. Questions are grouped into 5 multi-item functional scales (physical, role, emotional, cognitive, and social); 3 multi-item symptom scales (fatigue, pain, and nausea/vomiting); a 2-item global QoL scale; 5 single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation, and diarrhea), and one item on the financial impact of the disease. The EORTC QLQ-C30 is a valid and reliable PRO instrument in this patient population.

8.1.4.2 EORTC QLQ-H&N35

The EORTC QLQ-H&N35 module is a 35-item self-administered questionnaire (see Appendix I 2). 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.

8.1.4.3 CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI

8.1.4.4 CCI

CCI

CCI

CCI

8.1.4.5 CCI

CCI

8.1.4.6 CCI

CCI

8.1.4.7 Administration of Electronic PRO Questionnaires

Participants will complete the PRO assessments using an electronic tablet (ePRO) during clinic visits at the time points indicated in the SoA (see Section 1.3). It is important that the ePRO device is charged and set up for the participant prior to their arrival at the site for their

baseline PRO assessments (close to when the participant will be randomized), to ensure it is functioning properly and ready for use, in accordance with device training. The participant should be trained on the use of the device, including the importance of completing the PRO questionnaires throughout the study in accordance with the SoA.

The below instructions should be followed when collecting PRO data via an electronic device:

- Patient-reported outcome questionnaires must be completed prior to treatment administration and ideally before any discussions of health status to avoid biasing the participant's responses to the questions. As feasible, site staff should also ensure PRO questionnaires are completed prior to other study procedures, such as collection of laboratory samples, to further minimize bias.
- When each instrument is due to be completed, the following order is observed; EORTC QLQ-C30 should be administered first followed by EORTC QLQ-H&N35, CCI .
- Patient-reported outcome questionnaires should be completed by the participant in a quiet and private location.
- The participant should be given sufficient time to complete the questionnaires at their own speed.
- The research nurse or appointed site staff must explain to participants the value and relevance of ePRO participation so they are motivated to comply with questionnaire completion. Inform the participant that these questions are being asked to find out, directly from them, how they feel.
- The research nurse or appointed site staff should stress that the information is not routinely shared with study staff. Therefore, if the participant has any medical problems, they should discuss them with the doctor or research nurse separately from the ePRO assessment.
- The research nurse or appointed site staff must train the participant on how to use the ePRO device, using the materials and training provided by the ePRO vendor.
- All PRO questionnaires are to be completed using the ePRO device. If technical or other device-related issues prohibit completion on the device, an appropriate backup option may be considered with prior approval from AstraZeneca.
- The research nurse or appointed site staff must remind participants that there are no right or wrong answers, and avoid introducing bias by not clarifying items for the participant.
- The participant should not receive help from relatives, friends, or clinic staff to decide on answers to the ePRO questionnaires. The responses are the participant's alone.
- On completion of the questionnaire at the site, it should be handed back to the designated responsible person, who should check that all questionnaires were completed.

- If a participant needs visual aids (eg, spectacles or contact lenses) for reading and does not have them when he or she attends the clinic, the participant will be exempted from completing the ePROs at that clinic visit.
- Site staff must not read the ePRO questionnaires on behalf of the participant. If the participant is unable to read the questionnaire (eg, is blind or illiterate, or not fluent in the available language), that participant is exempted from completing PRO questionnaires but may still participate in the study. If the participant cannot complete the ePRO questionnaires due to reasons other than being blind, illiterate, or fluent in language, the AstraZeneca study team must be contacted to determine if they can be exempted. Participants exempted in this regard should be flagged appropriately by the site staff in the source documents and in the REVPRDI eCRF.
- Questions must not be translated from an available language in the device into the language the participant speaks.
- It is vital that the ePRO reporting is initiated at Cycle 1 Day 1 dosing visit (baseline) as specified in the SoA to capture the effect of study treatment. The ePRO device must be charged and fully functional at the beginning of the baseline visit to ensure that the PROs can be completed at the start of the visit.
- Finally, the research nurse or appointed site staff will review the completion status of questionnaires during site visits and document the reason(s) why a participant could not complete assessments in the designated eCRF.

The research nurse or appointed site staff must monitor compliance since 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 the site receives an email notification regarding the participant's compliance, appropriate action should be taken (eg, discussion with participant to improve compliance, a check in call from the site to ask the participant if they have any difficulties in completing questionnaires on schedule, etc). A solution to enhance/resolve compliance should be discussed with the participant. Discussions and compliance review should be reflected in source documents.

8.1.4.8 WHO/ECOG PS

World Health Organization/ECOG PS will be assessed at the time points specified in the SoA (Section 1.3) based on the following:

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

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

2 Ambulatory and capable of self-care, but unable to carry out any work activities; up and about more than 50% of waking hours

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

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

5 Dead

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

The ECOG status collected at screening must be reported in IRT and not re-assessed.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical Examinations

Physical examination, as well as assessment of height and weight, will be performed at time points specified in the SoA (Section 1.3).

- A full physical examination will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. In addition, targeted physical examinations, eg, urogenital, are to be performed by the investigator based on clinical observations and symptomatology.
- Targeted physical examinations are to be performed by the investigator on the basis of clinical observations and symptomatology.

Situations in which physical examination results should be reported as AEs are described in Section 8.3.5.

8.2.2 Vital Signs

Vital signs will be performed at time points specified in the SoA (Section 1.3).

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Vital signs will be measured after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate.

First infusion

On the first infusion day, participants will be monitored and vital signs collected/recorded in eCRF prior to, during, and after infusion of monalizumab/placebo as presented in the bulleted list below.

Blood pressure and pulse will be collected from participants before, during, and after each monalizumab/placebo infusion 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 infusion (**halfway** through infusion)
- At the end of the infusion (approximately 60 minutes ± 5 minutes)

If the monalizumab/placebo infusion takes longer than 60 minutes, then blood pressure and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. A one-hour observation period is recommended after the first infusion of monalizumab/placebo.

Vital signs will be collected in all participants before cetuximab dosing (approximately 30 minutes before up to 0 minutes) and as clinically indicated during and after dosing, as per the local label and institutional standard. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs eCRF.

Subsequent infusions

Blood pressure, pulse, and other vital signs should be measured (approximately 30 minutes before up to 0 minutes), collected/recorded in the eCRF prior to the start of the infusions of monalizumab/placebo and cetuximab. Participants should be carefully monitored, and blood pressure and other vital signs should be measured during and post infusions as per institutional standard and as clinically indicated (and in line with the local label for cetuximab). Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs eCRF.

Situations in which vital signs results should be reported as AEs are described in Section 8.3.5. For any AEs of infusion reactions, the vital signs values should be entered into eCRF.

8.2.3 Electrocardiograms

Triplicate 12-lead ECGs will be recorded at scheduled visits and as clinically indicated per the SoA (Section 1.3). An ECG will be obtained after the participant has been resting semi-recumbent or supine for at least 5 minutes and recorded while the participant remains in that position using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals.

Three individual ECG tracings should be obtained in succession, no more than 2 minutes apart. The full set of triplicates should be completed within 5 minutes. The machine-derived

QTc must be manually verified and interpreted by the investigator. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal.

Situations in which ECG results should be reported as AEs are described in Section 8.3.5.

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the visits indicated in the SoA (Section 1.3). Samples for determination of coagulation parameters are to be collected at baseline on Day 1 (unless all screening laboratory hematology assessments are performed within 3 days prior to Day 1), and then as clinically indicated. 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.

Clinical laboratory safety tests, including serum pregnancy tests, will be performed at a licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. Pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

Table 8 presents the laboratory variables to be measured. Other safety tests to be performed at screening include assessments for hepatitis B surface antigen, hepatitis C antibodies, and HIV antibodies.

Table 8 Laboratory Safety Variables

Hematology/Hemostasis (whole blood)	Clinical chemistry (serum or plasma)
Hb	Creatinine [a]
Platelet count	Bilirubin, total [b]
Absolute neutrophil count [c]	ALP [b]
Absolute lymphocyte count [c]	AST [b]
Total WBC count	ALT [b]
Coagulation [d]	Albumin
aPTT, fibrinogen, and INR	Potassium
	Calcium, total
Urinalysis [e]	Sodium
Bilirubin	Magnesium
Blood	Phosphate
Protein/Albumin	Amylase [f]
Glucose	Lipase [f]
Color and appearance	Gamma-glutamyl transferase
Ketones	Glucose
Specific gravity	Bicarbonate (where available)

Table 8 Laboratory Safety Variables

Hematology/Hemostasis (whole blood)	Clinical chemistry (serum or plasma)
pH	Chloride
	LDH
	Protein, total
	TSH [g]
	free T4 [h]
	free T3 [h]
	Urea or blood urea nitrogen, depending on local practice

[a] Creatinine clearance will be calculated by the site using Cockcroft-Gault (using actual body weight).
[b] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥ 2 × ULN (and no evidence of Gilbert's syndrome), then fractionate into direct and indirect bilirubin.
[c] Can be recorded as absolute counts or as percentages, except at screening when absolute neutrophil count must be recorded. Total WBC count therefore has to be provided.
[d] Coagulation parameters are to be assessed at baseline on Day 1 (unless all screening laboratory hematology assessments are performed within 3 days prior to Day 1), and then as clinically indicated.
[e] Urinalysis should be done at baseline (screening) and then as clinically indicated.
[f] It is preferable that both amylase and lipase parameters are assessed. For sites where only one of these parameters is routinely measured, either lipase or amylase is acceptable.
[g] If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at Day 1.
[h] Free T4 or/and free T3 (per local standard clinical practice) will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

ALP = alkaline phosphate; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; INR = International Normalized Ratio; LDH = lactate dehydrogenase; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; ULN = upper limit of normal; WBC = white blood cell count.

In case a participant shows an AST **or** ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN, please refer to Appendix F (Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law) for further instructions.

8.3 Adverse Events and Serious Adverse Events

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

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

For guidance in relation to the novel coronavirus (COVID-19) outbreak, see Appendix C.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from time of signature of the ICF until 90 days after the last dose of study intervention (see SoA, Section 1.3). Collection and reporting of AEs and SAEs

after the final DCO is described in Section 8.3.11.

Serious adverse events will be recorded from the time of signing of ICF.

If the investigator becomes aware of an SAE with a suspected causal relationship to the IMP that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the Sponsor.

8.3.2 Follow-up of AEs and SAEs

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

Adverse event variables

The following variables will be collected for each AE;

- Adverse event (verbatim)
- The date when the AE started and stopped
- Select the appropriate as required:
  - The maximum CTCAE grade reported
  - Changes in CTCAE grade (report only the maximum CTCAE grade for a calendar day)
- Whether the AE is serious or not
- Investigator causality rating against the IMP(s) (yes or no)
- Action taken with regard to IMP(s)
- Administration of treatment for the AE
- Outcome

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

- Date AE met criteria for serious AE
- Date investigator became aware of serious AE
- Adverse event is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death

- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication

The grading scales found in the NCI CTCAE, Version 5.0 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 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

8.3.3 Causality Collection

The investigator should assess causal relationship between IMP 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 should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: '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.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the CSP-mandated laboratory tests and vital signs will be summarized in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, and ECGs should therefore only be reported as an AE if it fulfills any of the SAE criteria, is the reason for discontinuation of treatment with the IMP, or is considered to be clinically relevant as judged by the investigator (this may include but is not limited to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting investigator uses the clinical, rather than the laboratory term (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 AE(s).

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.6 Hy's Law

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

8.3.7 Disease Progression

Disease progression can be considered as a worsening of a participant's condition attributable to the disease for which the IMP 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.

8.3.8 New Cancers

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

8.3.9 Deaths

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

- Death clearly resulting from disease progression should be documented in the eCRF in the Statement of Death page. 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 as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co-involvement of disease progression, if appropriate, and should assign the main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE and documented in the Statement of Death page in the eCRF, but every effort should be made to determine a cause of death. 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 Patient Safety or its representative within the usual time frames.

Deaths occurring after the protocol-defined follow-up period after the administration of the last dose of study intervention should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the defined follow-up period and the event is considered to be due to a late-onset toxicity to study treatment, then it should also be reported as an SAE.

8.3.10 Adverse Events of Special Interest

Adverse events of special interest are events of scientific and medical interest specific to the further understanding of study intervention safety profile and require close monitoring and rapid communication by the investigators to the Sponsor. An AESI can be serious or non-serious. All AESIs will be recorded in the eCRF. Serious AESIs will be recorded and reported as per Section 8.3.12.

Adverse events of special interest for monalizumab include events with a potential immune-mediated inflammatory mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants, and/or hormone replacement therapy. An imAE 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 imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxic, or other etiologic causes of the imAE.

If the investigator has any questions in regard to an event being an imAE, the investigator should promptly contact the Study Clinical Lead.

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

Further information on these risks (eg, presenting symptoms) can be found in the current version of the monalizumab IB. More specific guidelines for their evaluation and treatment

are described in detail in the monalizumab TMG (see Section 8.3.15).

8.3.11 Safety Data to be Collected Following the Final DCO of the Study

For participants continuing to receive open-label IMP after the final DCO and database closure (see Section 6.7), it is recommended that the participant continue the scheduled site visits and investigators monitor the participant's safety laboratory results prior to and periodically during treatment with IMP in order to manage AEs in accordance with toxicity-management guidelines (see Section 8.3.15). All data post the final DCO and database closure will be recorded in the participant notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

All SAEs that occur in participants still receiving IMP (or within the 90 days following the last dose of IMP) post the final DCO and database closure must be reported as detailed in Section 8.3.12.

8.3.12 Reporting of Serious Adverse Events

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

If any SAE occurs in the course of the study, then investigators or other site personnel inform the appropriate Sponsor representatives within one day ie, immediately but **no later than 24 hours** of when they become aware of it.

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

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

Once the investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated Sponsor representative.

If the EDC system is not available, then the investigator or other study site staff reports an SAE to the appropriate Sponsor representative by telephone.

The Sponsor representative will advise the investigator/study site staff how to proceed.

The reference documents for definition of expectedness/listedness are the IB for monalizumab

and the appropriate label for cetuximab.

8.3.13 Pregnancy

All pregnancies and outcomes of pregnancy with conception dates following the first date of study intervention, including pregnancy in the partner of male participants, should be reported to AstraZeneca except if the pregnancy is discovered before the study participant has received any study intervention.

8.3.13.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, IMP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/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 anomaly) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate Sponsor representatives within one day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative works with the investigator to ensure that all relevant information is provided to the Sponsor Patient Safety data entry site within one or 5 calendar days for SAEs (see Section 8.3.12) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy.

8.3.13.2 Paternal Exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 4 months after the last dose of study intervention.

Pregnancy of the participant'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 anomaly) occurring from the date of the first dose of study intervention until 4 months after the last dose of study intervention should, if possible, be followed up and documented in the Pregnancy Report Form. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the investigator must obtain the consent of the participant's partner. The local study team should adopt the Master Pregnant Partner Form in line with local procedures/requirements and submit it to the relevant Regulatory Authority/IRB/IEC prior to use.

8.3.14 Medication Error

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate Sponsor representatives within one day, ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated Sponsor representative works with the investigator to ensure that all relevant information is completed on the specific medication error eCRF within one (initial fatal/life-threatening or follow up fatal/life-threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error (see Section 8.3.1) and within 30 days for all other medication errors.

The definition of a medication error can be found in Appendix B.

8.3.15 Management of IMP-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 IMP 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 IMP 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.

See Section 6.6, and Sections 8.3.15.1 and Section 8.3.15.2 below for dose modification guidance.

All toxicities will be graded according to NCI CTCAE, Version 5.0.

8.3.15.1 Monalizumab

The monalizumab TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune mediated reactions that may be observed with monalizumab, with specific instructions for dose modifications (omissions and discontinuations) and treatment interventions. The most current version of the TMGs is provided to the investigative site as a supplement to the CSP and is maintained within the Site Master File.

Participants should be thoroughly evaluated, and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxic, or other etiologic causes of the suspected 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 monalizumab should be permanently discontinued (see Section 7.1 and the monalizumab TMGs). Following the first dose of monalizumab, subsequent administration of monalizumab can be modified based on toxicities observed as described in the TMGs. These guidelines have been prepared by the Sponsor to assist the investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to monalizumab regimen by the reporting investigator.

Dose reductions are not permitted. In case of doubt, the investigator should consult with the Study Clinical Lead.

8.3.15.2 Cetuximab

Please refer to the local label (where available) for the management of AEs with cetuximab.

In case of infusion-related reactions to cetuximab, manage as per local label (where available) for cetuximab and institutional guidance on management of infusion-related reactions.

For management of AEs with cetuximab, refer to the local label.

8.4 Overdose

Use of monalizumab or cetuximab in doses exceeding those specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of overdose of monalizumab, and possible symptoms of overdose are not established. If an overdose of cetuximab occurs, please refer to the local label (where available).

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module

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

The designated Sponsor representative works with the investigator to ensure that all relevant information is provided to the Sponsor Patient Safety data entry site within 1 or 5 calendar days for overdoses associated with an SAE (see Section 8.3.12) and within 30 days for all

other overdoses.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Sample see Appendix D.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - Pharmacokinetic samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterization of any ADAs, confirmation and/or requalification of the assay, as well as additional assay development work. The results from future analysis will not be reported in the CSR.

8.5.1 Pharmacokinetics

- Blood samples will be collected for measurement of serum concentrations of monalizumab and cetuximab as specified in the SoA.
- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the Sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.
- Serum samples will be used to analyze the PK of monalizumab and cetuximab. Samples collected for analyses of monalizumab and cetuximab serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentration in serum will be assayed by bioanalytical test sites operated by or on behalf of the Sponsor, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel [until the study has been unblinded].

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

8.5.2 Immunogenicity Assessments

Blood samples for determination of ADA in serum will be assayed by bioanalytical test sites operated by or on behalf of the Sponsor, using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate report.

Antidrug antibody samples may also be further tested for characterization of the ADA response.

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

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

Samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA (Section 1.3). Details for sample collection, processing, and testing are provided in the Laboratory Manual.

At screening, all participants will be asked to provide formalin-fixed paraffin-embedded samples from archival or fresh tumor biopsy (acquired ≤ 3 months prior to screening). Tumor tissue beyond the 3-month window and up to 6 months old may be considered upon Sponsor consultation, provided that no intervening systemic regimen was ongoing at the time of sample collection (see the Laboratory Manual for more information). Archival tumor biopsies older than 6 months (> 6 months) or collected when previous treatments were still ongoing are not acceptable. Participants whose archival tumor tissue is unavailable or unsuitable for use will be asked to provide a fresh tumor biopsy. Fresh tumor biopsy should not be collected from lesions in proximity to cardiopulmonary, visceral, or vital neurovascular structures that could make the collection procedure high risk.

The screening tumor biopsy will be evaluated for the expression of HLA-E and NKp46 in the

TME by IHC. Associations between HLA-E and NKp46 expression and the participant's radiologic response (RECIST 1.1) will be assessed. CCI

CCI

8.6.2 Collection of Optional Biomarker Samples

Optional samples may be collected for biomarker research as listed in the SoA (Section 1.3).

All participants will be asked to provide consent for collection of tumor biopsies once during treatment and at time of progression. CCI

8.6.3 Other Study-related Biomarker Research

CCI

8.7 CCI

CCI

CCI

CCI

CCI

CCI

8.8 Medical Resource Utilization and Health Economics

For economic evaluation for payer submissions, it is necessary to capture healthcare resource utilization related to the intervention and the underlying disease. Within this study, the following will be captured:

CCI

- Treatment-related to AEs (including the method of delivery of the treatment) captured in AE/SAE assessment module
- Treatment not related to the study obtained in Concomitant Medications eCRF

8.9 Study Participant Feedback Questionnaire

Participants will have the option to complete the anonymized SPFQ assessing their clinical study experience (see Appendix J; assessment schedule is presented in Section 1.3). Participants who do not wish to complete this questionnaire may still participate in the study. Individual participant-level responses will not be reviewed by investigators. Responses would be used by the Sponsor to understand where improvements can be made in the clinical study process. This questionnaire does not collect data about the participant's disease, symptoms, treatment effect, or AEs and therefore would not be study data.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The formal statistical analysis will be performed to test the following main hypotheses for monalizumab plus cetuximab (Arm A) or placebo plus cetuximab (Arm B):

- H0: No difference between Arm A and Arm B
- H1: Difference between Arm A and Arm B

9.2 Sample Size Determination

Approximately 624 participants will be randomized 2:1 to monalizumab plus cetuximab (Arm A) or placebo plus cetuximab (Arm B). Randomization will be stratified by HPV status (OPC HPV positive or HPV-unrelated), WHO/ECOG PS (0 or 1), or number of prior lines of

therapy in the R/M setting (1 or 2).

The study is powered to demonstrate superiority in the OS benefit of Arm A vs Arm B in HPV-unrelated participants with R/M SCCHN previously treated with an ICI.

There will be two planned IAs and one FA for the study.

Interim Analysis 1 (IA1): Futility in OS will be evaluated when approximately 99 OS events have occurred across Arm A and Arm B in HPV-unrelated participants (25% information fraction) and randomized at least 2 months before the DCO for the futility analysis (ie, with a minimum follow-up of 2 months).

Interim Analysis 2 (IA 2): A hypothesis of monalizumab plus cetuximab (Arm A) prolongs OS compared to placebo plus cetuximab (Arm B) will be tested at IA2 when approximately 278 OS events have occurred across Arm A and Arm B in HPV-unrelated participants (approximately 70% information fraction, 56% maturity).

Final Analysis (FA): A hypothesis of improved OS will be tested at the final analysis when approximately 397 OS events have occurred across Arm A and Arm B in HPV-unrelated participants (approximately 80% maturity).

If the true OS HR is 0.72, corresponding to an approximate 3-month improvement in median OS compared to Arm B of 7.7 months, approximately 397 OS events in HPV-unrelated participants will provide approximately 86.5% power to demonstrate statistical significance at the 5% level (using a 2-sided test) for the FA. The 5% (2-sided) alpha for the OS analysis will be controlled at the IA2 and FA time points by using the Lan-DeMets (Lan and DeMets 1983) spending function that approximates the O'Brien-Fleming approach, where the significance level applied depends upon the proportion of information (ie, information fraction) available at time of IA2. For example, if the information fraction for OS at IA2 is 70% then the two-sided significance levels of 1.48% and 4.55% will be applied to IA2 and FA for OS, respectively. The smallest detectable treatment difference in HR, ie, critical value, that could be statistically significant at the FA is 0.81. With a planned recruitment period of 30 months, it is expected that a total of 498 HPV-unrelated participants are needed in order to achieve 397 OS events with a follow-up period of approximately 12 months. The 278 OS events for the IA2 are expected to be reached approximately 30.5 months after the randomization of the first participant.

The number of OPC HPV-positive participants will be closely monitored throughout the study and are planned to be capped at approximately 20%of the total sample size. With the assumption of 20% OPC HPV-positive participants in the overall participants, approximately 624 randomized participants will be needed in overall population. Under the same assumption of effect size in HR and median OS stated above, approximately 498 OS events are expected

in all participants which will provide approximately 93.0% power to demonstrate statistical significance at the 5% level (using a 2-sided test) for the FA.

9.3 Populations for Analyses

Definitions of the analysis sets for each endpoint are provided in Table 9.

Table 9 Summary of Outcome Variables and Analysis Populations

Endpoint	Population
Efficacy data	
OS	HPV-unrelated Analysis Set and Full Analysis Set
PFS	HPV-unrelated Analysis Set and Full Analysis Set
ORR [a], DoR, and PRO [b] endpoints	HPV-unrelated Analysis Set and Full Analysis Set
Demography and other baseline characteristics	HPV-unrelated Analysis Set and Full Analysis Set
PK data	
PK data	PK Analysis Set
Biomarker data	
Biomarker data	HPV-unrelated Analysis Set and Full Analysis Set
Safety data	
Exposure	Safety Analysis Set
AEs	Safety Analysis Set
Laboratory measurements	Safety Analysis Set
Vital signs and other safety	Safety Analysis Set
ADA data	ADA Analysis Set

[a] ORR: measurable disease at baseline.
[b] PRO: evaluable PRO measurements
ADA = antidrug antibody; AE = adverse event; DoR = duration of response; HPV = human papillomavirus; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic(s); PRO = patient-reported outcome.

9.3.1 HPV-unrelated Analysis Set

The primary population is the HPV-unrelated Analysis Set which will include all randomized participants who are either OPC HPV negative or non-OPC regardless of the HPV status. The HPV status will be determined by HPV status in the CRF and not the IVRS value. The HPV-unrelated Analysis Set will be used for summarizing baseline characteristics, all efficacy analyses, including PROs and biomarker analyses. Treatment arms will be compared on the basis of randomized study intervention, regardless of the intervention actually received. Participants who were randomized but did not subsequently go on to receive study intervention are included in the analysis in the treatment arm to which they were randomized.

Analysis for ORR will be based on participants in the FAS who had measurable disease at baseline. Analysis of DoR will be based on participants in the FAS who achieved objective response.

9.3.2 Full Analysis Set

The FAS will include all randomized participants. The FAS will be used for summarizing baseline characteristics, all efficacy endpoints (including PROs) and biomarker analyses as secondary analyses. Treatment arms will be compared on the basis of randomized study intervention, regardless of the intervention actually received. Participants who were randomized but did not subsequently go on to receive study intervention are included in the analysis in the treatment arm to which they were randomized.

9.3.3 Safety Analysis Set

The SAF will consist of all participants who received any amount of study treatment. Safety data will not be formally analyzed but summarized descriptively using the SAF according to the intervention received; that is, erroneously-treated participants (eg, those randomized to Arm A but actually given Arm B intervention) will be summarized according to the study intervention they actually received.

9.3.4 Pharmacokinetic Analysis Set

All participants who receive at least one dose of CCI per the protocol for whom there is at least one reportable PK concentration and who do not violate or deviate from the protocol in ways that would significantly affect the PK analyses will be included in the PK Analysis Set. The population will be defined by the Study Clinical Lead, pharmacokineticist, and statistician prior to any PK analyses being performed.

9.3.5 ADA Analysis Set

The ADA Analysis Set will include all participants who have non-missing baseline ADA and at least one non-missing post-baseline ADA results. All major ADA analyses will be based on the ADA Analysis Set.

9.4 Statistical Analyses

Analyses will be performed by the Sponsor or its representatives. A comprehensive SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the CSR.

9.4.1 General Considerations

A hypothesis of improved OS will be tested at IA2 when approximately 278 OS events have

occurred across Arm A and Arm B in HPV-unrelated participants (approximately 56% maturity; IA2).

A hypothesis of improved OS will be tested at the final analysis when approximately 397 OS events have occurred across Arm A and Arm B in HPV-unrelated participants (approximately 80% maturity; FA).

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 IMP, except for efficacy variables. For efficacy variables, baseline is defined as the last visit prior to randomization.

All data collected will be listed. Efficacy and PRO data will be summarized and analyzed based on the HPV-unrelated Analysis Set and will be repeated for FAS as a secondary analysis. PK data will be summarized and analyzed based on the PK Analysis Set. Safety data will be summarized on the SAF. Antidrug antibody data will be summarized on the ADA Analysis Set.

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

The following table details which endpoints are to be subjected to formal statistical analysis, together with pre-planned sensitivity analyses, making it clear which analysis is regarded as primary for that endpoint.

Table 10 Pre-planned Statistical and Sensitivity Analyses to be Conducted for Efficacy and COA Endpoints

Endpoints analyzed	Notes
Overall survival (Primary) in HPV-unrelated Analysis Set	Primary confirmatory analysis Stratified log-rank test adjusting for, WHO/ECOG PS and number of prior lines of therapy in the R/M setting for primary comparison of survival between randomized treatment arms Sensitivity and supplemental analysis Assessment of assumption of proportionality and stratified max combo test Subgroup analysis using Cox model

Table 10 Pre-planned Statistical and Sensitivity Analyses to be Conducted for Efficacy and COA Endpoints

Endpoints analyzed	Notes
Overall survival (Secondary) in FAS	Secondary confirmatory analysis Stratified log-rank test adjusting for HPV status, WHO/ECOG PS, number of prior lines of therapy in the R/M setting Sensitivity and supplemental analysis Subgroup analysis using Cox model
Progression-free survival (Secondary) in HPV-unrelated Analysis Set and FAS	PFS according to RECIST 1.1 based on investigator assessments will be analyzed as a secondary variable. Secondary confirmatory analysis For HPV-unrelated Analysis Set, stratified log-rank tests adjusting for WHO/ECOG PS and number of prior lines of therapy in R/M setting, using PFS according to RECIST 1.1 based on investigator assessments For FAS, stratified log-rank tests adjusting for HPV status, WHO/ECOG PS, number of prior lines of therapy in R/M setting, using PFS according to RECIST 1.1 based on investigator assessments Sensitivity and supplemental analysis Analysis using alternative censoring rules – attrition bias Subgroup analysis using Cox proportional hazards model
Objective response rate (Secondary) in HPV-unrelated Analysis Set and FAS	For HPV-unrelated Analysis Set, logistic regression adjusted for WHO/ECOG PS, number or prior lines of therapy in the R/M setting, using tumor data according to RECIST 1.1 based on investigator assessment For FAS, logistic regression adjusted HPV status, WHO/ECOG PS, number or prior lines of therapy in the R/M setting, using tumor data according to RECIST 1.1 based on investigator assessment
Duration of response (Secondary) in HPV-unrelated Analysis Set and FAS	KM plots based on the tumor data using investigator assessment of RECIST 1.1. Median DoR calculated from the KM curve.
CCI [redacted]	
Each scale/item of EORTC QLQ-C30 and QLQ-H&N35 (Secondary) in HPV-unrelated Analysis Set and FAS	Summary and descriptive statistics Unadjusted change from baseline
Key symptoms, functions, global health status/QoL of EORTC QLQ-C30 and QLQ-H&N35 (Secondary) in HPV-unrelated Analysis Set and FAS	MMRM analysis (overall and by each visit)

Table 10 Pre-planned Statistical and Sensitivity Analyses to be Conducted for Efficacy and COA Endpoints

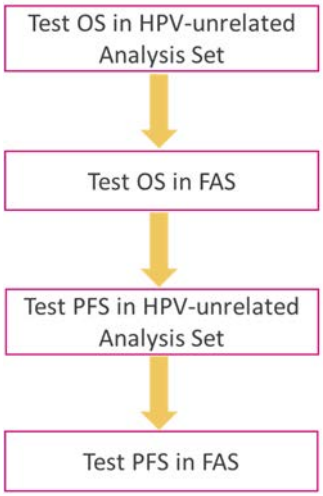
Endpoints analyzed	Notes
Time to symptom, function, or HRQoL deterioration of key COA endpoints using EORTC QLQ-C30 and QLQ-H&N35 (Secondary) in HPV-unrelated Analysis Set and FAS	Stratified log-rank test
CCI	

COA = clinical outcome assessment; CR = complete response; DCR = disease control rate; DoR = duration of response; EORTC = European Organisation for Research and Treatment of Cancer; CCI FAS = Full Analysis Set; HPV = human papillomavirus; HR = hazard ratio; HRQoL = health related quality of life; KM = Kaplan Meier; MMRM = mixed-effect model repeated measure; OS = overall survival; PFS = progression-free survival; CCI CCI PR = partial response; CCI PS = performance status; QLQ-C30 = 30-item Core Quality of Life Questionnaire; QLQ-H&N35 = 35-Item Head and Neck Cancer Quality of Life Questionnaire; QoL = quality of life; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; R/M = recurrent/metastatic; SAP = statistical analysis plan; SD = stable disease; WHO/ECOG = World Health Organization/Eastern Cooperative Oncology Group.

9.4.1.1 Methods for Multiplicity Control

Strong control of the FWER at 5% level (2 sided) across the testing of OS and PFS endpoints will be achieved through a combined approach of alpha allocation to the OS analyses (IA2 and the FA) via alpha spending function and a hierarchical testing procedure; that is, OS in FAS will be tested only if OS in HPV-unrelated analysis set met significance at IA2 or FA; PFS will be tested only if OS met statistical significance at IA2 or FA and PFS in FAS will be tested only if PFS in HPV-unrelated analysis set met statistical significance at IA2 or FA (Glimm et al 2010) (Figure 3). The IA2 for OS will be conducted when approximately 278 of the 397 expected OS events (ie, 70% information fraction) have occurred in HPV-unrelated participants. Using the Lan-DeMets spending function approximating O'Brien-Fleming boundaries, 2-sided significance levels of 0.0148 and 0.0455 will be applied to OS IA2 and FA, respectively (Lan and DeMets 1983).

Figure 3 Graphical Presentation of the Propose Multiple-Testing Procedure at IA2 and FA



FA = final analysis; FAS = full analysis set; HPV = human papillomavirus; IA2 = interim analysis 2; OS = overall survival; PFS = progression-free survival.
Notes: At each analysis (IA2 and FA), PFS will be formally tested only if OS meets statistical significance.

Each statistical test will be performed only if the preceding test is statistically positive. At the time of OS IA2, the PFS data will be mature given its expected short median of 2.3 months in this population (Cohen et al 2019b, Ferris et al 2016, Rischin et al 2019) and it will be tested at 5% significance level.

9.4.2 Efficacy

9.4.2.1 Primary Endpoint

Derivation of primary endpoint

The primary endpoint OS is defined as the time from the date of randomization until date of death due to any cause. Any participant not known to have died at the time of analysis will be censored based on the last recorded date on which the participant was known to be alive.

Note: Survival calls will be made following the date of DCO for the IAs or FA (these contacts should generally occur within 7 days of the DCO). If participants are confirmed to be alive or if the death date is post the DCO date, these participants will be censored at the date of DCO. Death dates may be found by checking publicly available death registries.

Primary analysis

Overall survival in the HPV-unrelated Analysis Set will be analyzed using a stratified log-rank test, adjusting for WHO/ECOG PS (0 or 1) and number of lines of prior therapy in the R/M setting (1 or 2). The HR and its CI will be estimated from a stratified Cox Proportional Hazards model. The effect in Arm A vs Arm B will be estimated by the HR together with its

corresponding CI and p-value (from stratified log-rank test). Kaplan-Meier plots will be presented by treatment arm. Summaries of the numbers and percentages of participants 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 arm.

Sensitivity analysis

The assumption of proportionality will be assessed first by examining the plots of complementary log-log (event times) versus log (time) and, if these raise concerns, by fitting a time-dependent covariate to assess the extent to which this represents random variation. If a lack of proportionality is evident, a stratified max-combo test will be used as a sensitivity analysis with the same stratification factors as the primary analysis. The max-combo test is based on an adaptive procedure, optimizing test statistics among log rank test ($FH^{0,0}$) and the FH weighted log-rank test (Harrington and Fleming 1982) ($FH^{0,1}$ and $FH^{1,1}$) with alpha correction (Karrison 2016). It is a more robust and powerful test under NPH when compared to the log-rank test and is recommended by the Cross-Pharma Non-proportional Hazard Working Group in presence of NPH (Lin et al 2020). The variation in treatment effect will be described by presenting piecewise HR calculated over distinct time-periods. In such circumstances, the HR can still be meaningfully interpreted as an average HR over time unless there is extensive crossing of the survival curves. If lack of proportionality is found, this may be a result of treatment-by-covariate interactions, which will be investigated. In addition, the KM curve along with landmark analyses (eg, one-year OS rate) will also help in understanding the treatment benefit.

Analysis of OS in FAS

Overall survival in the FAS will be analyzed similarly except that the stratified log-rank test will be adjusted for HPV status (OPC HPV positive or HPV-unrelated), WHO/ECOG PS (0 or 1), and number of lines of prior therapy in the R/M setting (1 or 2).

Subgroup analysis

Subgroup analyses will be conducted comparing OS between Arm A vs Arm B in the following subgroups of the HPV-unrelated Analysis Set and FAS (but not limited to):

- Sex (male vs female)
- Age at randomization (< 65 vs ≥ 65 years of age)
- Human papillomavirus status (OPC HPV positive or HPV-unrelated) (applicable to FAS only)
- WHO/ECOG PS (0 or 1)
- Number of prior lines of therapy in the R/M setting (1 or 2)
- Race/ethnicity data (Asian vs non-Asian)

Other baseline variables may also be assessed if there is clinical justification or 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. Forest plots will be presented.

Additionally, for each subgroup, the HR (Arm A:Arm B) and 95% CI will be calculated from a Cox proportional hazards model with treatment as the only covariate. These will be presented on a forest plot including the HR and 95% CI from the overall population.

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 and PFS.

9.4.2.2 Secondary Endpoints

The analysis of the secondary efficacy endpoints, PFS, ORR, and DoR, will be primarily based on the site investigator assessments using RECIST 1.1.

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

At each visit, participants 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 28 days prior to enrollment. If a participant has had a tumor assessment that cannot be evaluated, then the participant will be assigned a visit response of NE (unless there is evidence of progression in which case the response will be assigned as PD).

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

9.4.2.2.1 Progression-free Survival

Derivation of PFS

The secondary endpoint PFS will be defined as the time from randomization until progression, per RECIST 1.1 as assessed by the investigator at local site or death due to any cause, whichever occurs first, regardless of whether the participant withdraws from study intervention or receives another anticancer therapy prior to progression (ie, date of event or censoring – date of randomization + 1). Participants 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 participant progresses or dies after 2 or more consecutively missed visits, the participant will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits. If the participant 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 on 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 assessment/scan dates of the component that indicates progression.
- When censoring a participant for PFS, the participant will be censored at the latest of the scan dates contributing to a particular overall visit assessment.

Analysis of PFS

The secondary endpoint PFS analysis will also be based on the programmatically derived RECIST 1.1 using the investigator tumor assessments. The analysis will be performed in both the HPV-unrelated Analysis Set and FAS using a stratified log-rank test, adjusting for HPV status (for FAS only), WHO/ECOG PS, and number of prior lines of therapy in the R/M setting. The effect of Arm A vs Arm B will be estimated by the HR together with its corresponding 95% CI and p-value.

Kaplan Meier plots of PFS will be presented by treatment arm. Summaries of the number and percentage of participants experiencing a PFS event and the type of event (RECIST 1.1 or death) will be provided along with median PFS for each treatment arm.

Sensitivity analysis of PFS

Sensitivity analyses will be performed to assess attrition bias by repeating the PFS analysis except that the actual PFS event times, rather than the censored times, of participants who progressed or died in the absence of progression immediately following 2 or more non-evaluable tumor assessments will be included. In addition, participants who take subsequent therapy prior to progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy. This analysis will be supported by a KM plot of the time to censoring where the censoring indicator of the PFS analysis is reversed.

Further sensitivity analysis may be documented in the SAP.

Subgroup analysis

Subgroup analyses will be conducted comparing PFS (per RECIST 1.1 using investigator assessments) between Arm A and Arm B in the subgroups, as specified in Section 9.4.2.1.

9.4.2.2.2 Objective Response Rate

Derivation of ORR

ORR is defined as the proportion of participants with measurable disease who have a confirmed CR or PR, as determined by the investigator at local site per RECIST 1.1. Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Participants who discontinue study intervention without progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR.

Analysis of ORR

Objective response rate will be based on the programmatically-derived RECIST using the investigator tumor data. ORR will be compared between Arm A and Arm B using a logistic regression model, adjusting for the same factors as the primary endpoint (HPV status [for FAS only], WHO/ECOG PS, number of prior lines of therapy in the R/M setting). The results of the analysis will be presented in terms of an odds ratio together with its associated profile likelihood 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 in the subset of participants in the HPV-unrelated Analysis Set who had measurable disease at baseline. This analysis will be repeated for the subset of participants in the FAS who had measurable disease at baseline.

Summaries will be produced that present the number and percentage of participants with a tumor response (CR/PR). Overall visit response data will be listed for all participants (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.

9.4.2.2.3 Duration of Response

Derivation of DoR

The secondary endpoint DoR (per RECIST 1.1 using investigator assessment) 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 participant does not progress following a response, then their DoR will be censored at the PFS censoring time. Duration of response will not be defined for those participants who do not have documented response.

Analysis of DoR

Kaplan Meier plots of DoR based on the investigator assessment of RECIST 1.1 will be

presented. Median DoR will also be summarized and calculated from the KM curve. Only participants who have a confirmed response will be included in this summary table. Swimmer plots that clearly show the profile of each participant who responds will also be produced.

9.4.2.2.4 Patient-reported Outcome: EORTC QLQ-C30

Scoring

The EORTC QLQ-C30 will be scored according to the EORTC QLQ-C30 Scoring Manual (Fayers et al 2001). An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales, each of the functional scales, and the global measure of health status scale in the EORTC QLQ-C30 according to the EORTC QLQ-C30 Scoring Manual. Higher scores on the global measure of health status and functional scales indicate better health status/function, but higher scores on symptom scales represent greater symptom severity. For each subscale, if < 50% of the subscale items are missing, then the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscales (Fayers et al 2001). If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded.

Analysis methods

A main PRO instrument identified in the secondary objectives are global health status/QoL, physical functioning, fatigue, pain, and appetite loss subscales of the EORTC QLQ-C30.

The primary assessment of global health status/QoL, physical functioning, or symptom will focus on comparing the mean change from baseline between treatment arms. The analysis population will be a subset of the HPV-unrelated Analysis Set, including all participants in the HPV-unrelated Analysis Set with an evaluable baseline assessment and at least one evaluable post-baseline assessment. Change from baseline will be analyzed using a mixed-model repeated measurements analysis of all the post-baseline scores. The model will include treatment arm, visit, and treatment by visit interaction as explanatory variables, and the baseline score and baseline score by visit as covariates. Adjusted mean change from baseline estimates per treatment arm and corresponding 95% CIs will be presented, along with an overall estimate of the treatment difference, 95% CI, and p-value.

Additional analyses will include time to deterioration.

The analysis will be repeated for a subset of the FAS, including all randomized participants with an evaluable baseline assessment and at least one evaluable post-baseline assessment.

Details of all statistical analyses and appropriate sensitivity analyses will be described in full in the SAP.

9.4.2.2.5 Patient-reported Outcome: EORTC QLQ-H&N35

Scoring

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.

Analysis methods

Another main PRO instrument identified in the secondary objectives are from the 4-symptom scales/items in the QLQ-H&N35 (pain, swallowing, senses, and speech).

The primary assessment of symptoms will focus on comparing the mean change from baseline between treatment arms. The analysis population will be a subset of the HPV-unrelated Analysis Set, including all participants in HPV-unrelated Analysis Set with an evaluable baseline assessment and at least one evaluable post-baseline assessment. Change from baseline will be analyzed using a mixed-model repeated measurements analysis of all the post-baseline scores. The model will include treatment arm, visit, and treatment by visit interaction as explanatory variables, and the baseline score and baseline score by visit as covariates. Adjusted mean change from baseline estimates per treatment arm and corresponding 95% CIs will be presented, along with an overall estimate of the treatment difference, 95% CI, and p-value.

Additional analyses will include time to deterioration.

The analysis will be repeated for a subset of the FAS, including all randomized participants with an evaluable baseline assessment and at least one evaluable post-baseline assessment.

Details of all statistical analyses and appropriate sensitivity analyses will be described in full in the SAP.

9.4.2.3 Exploratory Endpoints

9.4.2.3.1 CCI

CCI

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9.4.2.3.2 CCI

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9.4.2.3.3 CCI

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9.4.2.3.4 CCI

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9.4.3 Safety

9.4.3.1 Calculation or Derivation of Safety Variables

9.4.3.1.1 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 participants. 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 IMP (ie, the last dose of monalizumab, cetuximab, or placebo). For AEs, on-treatment (or treatment-emergent) AEs will be defined as any AEs that started after dosing or prior to dosing and which worsen following exposure to the study treatment.

Adverse events observed up until 90 days following discontinuation of the IMP or until the initiation of the first subsequent therapy following discontinuation of treatment (whichever occurs first) will be used for the reporting of the AE summary tables. This will more accurately depict AEs attributable to study treatment only, as a number of AEs up to 90 days following discontinuation of the IMP are likely to be attributable to subsequent therapy. However, to assess the longer-term toxicity profile, AE summaries will also be produced containing AEs observed up until 90 days following discontinuation of the IMP (ie, without taking subsequent therapy into account). Any events in this period that occur after a participant has received further therapy for cancer (following discontinuation of study treatment) will be flagged in the data listings.

The SAF will be used for reporting of safety data.

A separate data listing of AEs occurring > 90 days after discontinuation of IMP will be produced. These events will not be included in AE summaries.

9.4.3.1.2 Other 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 formula:

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

The denominator used in laboratory summaries will only include evaluable participants, 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 participants 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 participant need only have 1 post-dose value recorded.

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

9.4.3.2 Analysis of safety variables

All safety analyses will be performed on the SAF. Safety and tolerability data will be presented by treatment arm based on actual treatment received.

Data from all cycles of treatment will be combined in the presentation of safety data. Adverse events (both in terms of Medical Dictionary for Regulatory Activities preferred terms and CTCAE grade) will be listed individually by participant. The number of participants 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.

Other safety data will be assessed in terms of physical examination, clinical chemistry, hematology, vital signs, WHO ECOG/PS, and ECGs. Exposure to monalizumab plus cetuximab combination therapy and cetuximab will be summarized. Time on study, dose delays/dose modifications of monalizumab and cetuximab will also be summarized. At the end of the study, appropriate summaries of all safety data will be produced, as defined in the SAP.

9.4.4 Other Analyses

9.4.4.1 Healthcare Resource Use

The potential impact the disease and treatment have on healthcare resource use will be analyzed for the purposes of submissions to payers (eg, pricing and reimbursement agencies and health technology assessment bodies). Descriptive statistics (as appropriate, including means, median, counts and frequencies, standard deviation, interquartile range, skew, and range) will be provided for each treatment arm on the different types of hospital admissions, the length of stay for participants admitted to the hospital (eg, inpatient, emergency room, intensive care unit), as well as the participant's primary sign or symptom. To support submissions to payers, additional analyses may be undertaken and will be outlined in a separate Payer Analysis Plan.

9.4.4.2 Pharmacokinetic Data

Monalizumab serum concentration data will be listed for each participant by monalizumab treatment and each dosing day; cetuximab serum concentration data will be listed for each participant with cetuximab treatment and each dosing day. Summary will be provided for PK Analysis Set.

9.4.4.3 Immunogenicity Data

Immunogenicity results will be listed by participant, and a summary will be provided by the number and percentage of participant who develop detectable CCI [redacted]

and anti-cetuximab antibodies. The immunogenicity titer will be listed for samples confirmed positive for the presence of CCI and anti-cetuximab antibodies.

The effect of immunogenicity as well as the effect of its neutralizing properties on PK, pharmacodynamics, efficacy, and safety will be evaluated, if the data allow. A detailed plan will be written by the Sponsor Clinical Pharmacology group or designee.

9.4.4.4 Pharmacokinetic/Pharmacodynamic Relationships

If the data are suitable, the relationship between PK exposure and efficacy/safety parameters may be investigated graphically or using an appropriate data modeling approach.

9.4.4.5 Biomarker Data

CCI

9.5 Interim Analyses

Two IAs are planned as described below.

IA1: The first interim analysis will be performed when approximately 99 OS events have been observed in the HPV-unrelated participants (25% information fraction) in participants randomized at least 2 months before the DCO for the futility analysis (ie, with a minimum follow-up of 2 months). Based on enrollment assumptions, it is expected that this will occur approximately 19 months after randomization of the first participant. The objective of IA1 is to evaluate futility of the Arm A compared to Arm B in terms of OS in the HPV-unrelated participants.

OS will be analyzed using a stratified Cox Proportional Hazards model as described in Section 9.4.2.1 and HR with its CI will be reported. The futility criteria are determined as observed HR at IA1 > CCI which corresponds to CCI conditional power assuming future data is consistent with current IA trend.

IA2: The second interim analysis will be performed when approximately 278 OS events have been observed in the study (56% maturity or 70% information fraction) in the HPV-unrelated population. Based on enrollment assumptions, it is expected that this will occur approximately 30 months after randomization of the first participant.

The IA2 will evaluate the efficacy of Arm A compared to Arm B in terms of OS in the HPV-unrelated population (primary objective).

The SAP will describe the planned IAs in greater detail.

9.6 Data Monitoring Committee

For details on the Independent Data Monitoring Committee, refer to Appendix A 5

9.7 Impact of COVID-19 on Data

Depending on the extent of any impact, summaries of data relating to participants diagnosed with COVID-19, and impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued study treatments, and other protocol deviations) may be generated. More detail will be provided in the SAP.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulation
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Sponsor will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with the Sponsor.

Regulatory reporting requirements for SAEs

- Prompt notification by the investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the [IB or state other documents] and will notify the IRB/ IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- If a participant declines to participate in a voluntary exploratory genetic research component of the study, there will be no penalty or loss of benefit to the participant and he/she will not be excluded from other aspects of the study.
- If a participant's partner becomes pregnant during or within 90 days after the last dose of study intervention, the partner is asked to sign the "Adult Study Informed Consent Form for Pregnant Partners of Study Patients" and provide information about the pregnancy accordingly.

Participants who are rescreened will resign and date their original ICF(s), next to their original signature and date, or according to local or site-specific procedures.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the

samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

The safety of all Sponsor clinical studies is closely monitored on an on-going basis by Sponsor representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the CSP and letters to investigators.

An IDMC comprised of independent experts will be convened and will meet approximately 6 months after the study has started or after the first 60 participants have been randomized, whichever occurs first. The IDMC will review safety assessments and make recommendations to continue, amend, or stop the study based on safety findings. The committee will meet approximately every 6 months thereafter. For the IAs, the IDMC will review unblinded interim data and inform the Sponsor whether the interim boundaries specified in Section 9.5 are met. The IDMC will inform the Sponsor of its recommendation according to the IDMC Charter.

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

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the relevant study plans.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A 9 Study and Site Start and Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant(s) in the study and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

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

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

B 2 Definitions of Serious Adverse Event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, 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.
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

AEs for **malignant tumors** reported during a study should generally be assessed as **Serious** AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **Non-Serious** AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumor event in question is a new

malignant tumor (ie, it is *not* the tumor for which entry into the study is a criterion and that is being treated by the IMP under study and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumor.

Life threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the participant'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 participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical treatment

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 participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Intensity rating scale

The grading scales found in the revised NCI CTCAE, Version 5.0 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 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 Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 3 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 participant 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, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? The Sponsor 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 no available facts or arguments to suggest a causal relationship, 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.

B 4 Medication Error

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

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

Medication error includes situations where an error.

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

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

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT errors)

- Wrong drug administered to participant (excluding IRT errors)

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

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

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

Appendix C Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis, including COVID-19 Outbreak

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following agreement from the sponsor.

C 1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections C 2 to C 4. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

C 2 Rescreening of Participants to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened participants. The investigator should confirm this with the designated Study Clinical Lead.

In addition, during study disruption there may be a delay between confirming eligibility of a participants and either enrolment into the study or commencing of dosing with IMP. If this delay is outside the screening window specified in Section 6.3.1 the participant will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a participant in addition to that detailed in Section 5.4. The procedures detailed in Section 6.3.1 must be undertaken to confirm eligibility using the same randomization number as for the participant.

C 3 Telemedicine Visit to Replace On-site Visit (Where Applicable)

In this appendix the term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow AEs and concomitant medication to be reported and documented.

C 4 Data Capture During Telemedicine or Home/Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP from the study site or TPV service in the source documents, or by the participant themselves.

C 5 COVID-19 Risk Assessment

The safety of participants is of primary importance. Any potential risks of participating in the study, particularly with the added challenges due to COVID-19 outbreak, should be weighed against the anticipated benefit (see also Principle 2.2 of ICH GCP). Investigators are advised to use clinical judgment in determining infection prevention precautions for study participants.

The emergence of SARS-CoV-2 presents a potential safety risk for cancer patients. Participants enrolling in this study may require more frequent visits to the site for study treatment administration and for study assessments compared to participants receiving standard of care. Therefore, several risk mitigation factors have been implemented related to study conduct during the COVID-19 outbreak, for patient management in an event of COVID-19, and actions to be taken on study treatment (see Section C 8). With these measures in place, it is considered that the anticipated potential benefits for the participants enrolled in this study outweigh the potential risks. All implemented measures prioritize trial participant safety and data validity; in case these two conflict with each other, trial participant safety should always prevail (see also European Medicines Agency Guidance on the management of clinical trials during the COVID-19 [coronavirus] pandemic [EMA 2020]).

Notably, participants with active COVID-19 infection confirmed by local laboratory testing will not be eligible for study enrolment (see CSP Section 5.2, Exclusion Criterion 11).

C 6 Potential Risks during COVID-19

Every effort should be made to follow the CSP. Section C 9 provides a dose modification and management plan for participants with confirmed or suspected COVID-19 who are being treated with IMP (monalizumab/placebo and cetuximab). The risk-benefit assessment should be carefully considered for each participant enrolling in the study based on the known safety risks related to COVID-19, individual needs, and local guidelines and restrictions. Investigators must continue to use their best clinical judgment in determining the most optimal care for participants and utmost diligence in determining their eligibility for study participation, continued study treatment, and overall assessment of benefit/risk of study

treatment or participation.

The sponsor must be promptly notified of a site's inability to perform study activities due to COVID-19 outbreak in order to minimize any potential risks.

C 7 New Participant Enrolment

Study sites may continue to recruit new participants into the study provided the following activities to preserve study integrity can be met:

- Upon discussion with the site monitor, the study site has confirmed the ability to enroll and manage new participants effectively and in compliance with the protocol.
- Data will continue to be entered into the eCRF and queries resolved in a timely manner.

Per CSP Exclusion Criterion 11 (see CSP Section 5.2), participants with uncontrolled intercurrent illness, including but not limited to, ongoing or active infection are not eligible for the study participation and hence such participants (including those who have confirmed COVID-19) should not be included for study participation.

C 8 Study Treatment Administration

If an AE or SAE is associated with COVID-19, the investigator should determine whether the participants' treatment with investigational product should continue, be interrupted, or be discontinued in accordance with the CSP.

Adverse events, SAEs, cycle delays and/or treatment suspensions associated with COVID-19 along with logistical issues should be reported according to the eCRF Completion Guidelines.

For dosing discontinuations, where applicable, the dosing discontinuation guidelines should be followed, and the End of Treatment Form(s) completed

C 9 Ongoing Participants

Participants receiving study intervention should continue to undergo safety assessments prior to dosing in accordance with the CSP. In case it is not feasible to perform safety assessments, study intervention should be interrupted until such assessments can be completed.

C 9.1 If a Participant has an Event Suspected to be COVID-19

Delay or omit study intervention as appropriate and test for COVID-19 per local health authority or institutional guidance.

- Signs and symptoms of COVID-19 include but are not limited to new onset of fever, new or worsening cough, shortness of breath, difficulty breathing and sometimes

abnormal chest imaging and may be similar to those of an imAE. Toxicity management guidelines for imAEs should be considered if the symptoms are consistent with an imAE.

- In accordance with the CSP and the TMGs for imAEs, thorough evaluation should be performed to accurately identify the underlying pathology in case an AE is encountered for a participant.
- If COVID-19 is ruled out, study intervention may be resumed per the CSP and TMGs (if applicable).
- If COVID-19 **is confirmed or diagnosis still suspected after evaluation**, manage COVID-19 per local guidance until full recovery.

C 9.2 Participants with Confirmed COVID-19

Participants with confirmed COVID-19 (by local laboratory testing and/or combination of key symptoms) should have study intervention withheld and COVID-19 managed per local guidance.

In case of confirmed COVID-19 and a simultaneous imAE requiring treatment, investigators are advised to apply clinical judgement regarding the use of corticosteroids as per the monalizumab TMGs. This includes also the consideration of alternate immunosuppressive agents other than corticosteroids for imAE management, depending on the individual participant's presentation (Curigliano et al 2020).

C 9.3 Restarting Study Intervention

Study intervention must not be resumed until recovery from COVID-19 (eg, confirmed by imaging, lab testing and/or absence of symptoms) and COVID-19-specific treatment has been completed per local guidance.

The Study Clinical Lead should be contacted if any additional guidance or clarification is needed.

C 9.4 Vaccination Against COVID-19

Protocol restrictions applying to live attenuated vaccines are relevant for live attenuated COVID-19 vaccines as well. Investigators should apply their discretion assessing the risk-benefit of other types of COVID-19 vaccines for participants in clinical trials. Ideally, administration of the vaccine should be done on a different day other than the day of study drug administration to differentiate any potential AEs seen from the vaccine and study drug. The administration of the vaccine and any potential AEs associated with the vaccine are to be documented on the concomitant medication and AE eCRFs, respectively.

C 10 References

Curigliano et al 2020
Curigliano G, Banerjee S, Cervantes A, Garassino M, Garrido P, Girard N et al. Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. Ann Oncol 2020;31(10):1320-35.

EMA 2020
EMA, Clinical Trials Facilitation and Coordination Group, European Commission. Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic, Version 2, 27 March 2020. Available from: URL: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf. Cited date: 17 December 2020.

Appendix D Handling of Human Biological Samples

D 1 Chain of Custody

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

The investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

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

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

D 2 Withdrawal of Informed Consent for Donated Biological Samples

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

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the

withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action documented and study site notified.

D 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B, or Exempt

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. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900:

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, C, D, and E viruses. 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 - Substances that do not contain infectious substances or substances that are unlikely to cause disease in humans or animals are not subject to these regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

Appendix E CCI

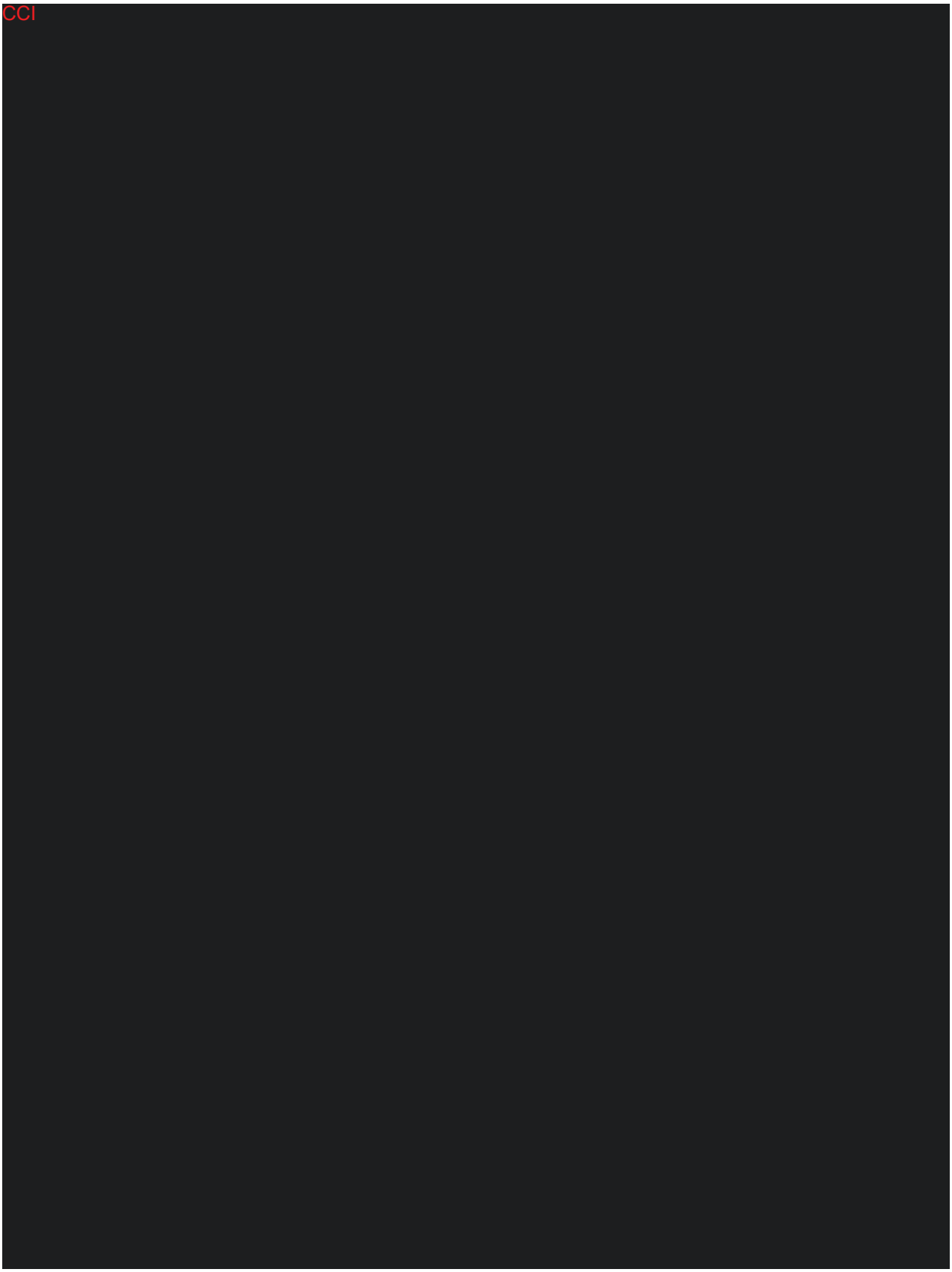
E 1 CCI

CCI

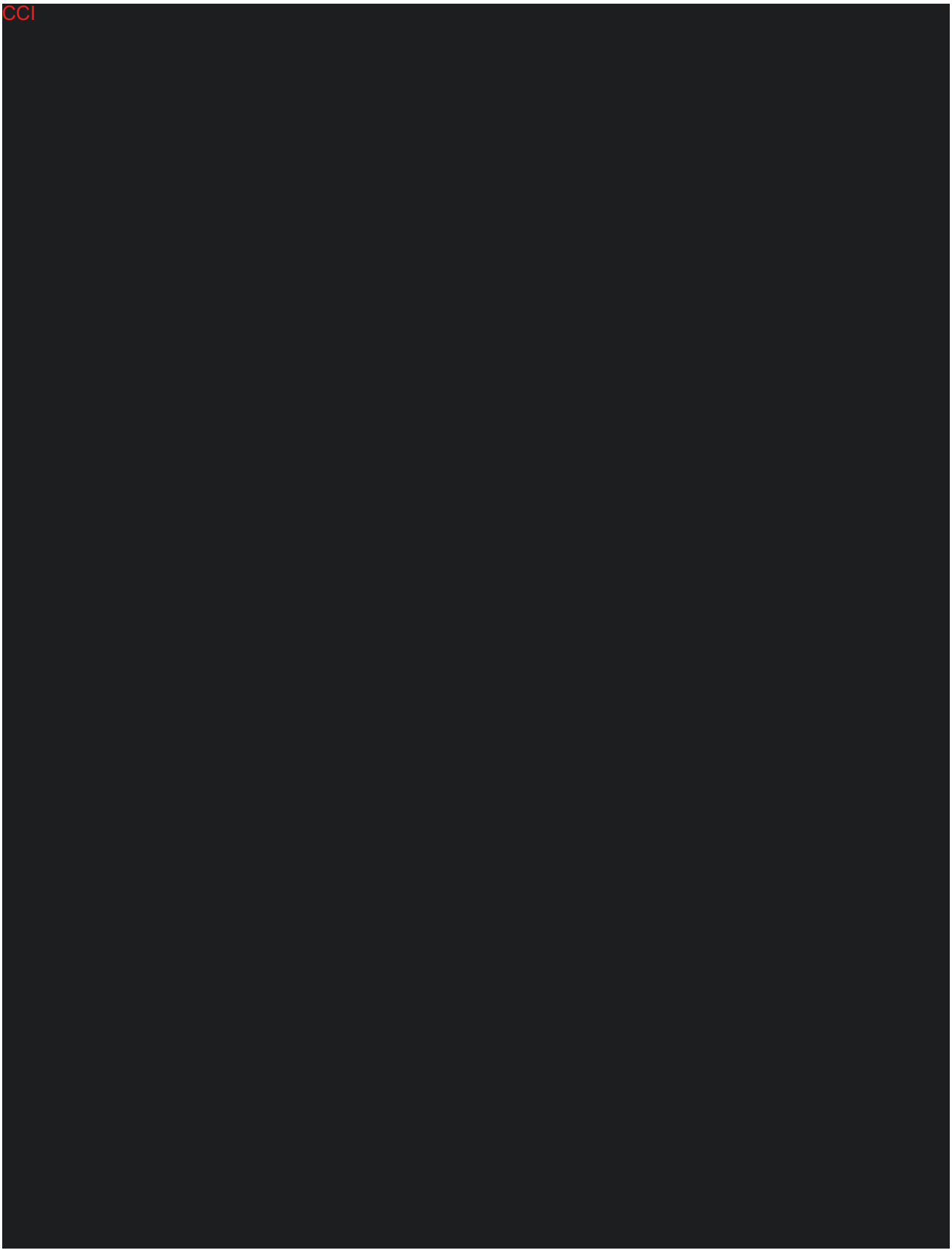
E 2 CCI

CCI

CCI



CCI



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

F 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with the Sponsor clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

F 2 Definitions

Potential Hy's Law
Aspartate aminotransferase or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law
Aspartate aminotransferase 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.

F 3 Identification of Potential Hy's Law Cases

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

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

Local laboratories being used:

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

Determine whether the participant meets PHL criteria (see Section F 2 Definitions within this appendix for definition) by reviewing laboratory reports from all previous visits

Promptly enter the laboratory data into the laboratory eCRF

F 4 Follow-up

F 4.1 Potential Hy's Law Criteria Not Met

If the participant does not meet PHL criteria the investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

F 4.2 Potential Hy's Law Criteria Met

If the participant does meet PHL criteria the investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Section F 6)
- Notify the Sponsor representative who will then inform the central study team
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of PHL; serious criteria 'important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For participants that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change # in the participant's condition

- The Study Clinical Lead contacts the investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data

- Subsequent to this contact the investigator will:

  – Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  – Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Clinical Lead.
  – Complete the three Liver eCRF Modules as information becomes available

 # A 'significant' change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the Study Clinical Lead if there is any uncertainty.

F 5 Review and Assessment of Potential Hy's Law Cases

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

As soon as possible after the biochemistry abnormality was initially detected, the Study Clinical Lead 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, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The Sponsor Global Clinical Lead or equivalent 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.

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF

- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the Sponsor's 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:

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

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

F 6 Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment

This section is applicable to participants 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 participants' 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 Sponsor representative, who will inform the central Study Team, then follow the subsequent process described in Section F 4.2

F 7 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a participant 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 eg, chronic or progressing malignant disease, severe infection, or liver disease or did the participant meet PHL criteria prior to starting study treatment and at their first on-study treatment visit as described in Section F 6?

If **No**: follow the process described in Section F 4.2 for reporting PHL as an SAE.

If **Yes**: Determine if there has been a significant change in the participant's condition # compared with when PHL criteria were previously met.

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section F 4.2 for reporting PHL as an SAE

A 'significant' change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the Study Clinical Lead if there is any uncertainty.

F 8 Laboratory Tests

These are recommended laboratory tests to be performed in cases of PHL. Any test results need to be recorded in the eCRF.

Hy's Law Laboratory Tests

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA IgG anti-HCV HCV RNA [a] IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-liver/kidney microsomal Ab (Anti-LKM) Anti-smooth muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

[a] HCV RNA is only tested when IgG anti-HCV is positive or inconclusive.

F 9 References

Aithal et al, 2011
Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

FDA Guidance for Industry, July 2009
FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'. Available from; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

Appendix G 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 RECIST 1.1 guidelines (Eisenhauer et al 2009). Investigator assessments will use the RECIST 1.1 guidelines described in this appendix. Additional special guidance is provided for evaluation of scans collected after a RECIST 1.1-defined radiological progression.

Imaging Modalities and Acquisition Specifications for RECIST 1.1

A summary of the imaging modalities that can be used for tumor assessment of TLs, NTLs, and NLs is provided in Table 11.

Table 11 Summary of imaging modalities for tumor assessment

Target lesions	Non-target lesions	New lesions
CT MRI	CT MRI Plain X-ray Chest X-ray	CT MRI Plain X-ray Chest X-ray Bone scan (Scintigraphy) FDG-PET/CT

CT = computed tomography; FDG-PET/CT = ^{18}F-Fluoro-deoxyglucose positron emission tomography/CT; MRI = magnetic resonance imaging.

CT and MRI

Computed tomography with iv contrast is the preferred imaging modality (although MRI with iv contrast is acceptable if CT is contraindicated) to generate reproducible anatomical images for tumor assessments (ie, for measurement of TLs, assessment of NTLs, and identification of NLs). It is essential that the same correct imaging modality, image acquisition parameters (eg, anatomic coverage, imaging sequences, etc), imaging facility, tumor assessor (eg, radiologist), and method of tumor assessment (eg, RECIST 1.1) are used consistently for each participant throughout the study. The use of the same scanner for serial scans is recommended, if possible. It is important to follow the image collection/tumor assessment schedule as closely as possible (refer to the SoA; Section 1.3), and this on-study imaging schedule MUST be followed regardless of any delays in dosing or missed imaging visits. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the participant has not progressed, every attempt should be made to perform the subsequent scan acquisitions at the next scheduled imaging visit.

Due to its inherent rapid acquisition (seconds), CT is the imaging modality of choice. Body

scans should be performed with breath-hold scanning techniques, if possible. Therefore, CT of the chest is recommended over MRI due to significant motion artifacts (eg, heart, major blood vessels, breathing) associated with MRI. MRI has excellent contrast and spatial and temporal resolutions; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. In general, local oncology diagnostic imaging parameters are applied for scan acquisition. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases.

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

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

Required anatomical regions to be imaged for assessment of tumor burden (TLs and/or NTLs) at baseline and follow-up visits vary according to the study, and these time points are specified in the SoA (Section 1.3). Examples include the following:

- Intravenous contrast-enhanced CT of chest-abdomen (including the entire liver and both adrenal glands) (-pelvis)
- Non-contrast CT of chest and IV contrast-enhanced abdomen (including the entire liver and both adrenal glands) (-pelvis)
- Intravenous contrast-enhanced CT or MRI of the head and neck
- Intravenous contrast-enhanced MRI (preferred) or CT of the brain

For chest-abdomen (-pelvis) imaging, the following are scanning options in decreasing order of preference, with additional options (2 to 4) for consideration when participants have sensitivity to iv contrast or have compromised renal function:

1 Chest-abdomen (-pelvis) CT with iv CT contrast (most preferred)
2 Chest CT without iv contrast + abdomen (-pelvis) MRI with IV MRI contrast, if CT iv contrast (iodine based) is medically contraindicated at any time during the study

3 Chest-abdomen (-pelvis) CT without iv contrast, if both iv CT and MRI contrast are medically contraindicated or the participant has compromised renal function

4 Chest-abdomen (-pelvis) MRI with iv MRI contrast, if CT cannot be performed at any time during the study

b. Intravenous contrast administration: Optimal visualization and measurement of metastases in solid tumors require consistent administration (dose and rate) of iv contrast as well as timing of scanning. An adequate volume of a suitable contrast agent should be given so that the tumor lesions are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. Oral contrast is recommended to help visualize and differentiate structures in the abdomen and pelvis.

c. Slice thickness and reconstruction interval: It is recommended that CT or MRI scans be acquired/reconstructed as contiguous (no gap) slices with ≤ 5-mm thickness throughout the entire anatomic region of interest for optimal lesion measurements. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses > 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

For CT scans, all window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study.

Chest X-ray

Chest X-ray assessment will not be used for the assessment of TLs. Chest X-ray can, however, be used to assess NTLs and to identify the presence of NLs. However, there is preference that a higher resolution modality, such as CT, be used to confirm the presence of NLs.

Plain X-ray

Plain X-ray may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

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 NTLs and followed by the same method per baseline assessment (CT, MRI, or X-ray).

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 may be recorded in case positive hot-spots appear on a bone scan that were not present on a previous bone scan; however, a newly

observed equivocal hot-spot on a bone scan that cannot be verified with correlative imaging (CT, MRI, or X-ray) of the same anatomical region shall not be the only trigger for a PD assessment at that time point.

FDG-PET/CT

[1]FDG-PET/CT scans may be used as a method for identifying new lesions for RECIST 1.1 assessments according to the following algorithm: NLs will be recorded where there is positive FDG uptake[1] not present on baseline or prior FDG-PET scan or in a location corresponding to a NL on a companion CT/MRI collected close in time to the FDG-PET scan. The PET portion of the PET/CT introduces additional data that may bias an investigator if it is not routinely or serially performed. Therefore, if there is no baseline or prior FDG-PET scan available for comparison, and no evidence of NLs on companion CT/MRI scans, then follow-up CT/MRI assessments should continue as per the regular imaging schedule to verify the unequivocal presence of NLs.

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

Ultrasound

Ultrasound examination will not be used for RECIST 1.1 assessment of tumors as it is not a reproducible acquisition method (operator dependent), is subjective in interpretation, and may not provide an accurate assessment of the true tumor size. Tumors identified by ultrasound will need to be assessed by correlative CT or MRI anatomical scan.

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1 A positive FDG-PET scan lesion should be reported only when an uptake (eg, SUV) greater than twice that of the surrounding tissue or liver is observed.

Other Tumor Assessments

Clinical examination

Clinical examination of skin/surface lesions (by visual inspection or manual palpation) will not be used for RECIST 1.1 assessments. Tumors identified by clinical examination will need to be assessed by correlative CT or MRI anatomical scans.

Endoscopy and laparoscopy

Endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor assessment.

Histology and cytology

Histology or tumor markers on tumor biopsy samples will not be used as part of the tumor response assessment as per RECIST 1.1.

Results of cytological examination for the neoplastic origin of any effusion (eg, ascites, pericardial effusion, and pleural effusion) that appears or worsens during the study will not be used as part of the tumor response assessment as per RECIST 1.1.

Furthermore, an overall assessment of CR (all other disease disappears/reverts to normal) would be changed to PR if an effusion remains present radiologically.

Measurability of Tumor Lesions at Baseline

RECIST 1.1 measurable lesions at baseline

A tumor lesion that can be accurately measured at baseline as ≥ 10 mm in the longest diameter nor non-nodal lesions or ≥ 15 mm in short axis[2] diameter for lymph node lesions with iv contrast-enhanced CT or MRI and that is suitable for accurate repeated measurements.

Non-measurable lesions at baseline

- Truly non-measurable lesions include the following:
  - Bone lesions (see exception below for soft tissue component)
  - Leptomeningeal disease
  - Ascites, pleural effusion, or pericardial effusion
  - Inflammatory breast disease
  - Lymphangitic involvement of skin or lung
- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10-mm to < 15-mm short axis diameter at baseline[3])
- Previously irradiated lesions [4]
  This study allows a previously irradiated lesion as a TL if there has been demonstrated progression in the lesion and it meets reproducible measurability and minimum size requirements and if this is the only lesion available.
- Brain metastasis

Special considerations regarding lesion measurability at baseline

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[2] The short axis is defined as the longest in-plane axis perpendicular to the long axis.

[3] Lymph nodes with <10-mm short axis diameter are considered non-pathological and should not be recorded or followed as NTLs.

[4] Localized post-radiation changes that affect lesion size may occur. Therefore, lesions that have been previously irradiated are typically considered non-measurable and as NTL at baseline and followed up as part of the NTL assessment.

- Bone lesions
  - Bone scan, PET scan, or plain X-ray are not considered adequate imaging techniques to measure bone lesions; however, these techniques can be used to confirm the presence or disappearance of bone lesions.
  - 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 lesions thought to represent 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 participant, these should be selected over cystic lesions as TLs.

RECIST 1.1 TL selection at baseline

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 TLs at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis diameter 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 that can be measured reproducibly should be selected.

Lymph nodes, in any location (local/regional and distant), are collectively considered as a single organ, with a maximum of 2 lymph nodes as TLs. A bilateral organ (eg, adrenal glands), a segmented organ (eg, liver), or a multilobed organ (eg, lung) is each considered as a single organ.

The site and location of each TL should be documented, as well as the longest axis diameter for non-nodal lesions (or short axis diameter for lymph nodes). All measurements should be recorded in millimeters. At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits, the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

Special cases for TL assessment at baseline

- For TLs 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 diameter.

- When lymph nodes are coalesced and no longer separable in a conglomerate mass, the maximal short-axis diameter of the coalesced mass should be recorded. Non-nodal lesions that coalesce should similarly be assessed by the long-axis diameter.
- Tumor lesions selected for fresh screening biopsy should not be selected as TLs, unless imaging occurred at least approximately 2 weeks after biopsy, allowing time for healing.
- 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 diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as an NL.

RECIST 1.1 NTL selection at baseline

All other lesions, including non-measurable lesions and surplus measurable lesions, not recorded as TLs should be identified as NTLs at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Evaluation of Tumor Response and Progression

RECIST 1.1 TL assessment at follow-up

This section defines the criteria used to determine objective tumor visit response for RECIST 1.1-defined TLs. The imaging modality, location, and scan date of each TL identified previously at baseline should be documented at follow-up visits with the long axis diameter for non-nodal lesions or short axis diameter for lymph node lesions. All measurements should be recorded in whole millimeters. The sum of the diameters for all TLs at each follow-up visit will be compared to the baseline sum of diameters (for response or SD) or to the smallest prior (nadir) sum of diameters (for progression).

Special cases for TL assessment at follow-up:

- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as an NL.
- If a TL splits into 2 or more parts, the sum of the diameters of those parts should be recorded.
- If 2 or more TLs merge, then the sum of the diameters of the combined lesion should be recorded for 1 of the lesions and 0 mm recorded for the other lesion(s). If the merged TLs are non-nodal lesions, record the long axis diameter of the merged lesion. If pathologic lymph nodes coalesce and are no longer individually separable within a conglomerate mass, the maximal short axis diameter is recorded.
- 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. The choice of "Too large to measure" in the case report form will trigger an overall visit response of PD.
- When a TL has had an unscheduled, non-protocol intervention, the following apply:
  - Target lesion intervention may include radiotherapy, embolization, excisional biopsy, surgery, etc. that is not a part of study treatment and might adversely affect the size of that TL.
  - If an intervention on a TL is ticked in the eCRF, the diameter of the lesion is still recorded (0mm if no longer present) and is included in the sum of diameters.
  - If a TL intervention is ticked, the intervention must be reported for all subsequent assessments of that TL.
  - If a TL has an intervention, the only Overall Visit Responses allowed to be recorded by the investigator are NE or PD, with PD if the sum of diameters exceeds a 20% increase and at least a 5 mm absolute increase in the visit sum of diameters compared to the previous minimum (nadir) sum of diameters.
  - No visit with a recorded TL intervention can be used as the minimum (nadir) sum of diameters.

Table 12 RECIST 1.1 Evaluation of TLs

CR	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis diameter to < 10 mm.
PR	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters.
SD	Neither sufficient decrease in the sum of diameters to qualify for PR nor sufficient increase to qualify for PD.
PD	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest previous sum of diameters (nadir) - this includes the baseline sum if that is the smallest on study. In addition to the relative increase of 20%, the sum must demonstrate an absolute increase of at least 5 mm from nadir.
NE	Only relevant if any of the TLs at follow-up were not assessed or NE (eg, missing anatomy) or had a lesion intervention at this visit. Note: If the sum of diameters meets the PD criteria, PD overrides NE as a TL response.
NA	Only relevant if no TLs present at baseline.

CR = complete response; NA = not applicable; NE = not evaluable; PD = progression of disease; PR = partial response; SD = stable disease; TL = target lesion.

RECIST 1.1 NTL assessment at follow-up

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs 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.

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 SD or PR in TLs, the overall tumor burden has increased sufficiently to merit unequivocal progression by NTLs. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

Table 13 RECIST 1.1 Evaluation of NTLs

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 NTLs.
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.
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 participants 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.
NA	Only relevant if no NTLs present at baseline

CR = complete response; NA = not applicable; NTL = non-target lesion; PD = progression of disease; TL = target lesion.

RECIST 1.1 NL identification at follow-up

Details, including the imaging modality, the date of scan, and the location of any NLs will also be recorded in the case report form. The presence of one or more NLs is assessed as progression. The finding of a NL 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 NL is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the previously (pre-existing) new lesion has been assessed as unequivocal at a follow-up visit, and then the progression date should be declared using the date of the initial scan when the NL first appeared.

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

RECIST 1.1 evaluation of overall visit response at follow-up

Derivation of overall visit response as a result of the combined assessment of TLs, NTLs, and NLs uses the algorithm shown in Table 14.

Table 14 RECIST 1.1 Overall Visit Response

Target lesions	Non-target lesions	New lesions	Overall visit response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE or NA	No	PR
SD	Non PD or NE or NA	No	SD
NA	Non-CR/Non-PD	No	SD (non-CR/non-PD)
NE	Non PD or NE	No	NE
NA	NE	No	NE
NA	NA	No	NED
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note: An overall assessment of CR (all other disease disappears/reverts to normal) would be changed to PR if ascites remains present radiologically.
CR = complete response; NA = not applicable (only relevant if there were no non-target lesions at baseline), NE = not evaluable; NED = no evidence of diseases (only relevant if there were neither TLs nor NTLs at baseline); PD = progression of disease; PR = partial response; SD = stable disease; TL = target lesion.

The following overall visit responses are possible depending on the extent of tumor disease at baseline:

- For participants with TLs (at baseline): CR, PR, SD, progression of disease (PD), or NE
- For participants with NTLs only (at baseline): CR, Non-CR/Non-PD, PD, or NE
- For participants with no disease at baseline: NED (available as an option in the eCRF), PD, or NE

Evaluation of scans subsequent to RECIST 1.1-defined progression

A follow-up scan is requested at least 4 weeks later and no longer than the next regularly scheduled imaging visit. The follow-up scans provide additional information to the investigator for participant management and further treatment decisions, and since the published RECIST 1.1 (Eisenhauer et al 2009) do not provide guidance on how to assess

scans acquired after RECIST 1.1-defined PD, supplemental instructions for investigators on how to evaluate these follow-up scans are provided below. A subsequent follow-up scan would be considered as having progressive disease if any of the following criteria are met:

- Greater than or equal to 20% increase and at least a 5-mm increase in the sum of diameters of TLs compared with the nadir sum of diameters at 2 consecutive visits, and a further increase of ≥ 5 mm in the sum of diameters at the follow-up scan time point compared with the immediate prior time point
- Significant progression (worsening) of NTLs at the follow-up scan time point compared with the immediate prior time point
- Significant progression (worsening) of previous NLs (pre-existing NLs) at the follow-up scan time point compared with the immediate prior time point
- Additional brand-new unequivocal lesions at the follow-up scan time point

Appendix H Contraception Requirements

Contraception requirements for this study are as follows.

H 1 Female Participant of Child-bearing Potential

Please note, females of childbearing potential are defined as those who are post-menarche, not surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

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

Female participants of childbearing potential who are not totally sexually abstinent (ie, refraining from heterosexual intercourse during the entire period of risk associated with study treatments) and intend to be sexually active with a nonsterilized male partner must use at least one highly effective method of contraception (Table 15) from the time of screening throughout the total duration of the drug treatment and for 4 months after the last dose of study intervention. Non-sterilized male partners of a female participant of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence (eg, calendar, symptothermal, post-ovulation methods), the rhythm method, the withdrawal method (coitus interruptus), and lactational amenorrhea method are not acceptable methods of contraception. Female participants should refrain from breastfeeding throughout this period.

H 2 Male Participants With a Female Partner of Childbearing Potential

Non-sterilized male participants (including males sterilized by a method other than bilateral orchidectomy, eg, vasectomy) who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) from the time of screening throughout the total duration of the drug treatment and for 4 months after the last dose of study

intervention. Periodic abstinence (eg, calendar, symptothermal, post-ovulation methods), the rhythm method, the withdrawal method (coitus interruptus), and lactational amenorrhea method are not acceptable methods of contraception. Male participants should refrain from sperm donation throughout this period.

Vasectomized (ie, sterile) males are considered fertile and should still use a male condom plus spermicide as indicated above during the clinical study.

Even if the female partner is pregnant, male participants should still use a condom, as indicated above during the clinical study, if there is a concern about damaging the developing fetus from drug in ejaculate.

Female partners (of childbearing potential) of male participants must also use a highly effective method of contraception throughout this period (Table 15).

H 3 Highly Effective Methods of Contraception

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly, are described in Table 15.

Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; spermicide alone; female cap, diaphragm, or sponge with or without spermicide; non copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills (also known as progesterone-only or “mini-pill”) where inhibition of ovulation is not the primary mode of action [excluding Cerazette®/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 15 Highly Effective Methods of Contraception (< 1% Failure Rate)

Barrier/intrauterine methods	Hormonal methods [b]
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (eg, Mirena®) [a]	• Implants: Etonogestrel-releasing implants (eg, Implanon® or Norplant®) • Intravaginal devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®) • Injection: Medroxyprogesterone injection (eg, Depo-Provera®) • Combined pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Ortho Evra®) • Minipill: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based pill

[a] This is also considered a hormonal method.

[b] The brand names in this table are examples only and availability will vary by country.

Appendix I Patient-reported Outcomes

I 1 EORTC QLQ-C30

I 2 EORTC QLQ-H&N35

I 3 CCI [redacted]

I 4 CCI [redacted]

I 5 CCI [redacted]

I 6 CCI [redacted]

I 1 EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): 31 _____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

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

I 2 EORTC QLQ-H&N35

ENGLISH

EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Have you had pain in your mouth?	1	2	3	4
32.	Have you had pain in your jaw?	1	2	3	4
33.	Have you had soreness in your mouth?	1	2	3	4
34.	Have you had a painful throat?	1	2	3	4
35.	Have you had problems swallowing liquids?	1	2	3	4
36.	Have you had problems swallowing pureed food?	1	2	3	4
37.	Have you had problems swallowing solid food?	1	2	3	4
38.	Have you choked when swallowing?	1	2	3	4
39.	Have you had problems with your teeth?	1	2	3	4
40.	Have you had problems opening your mouth wide?	1	2	3	4
41.	Have you had a dry mouth?	1	2	3	4
42.	Have you had sticky saliva?	1	2	3	4
43.	Have you had problems with your sense of smell?	1	2	3	4
44.	Have you had problems with your sense of taste?	1	2	3	4
45.	Have you coughed?	1	2	3	4
46.	Have you been hoarse?	1	2	3	4
47.	Have you felt ill?	1	2	3	4
48.	Has your appearance bothered you?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at all	A little	Quite a bit	Very much
49. Have you had trouble eating?	1	2	3	4
50. Have you had trouble eating in front of your family?	1	2	3	4
51. Have you had trouble eating in front of other people?	1	2	3	4
52. Have you had trouble enjoying your meals?	1	2	3	4
53. Have you had trouble talking to other people?	1	2	3	4
54. Have you had trouble talking on the telephone?	1	2	3	4
55. Have you had trouble having social contact with your family?	1	2	3	4
56. Have you had trouble having social contact with friends?	1	2	3	4
57. Have you had trouble going out in public?	1	2	3	4
58. Have you had trouble having physical contact with family or friends?	1	2	3	4
59. Have you felt less interest in sex?	1	2	3	4
60. Have you felt less sexual enjoyment?	1	2	3	4

During the past week:	No	Yes
61. Have you used pain-killers?	1	2
62. Have you taken any nutritional supplements (excluding vitamins)?	1	2
63. Have you used a feeding tube?	1	2
64. Have you lost weight?	1	2
65. Have you gained weight?	1	2

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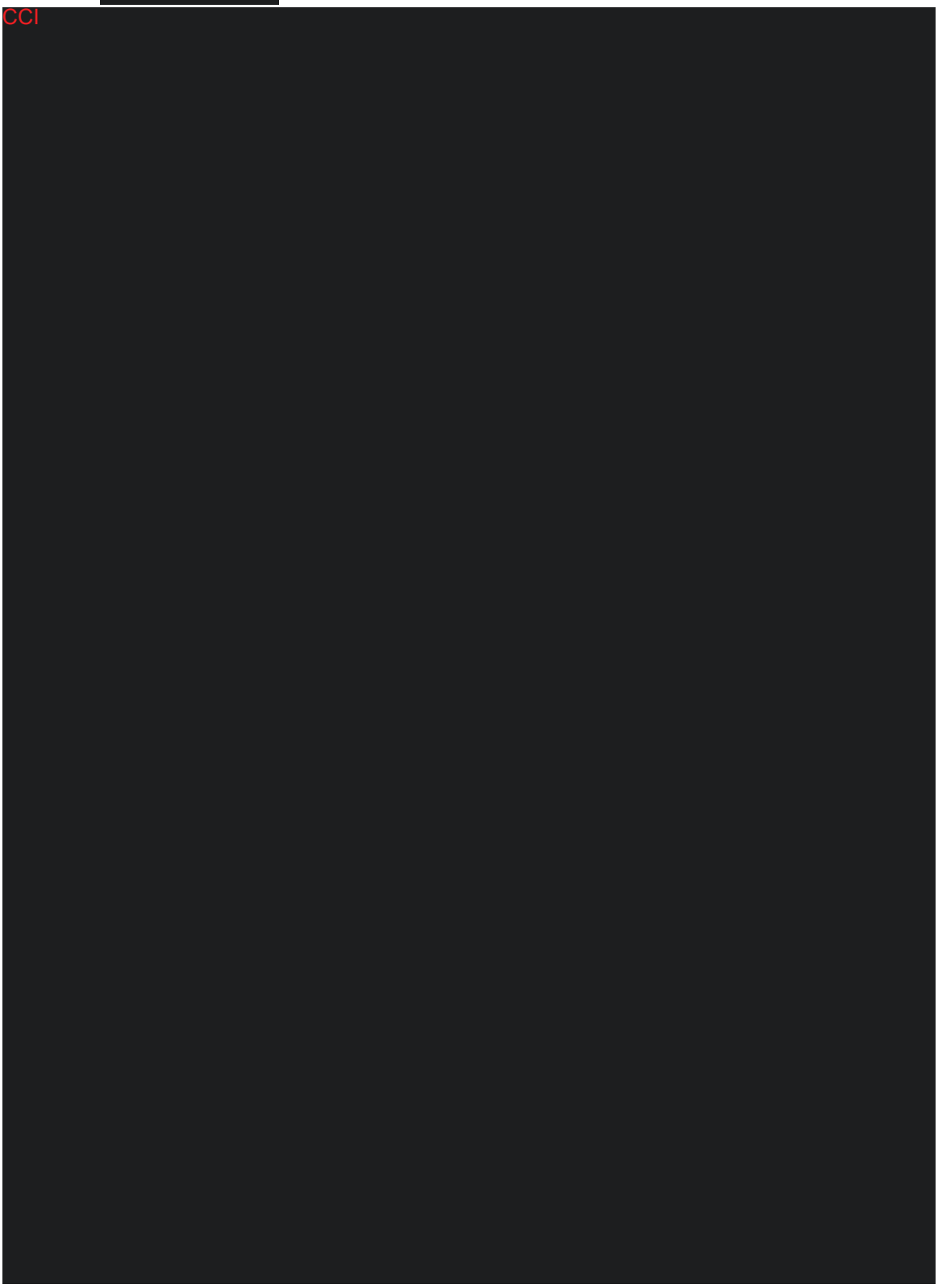

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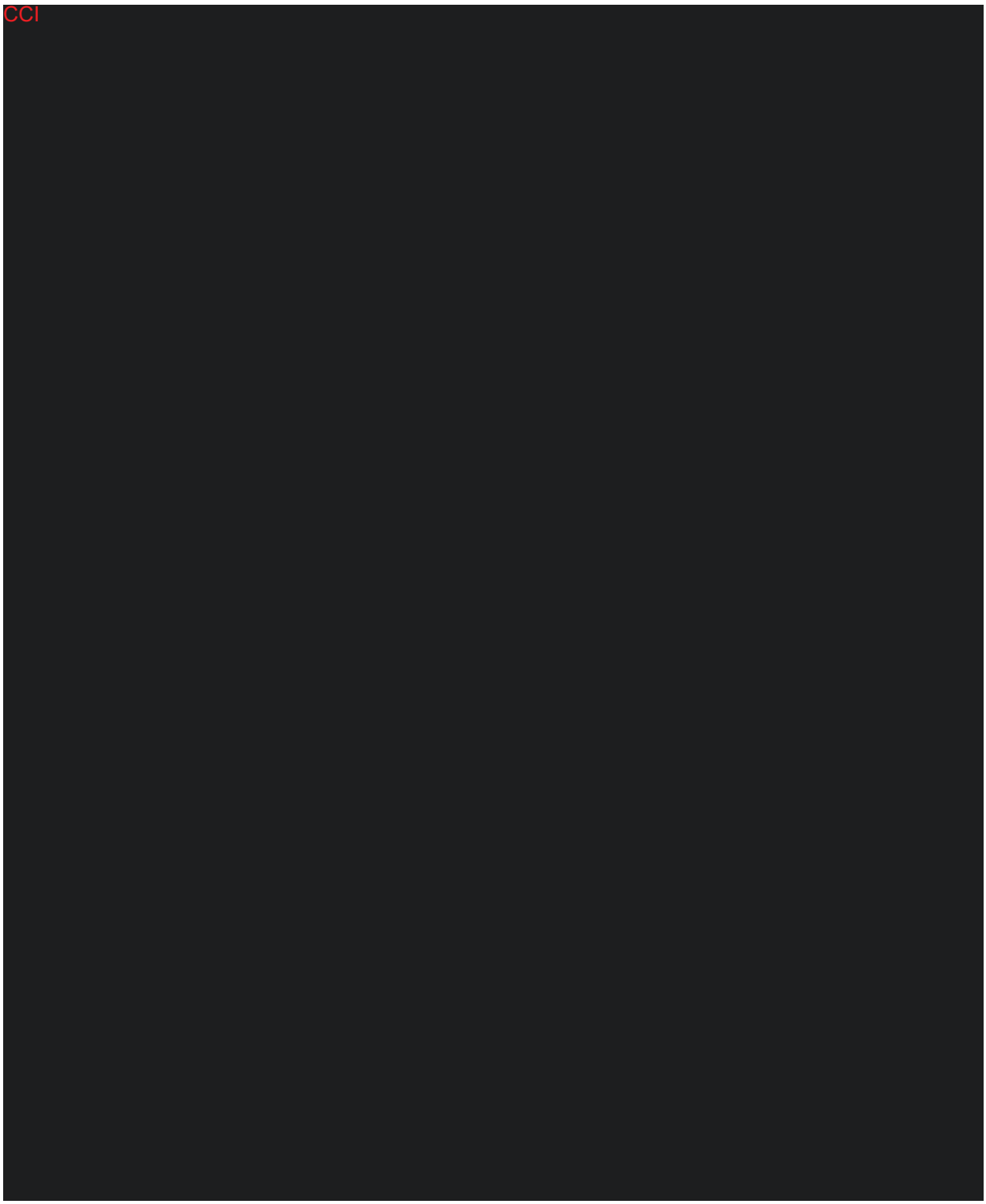

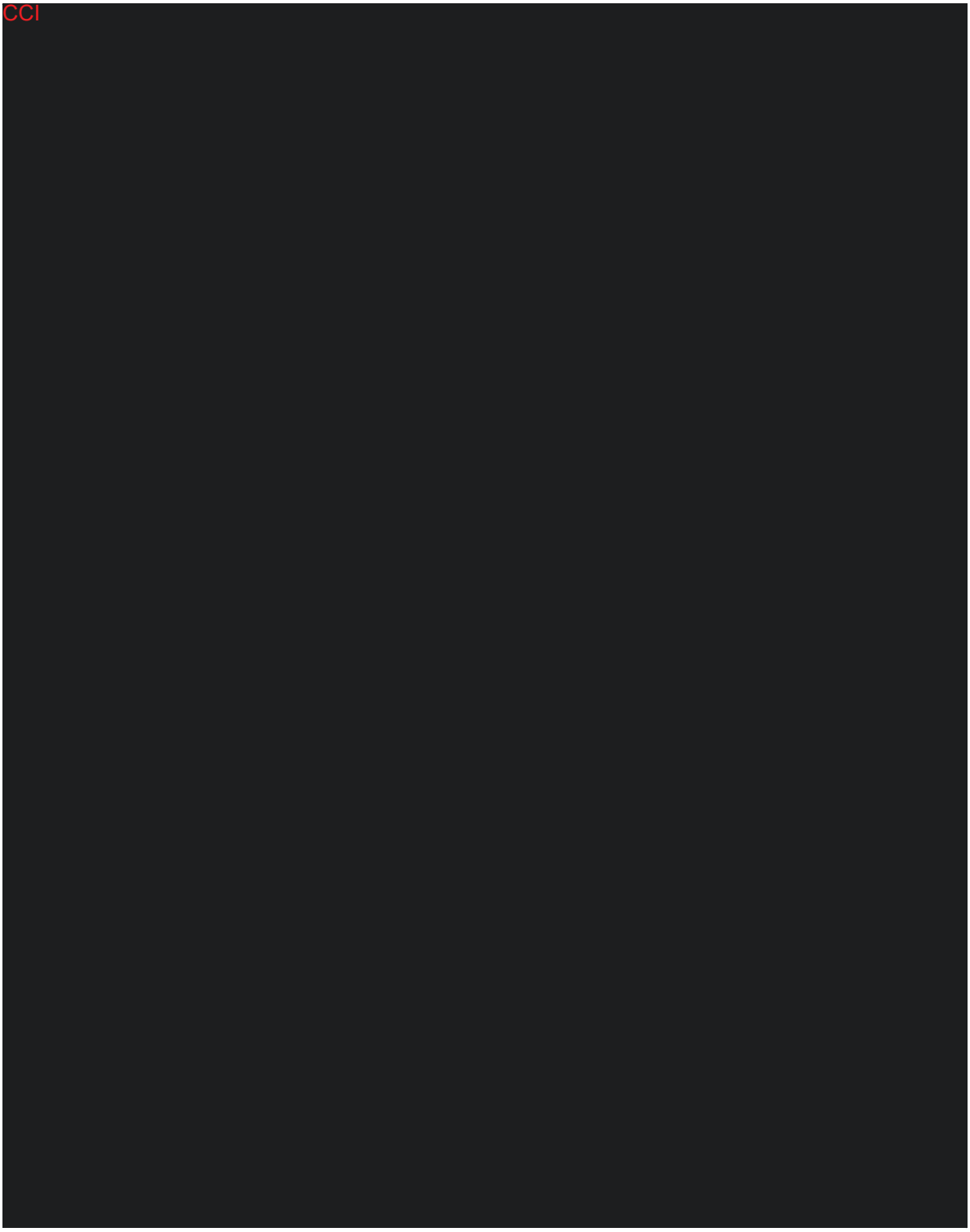
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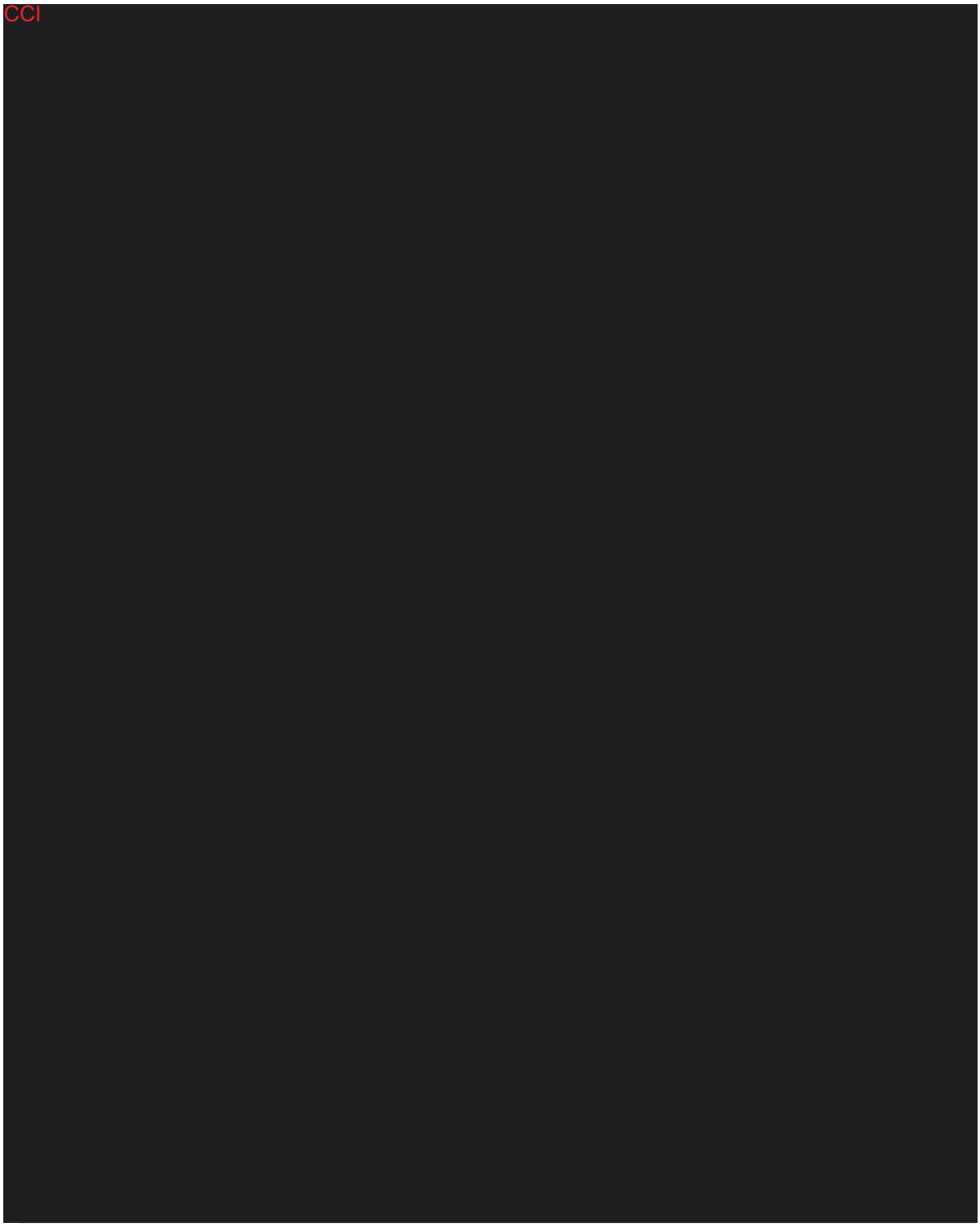
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Appendix J Study Participant Feedback Questionnaire

Patient Experience Initiative

Study Participant Feedback Questionnaire (SPFQ)

Version 1.0

Prepared by:

TransCelerate Patient Experience Initiative Team

TransCelerate BIOPHARMA INC.

Study Participant Feedback Questionnaire (SPFQ)

Your experience before you started the study

Thank you for your participation. Your experiences in this trial are important to us and we would like to hear about them. Your answers will help us improve future trials. There are no right or wrong answers, and it will take approximately 15 minutes to complete. Your answers will be kept anonymous and will not impact your participation in this trial.

Please select **one** response for each item.	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1. I understand the treatment process in this trial (for example: when and how to take or use a treatment)	0	1	2	3	4
2 The information given to me before I joined the trial was everything I wanted to know (for example: visits and procedures, time commitment, who to contact with questions)					
3 The information given to me before I joined the trial was easy for me to understand (for example: visits and procedures, time commitment, who to contact with questions)					
4 I felt comfortable that I could ask any questions before I joined the trial					

TransCelerate BIOPHARMA INC.

Study Participant Feedback Questionnaire (SPFQ)

Your experience during the trial

Thank you for your participation. Your experiences in this trial are important to us and we would like to hear about them. Your answers will help us improve future trials. There are no right or wrong answers, and it will take approximately 15 minutes to complete. Your answers will be kept anonymous and will not impact your participation in this trial.

Please select one response for each item.	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1. Overall I am satisfied with the trial site (for example: comfort and privacy of treatment area, waiting area, parking, ease of access to the site)	0	1	2	3	4
2. My trial visits have been well organized					
3. My trial visits are scheduled at a convenient time for me					
4. The staff treats me with respect					
5. I feel comfortable that I can ask questions during the trial					
6. I am satisfied with the answers I have received to my questions during the trial					
	No		Yes		
7. The time taken to collect data is acceptable to me (for example: in person visits, questionnaires, forms)					
8. The impact the trial has on my daily activities is acceptable (for example: household chores, work commitments, eating)					

TransCelerate BIOPHARMA INC.

Study Participant Feedback Questionnaire (SPFQ)

Your experience at the end of the trial

Thank you for your participation. Your experiences in this trial are important to us and we would like to hear about them. Your answers will help us improve future trials. There are no right or wrong answers, and it will take approximately 15 minutes to complete. Your answers will be kept anonymous and will not impact your participation in this trial.

Please select **one** response for each item.

1 I was informed when I had completed the trial	No		Yes		
2 . I was informed of any future opportunities to access the overall trial results if I wanted to					
	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
3 . Overall, I was satisfied with the information I received about future support after the trial (for example: future treatment, follow-up contact details)	0	1	2	3	4
4 . Overall, I was satisfied with my trial experience					
	Much less than expected	Somewhat less than expected	Same as expected	Somewhat more than expected	Much more than expected
5 . Compared to when the trial started, the overall commitment required was similar to what I expected	0	1	2	3	4

3

Appendix K Abbreviations

Abbreviation or special term	Explanation
1L	first line
5-FU	5-fluorouracil
ADA	antidrug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BoR	best overall response
CI	confidence interval
C_{max}	maximum serum concentration
COA	clinical outcome assessment
COVID-19	coronavirus disease 2019
CR	complete response
CrCL	creatinine clearance
CRO	Contract Research Organization
CSP	clinical study protocol
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough serum concentration
DCO	data cutoff
DILI	drug induced liver injury
DNA	deoxyribonucleic acid
DoR	duration of response
ECG	electrocardiograms
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	Electronic Data Capture
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EOT	end of treatment

Abbreviation or special term	Explanation
ePRO	electronic patient-reported outcome (questionnaire)
CCI [redacted]	CCI [redacted]
ESMO	European Society of Medical Oncology
EU SmPC	European Union Summary of Product Characteristics
EXTREME regimen	cetuximab + platinum (cisplatin or carboplatin) + 5-fluorouracil followed by cetuximab until progression or intolerance
FA	final analysis
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG	^{18}F-Fluoro-deoxyglucose
FH	Fleming-Harrington
FWER	familywise error rate
GCP	Good Clinical Practice
HBsAg	HBV surface antigen
HBV	hepatitis B
HCV	hepatitis C
HER	human epidermal growth factor receptor
HIV	human immunodeficiency virus
HL	Hy's Law
HLA-E	human leukocyte antigen E
CCI [redacted]	CCI [redacted]
HPV	human papillomavirus
HPV-unrelated	randomized participants who are either OPC HPV negative or non-OPC
HR	hazard ratio
HRQoL	health-related quality of life
IA	interim analysis
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICI	immune checkpoint inhibitor
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG4	immunoglobulin G4
IHC	immunohistochemistry

Abbreviation or special term	Explanation
imAE	immune-mediated adverse event
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	Interactive Response Technology
iv	intravenous
IVRS	interactive voice response system
KM	Kaplan Meier
LA	locally advanced
mAb	monoclonal antibody
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Research
NCI	National Cancer Institute
NE	not evaluable
NED	no evidence of disease
NK	natural killer
NL	new lesion
NPH	non-proportional hazards
NTL	non-target lesion
OPC	oropharyngeal cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand-1
PD-(L)1	programmed cell death-1 or programmed cell death ligand-1
PET	positron emission tomography
PFS	progression-free survival
CCI	CCI
CCI	CCI
CCI	CCI
PHL	potential Hy's Law
PK	pharmacokinetic
PR	partial response

Abbreviation or special term	Explanation
PRO	patient-reported outcome
PS	performance status
Q1W	once weekly
Q2W	every 2 weeks
Q4W	every 4 weeks
QLQ-C30	30-item Core Quality-of-life Questionnaire
QLQ-H&N35	Quality of Life Questionnaire Head and Neck Module
QoL	quality of life
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
REVPRDI	Review of PRO/Questionnaire/Diary
R/M	recurrent or metastatic
SAE	serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome-coronavirus-2
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SITC	Society for Immunotherapy of Cancer
SoA	schedule of activities
SPFQ	Study Participant Feedback Questionnaire
TBL	total bilirubin
TL	target lesion
TME	tumor microenvironment
TMG	toxicity management guidelines
ULN	upper limit of normal
USA	United States of America
US FDA	United States Food and Drug Administration
US PI	United States Package Insert
WHO	World Health Organization
w/v	weight/volume

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CCI [redacted]

Clinical Study Protocol	
Study Intervention	Monalizumab and cetuximab
Study Code	D7310C00001
Version	3.0
Date	12 July 2022

A Phase 3 Randomized, Double-blind, Multicenter, Global Study of Monalizumab or Placebo in Combination With Cetuximab in Participants With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck Previously Treated With an Immune Checkpoint Inhibitor

Sponsor Name:	**AstraZeneca AB**
Legal Registered Address:	151 85 Södertälje, Sweden
Regulatory Agency Identifier Number(s):	**IND number 145482**
	EudraCT number 2019-004770-25

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 Number: D7310C00001

Amendment Number: 1

Study Intervention: Monalizumab (IPH2201) and cetuximab

Study Phase: 3

Short Title: Study of Monalizumab Given With Cetuximab or Placebo Given with Cetuximab in Participants With Recurrent or Metastatic Head and Neck Cancer

Acronym: INTERLINK-1

Study Clinical Lead Name and Contact Information will be provided separately

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	12 July 2022
Amendment 1	07 July 2021
Original Protocol	10 February 2020

Amendment 2 (12 July 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the EU.

Overall Rationale for the Amendment

The protocol was updated to remove the exploratory objectives and the associated endpoints for assessment of cetuximab PK and ADA. The recent data from Study D419NC0001 and Study IPH2201-203 showed that there was no significant impact of co-administration of monalizumab on the PK exposure of monalizumab or cetuximab. In addition, cetuximab is an approved therapeutic across multiple tumour types in oncology, including head and neck cancer, with a well-established risk/benefit profile.

The observed Hazard Ratio at Interim Analysis 1 is revised from >0.85 to >0.874 and the corresponding conditional power from 29.4% to 20%.

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Protocol Amendment Summary of Changes Table	Section "Protocol Amendment Summary of Changes Table" was revised to add the Amendment 2.	To describe changes in Amendment 2	Non-substantial
Section 1.3 Schedule of Activities	**Table 1** Removed 'Cetuximab pre-dose serum sample for PK', 'Cetuximab post-dose serum sample for PK' and 'Cetuximab pre-dose serum sample for ADA'.	To align with removal of exploratory objective of cetuximab PK and ADA assessment.	Substantial
	Table 2 Removed 'Cetuximab serum sample for PK' and 'Cetuximab serum sample for ADA'.	To align with removal of exploratory objective of cetuximab PK and ADA assessment	Substantial
Section 3 Objectives and Endpoints	**Table 4** Removed Exploratory objective and associated Estimand Description/Endpoints	Removed because the recent data from	Substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	'To assess the PK of cetuximab' and 'To investigate the immunogenicity of cetuximab'.	Study D419NC0001 and Study IPH2201-203 showed that there was no significant impact of co-administration of monalizumab on the PK exposure of monalizumab or cetuximab	
Section 6.1.2 Dosing Instructions	**Dosing regimen** Text updated to read '*Approximately* 60 minutes after the end of monalizumab/placebo dosing, participants will receive cetuximab.'	For clarity	Non-substantial
Section 6.2.1.1 Monalizumab	Final monalizumab concentration revised from '3 to 20 mg/mL' to '0.9 to 20mg/mL' Added text 'however the selected iv bag size must be ≤250mL.'	To provide clarity and restrict iv bag size to ≤250 mL.	Non-substantial
Section 8.5.1 Pharmacokinetics	Removed the sample requirement for pharmacokinetics for cetuximab.	To align with removal of exploratory objective of cetuximab PK assessment	Substantial
Section 9.3.4 Pharmacokinetic Analysis Set	Removed cetuximab from the pharmacokinetic analysis set.	To align with removal of exploratory objective of cetuximab PK assessment	Substantial
Section 9.4.4.2 Pharmacokinetic Data	Removed cetuximab serum concentration data requirement for PK analysis set.	To align with removal of exploratory objective of cetuximab PK assessment	Substantial
Section 9.4.4.3 Immunogenicity Data	Removed requirement of anti-cetuximab antibodies from immunogenicity data	To align with removal of	Substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
		exploratory objective of cetuximab ADA assessment	
Section 9.5 Interim Analyses	Futility criteria revised to HR at IA1 from >0.85, corresponding to 29.4% conditional power, to >0.874 which corresponds to 20% conditional power.	Modified to relax futility criteria based on strategic considerations	Substantial

Amendment 1 (07 July 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the EU.

Overall Rationale for the Amendment

The protocol was updated to change the primary population of interest for the primary endpoint from the FAS to the HPV-unrelated Analysis Set (randomized participants who are either OPC HPV negative or non-OPC regardless of HPV status). To allow for the change in population assessed for the primary endpoint, the planned number of participants was increased and the hierarchical testing procedure was updated. A futility analysis for OS was added as a new interim analysis for the HPV-unrelated Analysis Set . Guidance relating to the COVID-19 pandemic was added.

In addition, a number of non-substantial changes were made and errors were corrected.

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Protocol Amendment Summary of Changes Table	Section “Protocol Amendment Summary of Changes Table” was added.	To describe changes in Amendment 1	Non-substantial
Section 1.1 Synopsis, Rationale	Text updated in line with changes to protocol body.	See below	See below
Section 1.1 Synopsis, Objectives and Endpoints	Text updated in line with changes to protocol body.	See below	See below
Section 1.1 Synopsis, Overall Design	Text updated in line with changes to protocol body. In addition, the number of sites was increased from 175 to 190.	See below	See below

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.1 Synopsis, Number of Participants	Text updated in line with changes to protocol body.	See below	See below
Section 1.1 Synopsis, Statistical Methods	Text updated in line with changes to protocol body.	See below	See below
Section 1.3 Schedule of Activities	**Table 1** Added collection of PD-L1 results at screening, if available. Clarification added (Footnote "d") that the most recent PD-L1 results should be provided and if PD-L1 results were not collected at screening, they will be collected retrospectively.	As part of the biomarker evaluation	Non-substantial
	Table 1 Added separate line for assessment of Coagulation parameters and footnote 'j' as mentioned in Section 8.2.4.	For clarification	Non-substantial
	Table 1 CCI [redacted]	Based on PK advice	Non-substantial
	Table 1 CCI [redacted]	Based on PK advice	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Table 1 and Table 2 Order of T3 and T4 changed to T4 followed by T3 in Table 1 and footnote "k" of Table 1 and in Table 2 and footnote "c" of Table 2; footnote "k" (Table 1)/footnote "c" (Table 2) changed from "Free T3 and free T4" to "Free T4 or/and free T3 (per local standard clinical practice)".	To correct an error	Non-substantial
Section 2.2 Background	Updated to reflect most recent NCCN guidelines.	To present most recent guidelines	Non-substantial
Section 3 Objectives and Endpoints	Population used for analysis of the primary objective was changed from the FAS to the HPV-unrelated Analysis Set (randomized participants who are either OPC HPV negative or non-OPC regardless of HPV status).	Primary population was updated to reflect the updated primary population of interest (HPV-unrelated participants)	Substantial
	The previous primary objective (to compare the effect of monalizumab and cetuximab (Arm A) relative to placebo and cetuximab (Arm B) by assessment of OS in all participants [ie, in the FAS]) was moved to a secondary objective. The population was confirmed as all randomized patients.	To allow for the primary objective to be assessed in the HPV-unrelated Analysis Set	Substantial
	For the secondary objective "To compare the effect of monalizumab and cetuximab (Arm A) relative to placebo and cetuximab (Arm B) by assessment of PFS, ORR, and DoR", the populations to be analyzed were changed to "participants who are HPV-unrelated" and "all randomized participants".	To clarify that the HPV-unrelated Analysis Set will also be used for this analysis	Substantial
	Text added to the following objectives to clarify they will be analyzed in the HPV-unrelated population and in all randomized participants: "To assess disease-related symptoms, functioning, and HRQoL in participants treated with monalizumab and cetuximab (Arm A) compared to placebo and	To clarify that these objectives will be analyzed in the HPV-unrelated Analysis Set and in all	Substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	cetuximab (Arm B) using the EORTC QLQ-C30 and the EORTC QLQ-H&N35 questionnaires” CCI	randomized participants	
Section 4.1 Overall Design	CCI	To allow for the change in planned sample size given the primary population has been changed to HPV-unrelated population	Substantial
	Now states that the IDMC will review data for both IAs (previously there was only one IA).	For clarity	Non-substantial
	Text added to describe a cap on the number of OPC HPV-positive participants of approximately 20%.	To ensure sufficient sample size for HPV-unrelated participants	Substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis	New section to provide instructions in the case of civil crisis, natural disaster, or public health crisis.	In response to COVID-19 pandemic, to reflect current AstraZeneca processes	Substantial
Section 4.2.1 Rationale for Study Design and Participant Population	Added clarification that unblinded pharmacists and 'unblinded Study Monitors' will be used in order to maintain the blind.	For clarification	Non-substantial
	Text added to give rationale for testing in the HPV-unrelated population.	To align with the change to the primary population	Non-substantial
Section 5.1 Inclusion Criterion 7	Added clarification that tumor tissue beyond the 3-month window and up to 6 months old may be considered, provided that no intervening systemic regimen was ongoing at the time of sample collection. A reference to the Laboratory Manual was also added.	For clarification	Non-substantial
Section 5.2 Exclusion Criterion 13	Triplicate ECG timings replaced with a cross reference to Section 8.2.3.	For clarity	Non-substantial
Section 6.1.1 Investigational Medicinal Products	**Table 5** [redacted]	Updated to align with CSP template	Non-substantial
	[redacted]	For clarification	Non-substantial
	[redacted]	For clarification	Non-substantial
	Clarified that cetuximab will be supplied by AstraZeneca, but if locally sourced the approved commercial product should be used.	For clarification	Non-substantial
Section 6.1.2 Dosing Instructions	**Dosing regimen**	For clarification	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Now states that the total infusion duration for both interventions must not exceed 8 hours. Also states the iv line will be flushed according to local practices to ensure the full dose is administered, and the infusion time does not include the final flush time.		
Section 6.2 Preparation/Handling/ Storage/Accountability of Interventions	Clarified that IMP *must* be kept in original packaging.	For clarification	Non-substantial
Section 6.2.1.1 Monalizumab	Removed the text stating that monalizumab should be protected from direct sunlight during preparation and handling. Clarified that the reconstitution and administration time of monalizumab *must* not exceed values stated. CCI [redacted]	For clarification	Non-substantial
	CCI [redacted]	CCI [redacted]	Non-substantial
Section 6.2.1.3 Placebo	Revised text to state an CCI [redacted] CCI [redacted] Clarified that the total infusion time *must* not exceed 8 hours at room temperature.	For clarification	Non-substantial
6.3.1 Participant Enrollment and Randomization	Text added to describe a cap on the number of OPC HPV-positive participants of approximately 20%.	To ensure sufficient sample size for HPV-unrelated participants	Substantial
	Amended to state all screening laboratory and imaging results must be obtained within 28 days of randomization (was "within 28 days of randomization/the first dose of study intervention").	For consistency with tumor assessment timings in	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
		Inclusion Criterion 6	
	Amended to state a tumor tissue sample *should* be submitted to the central laboratory.	To ensure samples are submitted for analysis	Non-substantial
Section 6.5 Concomitant Therapy	**Table 7** Text amended to state permitted vaccines are limited to non-live attenuated preparations. A reference to Appendix C was also added for details about vaccination against COVID-19.	To align with current AstraZeneca template	Non-substantial
Section 6.5.3 Rescue Medication	Removed the need to record the time of rescue medication administration.	Removed as this is not necessary	Non-substantial
Section 6.6 Dose Modification	Added reference for managing dose delays due to treatment-related toxicity.	To reflect current AstraZeneca processes	Non-substantial
	Added reference to the new COVID-19 Appendix C.	To reflect current AstraZeneca processes	Substantial
	Replaced the term “IMP” with the specified study treatment.	For clarity	Non-substantial
Section 8.1.1 Imaging Tumor Assessments	Clarified that screening/baseline imaging should be performed no more than 28 days before randomization (not 28 days before start of study intervention).	For clarification	Non-substantial
Section 8.1.4.7 Administration of Electronic PRO Questionnaires	Clarified that if technical or other device-related issues prohibit completion of the questionnaires on the device, an appropriate backup option may be considered.	For clarification	Non-substantial
	Clarified that relatives, friends, or clinic staff should not help participants decide on answers to the questionnaires.	For clarification	Non-substantial
	Clarified that if a participant *needs* (rather than *uses*) visual aids for reading and they do not have them when attending clinic, they will be exempted from completing the ePROs at that visit.	For clarification	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Clarified reasons for exemption from completing the ePROs, and added the need to contact AstraZeneca to determine if the participant is exempt.	For clarification	Non-substantial
	Wording regarding language of the questionnaires updated; questions must not be translated from an available language in the device into the language the participant speaks.	For clarification	Non-substantial
	Clarified (in relation to ePRO reporting) that Cycle 1 Day 1 is baseline.	For clarification	Non-substantial
	Removed "REVPRDI" as the eCRF onto which completion status is to be recorded.	For clarification	Non-substantial
	Text added to describe process regarding participant compliance.	For clarification	Non-substantial
Section 8.1.4.8 WHO/ECOG PS	Numbering of WHO/ECOG classification corrected.	To correct an error	Non-substantial
	Sentence added to state the ECOG status collected at screening must be reported in IRT and not re-assessed.	For clarification	Non-substantial
Section 8.2.2 Vital Signs	Added the approximate time window for collection of vital signs before cetuximab dosing	For clarification	Non-substantial
Section 8.2.3 Electrocardiograms	Resting ECG description changed to "semi-recumbent or supine".	To correct an error	Non-substantial
Section 8.2.4 Clinical Safety Laboratory Assessments	Timing of sampling for coagulation parameters aligned with Table 8: "baseline on Day 1 (unless all screening laboratory hematology assessments are performed within 3 days prior to Day 1), and then as clinically indicated"	For clarification	Non-substantial
	Table 8 Order of T3 and T4 changed to T4 followed by T3 in Table 8; footnote "h" amended to "Free T4 or/and free T3 (per local standard clinical practice)…".	To correct an error	Non-substantial
	Table 8 Footnote c clarified that absolute neutrophil counts must be recorded at screening ie, they must not be recorded as percentages.	For clarification	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	The calculation of absolute counts from percentages was removed as this is not currently achievable.		
	Table 8 Coagulation was moved from the clinical chemistry column to the hematology/hemostasis column.	To correct an error	Non-substantial
Section 8.3 Adverse Events and Serious Adverse Events	Cross reference to new COVID-19 Appendix C added.	To reflect current AstraZeneca processes	Substantial
Section 8.3.13.1 Maternal Exposure	"Congenital abnormalities/abnormality" changed to "congenital anomalies/anomaly".	This change is in line with regulatory requirements	Non-substantial
Section 8.3.13.2 Paternal Exposure	"Congenital abnormality" changed to "congenital anomaly".	This change is in line with regulatory requirements	Non-substantial
Section 8.3.14 Medication Error	Clarified that medication error information should be reported on the specific medication error eCRF.	Updated in line with new AstraZeneca requirements	Non-substantial
Section 8.3.15.2 Cetuximab	Management of AEs with cetuximab text amended to refer to local label (details of actions to take have been removed).	To avoid possible mis-alignment with future changes to prescribing information	Substantial
Section 8.6.1 Collection of Mandatory Samples for Biomarker Analysis	Added clarification that tumor tissue beyond the 3-month window and up to 6 months old may be considered, provided that no intervening systemic regimen was ongoing at the time of sample collection. A reference to the Laboratory Manual was also added.	For clarification	Non-substantial
	Added clarification that fresh tumor biopsy should not be collected from lesions in proximity to structures that would make the collection procedure high risk.	Per USA FDA request	Non-substantial
Section 9.2 Sample Size Determination	Number of randomized participants increased from 600 to 624.	To align with the changes in	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
		Section 4 Study Design	
	Text amended to reflect change in population analyzed for the primary endpoint.	To reflect the change in the primary population	Substantial
	Futility analysis for OS added for the HPV-unrelated Analysis Set.	Futility analysis was added for risk mitigation	Substantial
	Statistical methods for the primary endpoint were updated to reflect that analysis will be performed on HPV-unrelated participants.	To reflect the change in the primary population	Substantial
	Text added to describe a cap on the number of OPC HPV-positive participants of approximately 20%.	To ensure sufficient sample size for HPV-unrelated participants	Substantial
	Hypothesis text split to reflect hypotheses at each analysis (IA2 and final analysis).	For clarification	Substantial
Section 9.3 Populations for Analyses	**Table 9** HPV-unrelated Analysis Set added to analysis of OS, PFS, ORR, DoR, PRO endpoints, demography and other baseline characteristics, and biomarkers.	To allow analysis for the updated primary population	Substantial
	Table 9 Footnotes added to clarify definitions of ORR and PRO.	For clarification	Non-substantial
Section 9.3.1 HPV-unrelated Analysis Set	New section added to describe new analysis set.	To allow analysis for the updated primary population	Substantial
Section 9.3.2 Full Analysis Set	Amended to state FAS will be used for summarizing baseline characteristics, all efficacy endpoints (including PROs) and biomarker analyses as secondary analyses.	The HPV-unrelated Analysis Set is the primary analysis set	Substantial
	"Analysis for ORR will be based on participants in the FAS who had measurable disease at baseline. Analysis of DoR will be based on participants in the	It is more appropriate to include the description of the subset used for ORR and	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	FAS who achieved objective response" was removed.	DoR analyses in the sections for ORR and DoR	
Section 9.3.3 Safety Analysis Set	Clarified that all participants who received any amount of study treatment (not at least 1 dose) will be included in the Safety Analysis Set.	For clarification	Non-substantial
Section 9.4.1 General Considerations	Hypothesis text split to reflect hypotheses at each analysis (IA2 and final analysis).	For clarification	Substantial
	Number of OS events and % maturity updated to reflect change in primary analysis population to HPV-unrelated Analysis Set.	To reflect the change in the primary population	Substantial
	Text changed to reflect that the efficacy and PRO analyses will be performed on the HPV-unrelated population and repeated for the FAS as a secondary analysis.	Updated so that the PRO analysis is performed for both the primary and secondary populations	Substantial
	Table 10 Added populations analyzed and amended stratification factors for each endpoint to reflect populations analyzed. Added OS in FAS as a secondary endpoint.	To reflect the change in the primary population	Substantial
	Table 10 OS: KM plot of time to censoring removed from the sensitivity and supplemental analysis.	Removed as it is not considered necessary	Non-substantial
	Table 10 OS: Cox proportional hazards models removed from the sensitivity and supplemental analysis.	For consistency with the SAP that has changed during development	Non-substantial
Section 9.4.1.1 Methods for Multiplicity Control	Text was added to more fully describe the hierarchical testing procedure.	For clarification	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Number of OS events updated to reflect change in primary analysis population to HPV-unrelated Analysis Set; new figure added to describe multiplicity testing procedure.	To allow updated sample size justification with the change in the primary population. To allow clarification in the multiple testing procedure of OS and PFS with the primary population (HPV-unrelated Analysis Set) and the secondary population (FAS)	Substantial
	Statement that PFS will be formally tested only if OS is statistically positive replaced by statement that each statistical test will be performed only if the preceding test is positive.	To allow clarification in the multiple testing procedure of OS and PFS with the primary population (HPV-unrelated Analysis Set) and the secondary population (FAS)	Substantial
Section 9.4.2.1 Primary Endpoint	**Primary analysis** Analysis set changed from FAS to HPV-unrelated Analysis Set. As the population studied is now the HPV-unrelated Analysis Set, adjustment for HPV status was removed.	To allow analysis for the updated primary population and adjust the sensitivity analyses accordingly	Substantial
	Sensitivity analysis	Added max-combo test as it is	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Details added regarding the stratified max-combo test that will be used as a sensitivity analysis. Removal of KM plot for the time to censoring (attrition bias).	recommended by the Cross-Pharma Non-proportional Hazard Working Group in the presence of non-proportional hazards. Removed KM plot of time to censoring as it is not as informational.	
	Cox proportional hazards models removed from the sensitivity and supplemental analysis.	For consistency with the SAP that has changed during development	Non-substantial
	Analysis of OS in FAS New section to describe analysis of OS in the FAS.	To describe analysis of secondary endpoint	Substantial
	Subgroup analysis Clarified that subgroup analyses will be performed on HPV-unrelated Analysis Set and FAS, where applicable.	To allow analysis for the updated primary population	Substantial
	"Race" changed to "Race/ethnicity data" for clarification.	For clarification	Non-substantial
9.4.2.2.1 Progression-free Survival	**Analysis of PFS** Text amended to state PFS will be analyzed in the HPV-unrelated Analysis Set as well as the FAS.	To allow analysis in the primary population	Substantial
9.4.2.2.2 Objective Response Rate	**Analysis of ORR**	To allow analysis in the	Substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Text amended to state ORR will be analyzed in the HPV-unrelated Analysis Set as well as the FAS.	primary population	
Section 9.4.2.2.4 Patient-reported Outcome: EORTC QLQ-C30	Detailed information about PRO definitions were removed as the information will be included in the SAP. The number of analyses of PROs was reduced.	Information will be detailed in the SAP	Non-substantial
	Text amended to state analyses will be performed on the HPV-unrelated Analysis Set as well as the FAS.	To allow analysis in the primary population	Substantial
Section 9.4.2.2.5 Patient-reported Outcome: EORTC QLQ-H&N35	Detailed information about PRO definitions were removed as the information will be included in the SAP.	Information will be detailed in the SAP	Non-substantial
	Analysis methods Text amended to state the analyses will be performed for the HPV-unrelated Analysis Set as well as the FAS. The number of analyses of PROs was reduced.	To allow analysis in the primary population	Substantial
Section 9.4.2.3.1 Time from Randomization to Second Progression or Death	Removal of KM plot for the time to censoring (attrition bias).	Removed as it is not considered necessary	Non-substantial
CCI [redacted]			
Section 9.7 Impact of COVID-19 on Data	New section added to acknowledge possible impact of COVID-19 on the data: reference to SAP (where details will be supplied) included.	In response to COVID-19 pandemic, to reflect current AstraZeneca processes	Substantial
Appendix B 2 Definitions of Serious Adverse Event	"Congenital abnormality" changed to "congenital anomaly.	This change is in line with	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
		regulatory requirements	
Appendix C Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis, including COVID-19 Outbreak	New appendix added to describe study conduct details pertaining to COVID-19 outbreak. All subsequent appendices renumbered.	In response to COVID-19 pandemic, to reflect current AstraZeneca processes	Substantial
Appendix E 8 Laboratory Tests (now Appendix F 8)	Table of Hy's law laboratory tests: footnote "a" removed from HBV DNA as it is not applicable for HBV DNA; footnote "c" removed since the study is not expected to be conducted in China.	Amendment of error and clarification	Non-substantial
Throughout	The terms "Medical Monitor" and "Study Physician" were changed to "Study Clinical Lead".	In line with latest AstraZeneca template	Non-substantial

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3 Randomized, Double-blind, Multicenter, Global Study of Monalizumab or Placebo in Combination With Cetuximab in Participants With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck Previously Treated With an Immune Checkpoint Inhibitor

Short Title: Study of Monalizumab Given With Cetuximab or Placebo Given with Cetuximab in Participants With Recurrent or Metastatic Head and Neck Cancer

Rationale: The aim of this study is to assess the efficacy and safety of monalizumab and cetuximab compared to placebo and cetuximab in participants with R/M SCCHN after receiving an ICI and platinum-based chemotherapy, regardless of the sequence of these therapies. Monalizumab is a first-in-class ICI that blocks the inhibitory CD94/NKG2A receptor resulting in the stimulation of NK cell and CD8+ T cell cytolytic activity. Additionally, monalizumab enhances human NK-cell ADCC mediated by cetuximab. While monalizumab monotherapy has shown limited clinical activity, encouraging antitumor results have been observed following monalizumab and cetuximab combination therapy in patients with R/M SCCHN who have received prior platinum-based chemotherapy, including patients who have also received prior therapy with an ICI. This dual targeting could therefore provide greater antitumor activity than cetuximab alone. The combination of monalizumab and cetuximab could be a key option to improve clinical outcomes in patients with R/M SCCHN, regardless of HPV status, after receiving an ICI.

Objectives and Endpoints

Objective	Estimand [a] Description/Endpoint
Primary	
To compare the effect of monalizumab and cetuximab (Arm A) relative to placebo and cetuximab (Arm B) by assessment of OS in HPV-unrelated participants	• Population: The HPV-unrelated Analysis Set which will include all randomized participants who are either OPC HPV negative or non-OPC regardless of HPV status • Endpoint: OS, which is defined as time from randomization until the date of death due to any cause • Intercurrent events: If a participant is lost to follow-up or withdraws consent, OS will be censored based on the last recorded date on which the participant was known to be alive • Summary measure: p-value of treatment comparison using a stratified log rank test and hazard ratio of Arm A relative to Arm B with its confidence interval using a stratified Cox Proportional Hazards model
Secondary	
To compare the effect of monalizumab and cetuximab (Arm A) relative to placebo and cetuximab (Arm B) by assessment of OS in all randomized participants	• Population: The FAS which will include all randomized participants • Endpoint: OS, which is defined as time from randomization until the date of death due to any cause • Intercurrent events: If a participant is lost to follow-up or withdraws consent, OS will be censored based on the last recorded date on which the participant was known to be alive • Summary measure: p-value of treatment comparison using a stratified log rank test and hazard ratio of Arm A relative to Arm B with its confidence interval using a stratified Cox Proportional Hazards model
To compare the effect of monalizumab and cetuximab (Arm A) relative to placebo and cetuximab (Arm B) by assessment of PFS, ORR, and DoR in participants who are HPV-unrelated and in all randomized participants	• PFS is defined as time from randomization until disease progression, per RECIST 1.1 as assessed by the investigator at local site or death due to any cause, whichever occurs first. • ORR is defined as the proportion of participants with measurable disease who have a confirmed CR or PR, as determined by the investigator at local site per RECIST 1.1. • DoR is defined as the time from the date of first documented response until date of documented disease progression or death in the absence of disease progression.
To assess disease-related symptoms, functioning, and HRQoL in participants treated with monalizumab and cetuximab (Arm A) compared to placebo and	Symptoms, functioning, and global health status/QoL scale/item scores of the EORTC QLQ-C30 & EORTC QLQ-H&N35

Objective	Estimand [a] Description/Endpoint
cetuximab (Arm B) using the EORTC QLQ-C30 and the EORTC QLQ-H&N35 questionnaires in participants who are HPV-unrelated and in all randomized participants	• Change from baseline scores across visits • Time to clinically meaningful deterioration in scores
To assess the PK of monalizumab	Concentration of monalizumab in blood and PK parameters (such as C_{max}, C_{trough}, as data allow; sparse sampling)
To investigate the immunogenicity of monalizumab	Presence of ADAs for monalizumab (confirmatory results: positive or negative, titers)
To characterize the association between clinical outcome and protein expression in the tumor microenvironment in participants treated with monalizumab and cetuximab (Arm A) or placebo and cetuximab (Arm B) in participants who are HPV-unrelated and in all randomized participants	HLA-E and NKp46+ expression in pre-treatment and post-treatment tumor biopsies
Secondary safety	
To assess the safety and tolerability of monalizumab and cetuximab (Arm A) compared to placebo and cetuximab (Arm B) in participants with R/M SCCHN previously treated with ICI	AEs, vital signs, clinical laboratory results, ECGs

[a] Estimand is the target of estimation to address the scientific question of interest posed by the primary objective. Attributes of an estimand include the population of interest, the variable (or endpoint) of interest, the specification of how intercurrent events are reflected in the scientific question of interest, and the population-level summary for the variable.

ADA = antidrug antibodies; AE = adverse event; C_{max} = maximum serum concentration; CR = complete response; C_{trough} = trough serum concentration; DoR = duration of response; ECG = electrocardiogram; EORTC = European Organisation for Research and Treatment of Cancer; FAS = full analysis set; HLA-E = human leukocyte antigen E; HPV = human papillomavirus; HRQoL = health-related quality of life; NK = natural killer; OPC = oropharyngeal cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic(s); PR = partial response; QLQ-C30 = 30-item Core Quality of Life Questionnaire; QLQ-H&N35 = Quality of Life Questionnaire Head and Neck Module; RECIST 1.1 = Response Evaluation Criteria for Solid Tumors version 1.1; R/M = recurrent or metastatic; SCCHN = squamous cell carcinoma of the head and neck.

For exploratory objectives, see Section 3 of the protocol.

Overall Design

Study D7310C00001 is a Phase 3, randomized, double-blind, multicenter, global study assessing the safety and efficacy of monalizumab or placebo in combination with cetuximab in participants with R/M SCCHN not amenable to curative treatment previously treated with platinum-based chemotherapy and an ICI, regardless of the sequence of these therapies. Approximately 190 sites globally will participate in this study.

Following a 28-day screening period, eligible participants will be randomized on Day 1 in a

2:1 ratio to one of the following treatment arms: (1) Arm A: monalizumab and cetuximab or (2) Arm B: placebo and cetuximab. Participants will be stratified by:

- Human papillomavirus status: (i) OPC HPV positive or (ii) HPV-unrelated,
  - The number of OPC HPV-positive participants will be closely monitored throughout the study and is planned to be capped at approximately 20% of the total sample size.
- World Health Organization/ECOG PS (0 or 1), and
- Number of prior lines of therapy in the R/M setting (1 or 2)
  - The number of participants in each stratum (1 or 2 prior lines of therapy in the R/M setting) will be closely monitored throughout the study. If a disproportionate number of participants are enrolled in a single stratum (eg, > 75% of the total sample size), the Sponsor may elect to close further recruitment into that stratum.

Participants will receive study intervention until disease progression, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. An IDMC will review safety data regularly and make recommendations regarding further study conduct.

Disclosure Statement: This is a parallel group treatment study with 2 arms that is participant and investigator blinded.

Number of Participants:

Approximately 832 participants will be enrolled to achieve approximately 624 participants randomly assigned to study intervention while ensuring at least 498 participants who are either OPC HPV negative or non-OPC regardless of the HPV status (HPV-unrelated participants). This includes approximately 416 participants randomized to Arm A (monalizumab and cetuximab) and 208 participants randomized to Arm B (placebo and cetuximab) in the overall population; while for the HPV-unrelated population, this includes approximately 332 participants randomized to Arm A and 166 participants randomized to Arm B.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study but are not randomly assigned in the study are considered "screen failures".

Intervention Groups and Duration:

Participants will be randomized in a 2:1 ratio to Arm A or Arm B.

- Arm A: monalizumab and cetuximab
  Monalizumab CCI and cetuximab 400 mg/m^2 iv initial dose followed by 250 mg/m^2 iv Q1W

- Arm B: placebo and cetuximab
  Placebo iv Q2W and cetuximab 400 mg/m^2 iv initial dose followed by 250 mg/m^2 iv Q1W

Study intervention will continue until RECIST 1.1-defined radiological disease progression per investigator, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Crossover between treatment arms will not be permitted.

Follow-up of participants post discontinuation of study intervention

After discontinuation of study intervention, all participants will have safety assessment follow-up for 3 months after their last dose of study intervention.

Participants who have discontinued study intervention in the absence of RECIST 1.1-defined radiological disease progression per investigator will continue with scheduled tumor assessments until RECIST 1.1-defined disease progression or death regardless of whether the participant started a subsequent anticancer therapy, unless they have withdrawn all consent to study-related assessments.

Additionally, after study intervention discontinuation, all participants will be followed for survival status, subsequent anticancer therapy, and time to disease progression occurring during or after subsequent therapy (as determined per local standard clinical practice) until death, withdrawal of consent, or the end of the study.

Data Monitoring Committee: Yes

Statistical Methods

The primary objective of the study is to compare the effect of monalizumab and cetuximab (Arm A) relative to placebo and cetuximab (Arm B) in terms of OS in HPV-unrelated participants.

The primary endpoint OS is defined as the time from the date of randomization until death due to any cause. Secondary efficacy endpoints include PFS, ORR, DoR, and PROs.

The primary population is the HPV-unrelated Analysis Set which will include all randomized participants who are either OPC HPV negative or non-OPC regardless of the HPV status. The HPV status will be determined by HPV status in the eCRF and not the IVRS value. The HPV-unrelated Analysis Set and FAS (all randomized participants) will be used for summarizing baseline characteristics, all efficacy analyses, including PROs, and biomarker analyses. Treatment arms will be compared on the basis of randomized study intervention, regardless of the intervention actually received. Participants who were randomized but did not subsequently go on to receive study intervention are included in the analysis in the treatment arm to which they were randomized.

The primary analysis of OS in the HPV-unrelated Analysis Set will be performed using a stratified log-rank test, adjusting for WHO/ECOG PS (0 or 1) and number of prior lines of therapy in the R/M setting (1 or 2). The HR and its CI will be estimated from a stratified Cox Proportional Hazards model. The analysis of OS in the FAS will be additionally stratified by HPV status (OPC HPV-positive or HPV-unrelated). These stratification factors will be determined based on the randomization.

There will be two planned IAs and one FA for the study.

Interim Analysis 1 (IA1): Futility in OS will be evaluated when approximately 99 OS events have occurred across Arm A and Arm B in HPV-unrelated participants (25% information fraction) in participants randomized at least 2 months before the DCO for the futility analysis (ie, with a minimum follow-up of 2 months).

Interim Analysis 2 (IA2): A hypothesis of monalizumab plus cetuximab (Arm A) prolongs OS compared to placebo plus cetuximab (Arm B) will be tested at IA2 when approximately 278 OS events have occurred across Arm A and Arm B in HPV-unrelated participants (approximately 70% information fraction, 56% maturity).

Final Analysis (FA): A hypothesis of improved OS will be tested at the final analysis when approximately 397 OS events have occurred across Arm A and Arm B in HPV-unrelated participants (approximately 80% maturity).

If the true OS HR is 0.72, corresponding to an approximate 3-month improvement in median OS compared to Arm B of 7.7 months, approximately 397 OS events in HPV-unrelated participants will provide approximately 86.5% power to demonstrate statistical significance at the 5% level (using a 2-sided test) for the FA. The 5% (2-sided) alpha for the OS analysis will be controlled at the IA2 and FA time points by using the Lan-DeMets (Lan and DeMets 1983) spending function that approximates the O'Brien-Fleming approach, where the significance level applied depends upon the proportion of information (ie, information fraction) available at the time of IA2. For example, if the information fraction for OS at IA2 is 70% then the two-sided significance levels of 1.48% and 4.55% will be applied to IA2 and FA for OS, respectively. The smallest detectable treatment difference in HR, ie, critical value, that could be statistically significant at the FA is 0.81. With a planned recruitment period of 30 months, it is expected that a total of 498 HPV-unrelated participants are needed in order to achieve 397 OS events with a follow-up period of approximately 12 months. The 278 OS events for the IA2 are expected to be reached approximately 30.5 months after the randomization of the first participant.

The number of OPC HPV-positive participants will be closely monitored throughout the study and is planned to be capped at approximately 20% of the total sample size. With the assumption that 20% of participants will be OPC HPV positive, approximately

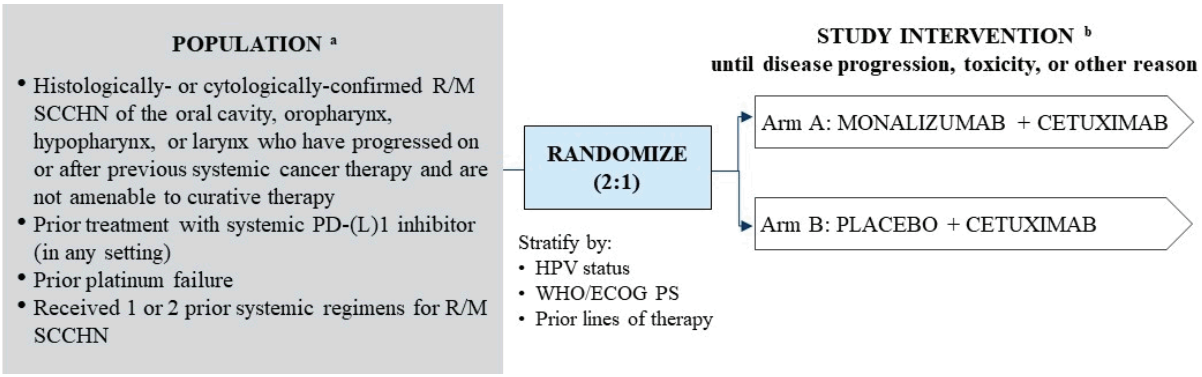
624 randomized participants will be needed in the overall population. Under the same assumption of effect size in HR and median OS stated above, approximately 498 OS events are expected in all participants which will provide approximately 93.0% power to demonstrate statistical significance at the 5% level (using a 2-sided test) for the FA.

Strong control of the FWER at 5% level (2 sided) across the testing of OS and PFS endpoints will be achieved through a combined approach of alpha allocation to the OS analyses (IA2 and the FA) via alpha spending function as previously mentioned and a hierarchical testing procedure; that is, OS in FAS will be tested only if OS in HPV-unrelated analysis set met significance at IA2 or FA; PFS will be tested only if OS met statistical significance at IA2 or FA and PFS in FAS will be tested only if PFS in HPV-unrelated analysis set met statistical significance at IA2 or FA (Glimm et al 2010).

1.2 Schema

The general study design is summarized in Figure 1.

Figure 1 Study Design



[a] Prior platinum failure is defined as either: (i) disease progression during or after treatment with a platinum-containing regimen for R/M disease or (ii) recurrence/progression during or within 6 months of the last dose of platinum as part of multimodal therapy for LA disease.
Eligible participants must not have received prior cetuximab, unless administered in the LA setting with radiotherapy and no disease progression for at least 6 months following the last cetuximab dose.

[b] Study intervention regimens: monalizumab [redacted]; cetuximab, 400 mg/m^2 iv initial dose then 250 mg/m^2 iv Q1W.

WHO/ECOG PS = World Health Organization/Eastern Cooperative Oncology Group performance status; iv = intravenous; HPV = human papillomavirus; LA = locally advanced; PD-(L)1 = programmed cell death-1 or programmed cell death ligand-1; [redacted]; [redacted]; R/M = recurrent/metastatic; SCCHN = squamous cell carcinoma of the head and neck.

1.3 Schedule of Activities

The SoA are presented in Table 1 for the screening and intervention periods and Table 2 for the follow-up period.

Table 1 Schedule of Activities – Screening Period and Intervention Period

Table 1 Schedule of Activities – Screening Period and Intervention Period

CCI

Table 1 Schedule of Activities – Screening Period and Intervention Period

CCI

Table 1 Schedule of Activities – Screening Period and Intervention Period

Procedure	Screening	Intervention period (1 cycle = 14 days)														For details see Section
		C1		C2		C3		C4		C5		C6		C7+		
		C1 D1	C1 D8	C2 D1	C2 D8	C3 D1	C3 D8	C4 D1	C4 D8	C5 D1	C5 D8	C6 D1	C6 D8	C7 D1	C7 D8	
Week	**-4 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13+**	**14+**	
Day	**-28 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85+**	**D92+**	
Window (days) [a]	**NA**	**+2**	**±1**	**+2**	**±1**	**+2**	**±1**	**+2**	**±1**	**+2**	**±1**	**+2**	**±1**	**+2**	**±1**	
Biomarker sampling																
CCI	X							X (optional)								
Tumor biopsy at time of progression (optional)			X													
CCI																

Table 1 Schedule of Activities – Screening Period and Intervention Period

Procedure	Screening	Intervention period (1 cycle = 14 days)														For details see Section
		C1		C2		C3		C4		C5		C6		C7+		
		C1 D1	C1 D8	C2 D1	C2 D8	C3 D1	C3 D8	C4 D1	C4 D8	C5 D1	C5 D8	C6 D1	C6 D8	C7 D1	C7 D8	
Week	-4 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13+	14+	
Day	-28 to -1	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85+	D92+	
Window (days) [a]	NA	+2	±1	+2	±1	+2	±1	+2	±1	+2	±1	+2	±1	+2	±1	
CCI																
Pharmacokinetic measurements																
CCI																
Immunogenicity measurements																
CCI																

Table 1 Schedule of Activities – Screening Period and Intervention Period

Procedure	Screening	Intervention period (1 cycle = 14 days)														For details see Section
		C1		C2		C3		C4		C5		C6		C7+		
		C1 D1	C1 D8	C2 D1	C2 D8	C3 D1	C3 D8	C4 D1	C4 D8	C5 D1	C5 D8	C6 D1	C6 D8	C7 D1	C7 D8	
Week	**-4 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13+**	**14+**	
Day	**-28 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85+**	**D92+**	
Window (days) [a]	**NA**	**+2**	**±1**	**+2**	**±1**	**+2**	**±1**	**+2**	**±1**	**+2**	**±1**	**+2**	**±1**	**+2**	**±1**	
Efficacy measurements																
Tumor imaging (RECIST 1.1)	X	Intravenous contrast-enhanced CT or MRI of the neck, chest, and abdomen (includes entire liver) Q8W (± 1 week) for the first 48 weeks after randomization and then Q12W (±1 week) thereafter (relative to randomization), until RECIST 1.1-defined radiological disease progression; plus at least 1 additional follow-up scan. This schedule MUST be followed regardless of any delays in dosing.														8.1.1, Appendix G
PRO (e-device) and health economic measurements																
Allocate ePRO device	X															8.1.4.7
ePRO device training	X															
EORTC QLQ-C30		X				X				X				X then Q4W		8.1.4.1
EORTC QLQ-H&N35		X				X				X				X then Q4W		8.1.4.2
CCI [redacted]																

Table 1 Schedule of Activities – Screening Period and Intervention Period

Procedure	Screening	Intervention period (1 cycle = 14 days)														For details see Section
		C1		C2		C3		C4		C5		C6		C7+		
		C1 D1	C1 D8	C2 D1	C2 D8	C3 D1	C3 D8	C4 D1	C4 D8	C5 D1	C5 D8	C6 D1	C6 D8	C7 D1	C7 D8	
Week	-4 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13+	14+	
Day	-28 to -1	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85+	D92+	
Window (days) [a]	NA	+2	±1	+2	±1	+2	±1	+2	±1	+2	±1	+2	±1	+2	±1	
CCI																
Other assessment																
CCI																
Study intervention administration																
CCI																

[a] Unless noted otherwise.
The interval between monalizumab/placebo and cetuximab interventions should be at least 14 days for monalizumab/placebo and at least 7 days for cetuximab. If either intervention is delayed > 2 weeks then consult the Sponsor. See Section 6.6 for action in case of a dose delay.

[b] May be obtained prior to 28-day screening window to permit tumor biopsy sample acquisition and analysis.

Table 1 Schedule of Activities – Screening Period and Intervention Period

Procedure	Screening	Intervention period (1 cycle = 14 days)														For details see Section
		C1		C2		C3		C4		C5		C6		C7+		
		C1 D1	C1 D8	C2 D1	C2 D8	C3 D1	C3 D8	C4 D1	C4 D8	C5 D1	C5 D8	C6 D1	C6 D8	C7 D1	C7 D8	
Week	-4 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13+	14+	
Day	-28 to -1	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85+	D92+	
Window (days) [a]	NA	+2	±1	+2	±1	+2	±1	+2	±1	+2	±1	+2	±1	+2	±1	

[c] As clinically indicated.
[d] The most recent PD-L1 results should be provided. If PD-L1 results were not collected at screening, they will be collected retrospectively.
[e] For AEs/SAEs reported during screening, additional information such as medical history and concomitant medications may be needed.
[f] Screening laboratory assessments must be obtained within 7 days prior to Day 1.
[g] Pregnancy test may occur on Day 1, but results must be reviewed by the treating physician/investigator prior to dosing.
[h] Results for urea and electrolytes, full blood count, and liver function tests must be available before commencing study intervention (samples must have been obtained within 3 days prior to initiating study intervention).
During the intervention period, clinical chemistry and hematology assessments may be performed more frequently if clinically indicated.
[i] If screening clinical chemistry and hematology assessments are performed within 3 days prior to Day 1, they do not need to be repeated on Day 1 if the participant's condition has not changed.
[j] Coagulation parameters are to be assessed at baseline on Day 1 (unless all screening laboratory hematology assessments are performed within 3 days prior to Day 1), and then as clinically indicated.
[k] If TSH is measured within 14 days prior to Day 1, it does not need to be repeated at Day 1. Free T4 or/and free T3 (per local standard clinical practice) will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
[l] No premedication is required prior to monalizumab administration. However, from Cycle 2, premedication with acetaminophen or an antihistamine might be prescribed, at the investigator's discretion, if the participant experienced any Grade 1 to 3 infusion-related AE at the previous cycle.
[m] Participants should be premedicated per US PI or local label (where available). Premedication may also be based on institutional guidance for management of infusion-related reactions.

ADA = antidrug antibody; AE = adverse event; C = cycle; CT = computed tomography; CCI [redacted]; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; ePRO = electronic patient-reported outcome; CCI [redacted] CCI [redacted] 5-level health state utility index; HIV = human immunodeficiency virus; CCI [redacted];
IHC = immunohistochemistry; IMP = investigational medicinal product; iv = intravenous; mos = months; MRI = magnetic resonance imaging; OPC = oropharyngeal cancer; PBMC = peripheral blood mononuclear cells; PD = progressive disease; PD-L1 = programmed cell death ligand-1; CCI [redacted] CCI [redacted] PK = pharmacokinetic; CCI [redacted];
PS = performance status; Q4W = every 4 weeks; Q6W = every 6 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; QLQ-C30 = 30-item Core Quality of Life

Table 1 Schedule of Activities – Screening Period and Intervention Period

Procedure	Screening	Intervention period (1 cycle = 14 days)														For details see Section
		C1		C2		C3		C4		C5		C6		C7+		
		C1 D1	C1 D8	C2 D1	C2 D8	C3 D1	C3 D8	C4 D1	C4 D8	C5 D1	C5 D8	C6 D1	C6 D8	C7 D1	C7 D8	
Week	-4 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13+	14+	
Day	-28 to -1	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85+	D92+	
Window (days) [a]	NA	+2	±1	+2	±1	+2	±1	+2	±1	+2	±1	+2	±1	+2	±1	

Questionnaire; QLQ-H&N35= Quality of Life Questionnaire Head and Neck Module; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; SAE = serious adverse event; CCI SPFQ = Study Participant Feedback Questionnaire; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; US PI = United States Package Insert; W = week; WHO = World Health Organization; WOCBP = women of childbearing potential.

Table 2 Schedule of Activities – Follow-up Period for Participants Who Discontinued Study Intervention Due to Disease Progression or Other Reason

Procedure	End of treatment	Follow-up period						For details see Section
Month (post last dose IMP)	1	2	3	4	6	9	12+	
Window	± 1 week	± 1 week	± 1 week	± 1 week	± 1 week	± 1 week	± 1 week	
Clinical procedures								
Full physical examination	X							8.2.1
WHO/ECOG PS [a]	X	X	X					8.1.4.8
Vital signs	X							8.2.2
Weight	X							8.2.1
12-lead ECG (triplicate)	X							8.2.3
Concomitant medications	X	X	X					6.5

Table 2 Schedule of Activities – Follow-up Period for Participants Who Discontinued Study Intervention Due to Disease Progression or Other Reason

Procedure	End of treatment	Follow-up period						For details see Section
Month (post last dose IMP)	**1**	**2**	**3**	**4**	**6**	**9**	**12+**	
Window	**± 1 week**	**± 1 week**	**± 1 week**	**± 1 week**	**± 1 week**	**± 1 week**	**± 1 week**	
Subsequent anticancer therapy [b]	X	X	X	X	X	X	X then Q6M (± 2 weeks)	8.1.2
CCI								
Safety measurements								
Adverse events	X	X	X					8.3
Pregnancy test; serum or urine (WOCBP only)	X	X (as clinically indicated)						8.2.4
Clinical chemistry	X	X	X					
Hematology	X	X	X					
TSH (and reflex free T4 or/and free T3) [c]	X		X					
Biomarker sampling								
Tumor biopsy at time of progression (optional)	X							
CCI								
Pharmacokinetic measurements								
CCI								
Immunogenicity measurements								
CCI								

Table 2 Schedule of Activities – Follow-up Period for Participants Who Discontinued Study Intervention Due to Disease Progression or Other Reason

Procedure	End of treatment	Follow-up period						For details see Section
Month (post last dose IMP)	**1**	**2**	**3**	**4**	**6**	**9**	**12+**	
Window	**± 1 week**	**± 1 week**	**± 1 week**	**± 1 week**	**± 1 week**	**± 1 week**	**± 1 week**	
Efficacy measurements								
Tumor imaging (RECIST 1.1)	Participants who discontinued study intervention due to reason other than disease progression or death (regardless of whether started subsequent anticancer therapy): intravenous contrast-enhanced CT or MRI of the neck, chest, and abdomen (includes entire liver) Q8W (± 1 week) for the first 48 weeks after randomization and then Q12W (±1 week) thereafter (relative to randomization), until RECIST 1.1-defined radiological disease progression; plus at least 1 additional follow-up scan..							8.1.1, Appendix G
Survival status: phone call for participants who refuse to return for evaluations and agree to be contacted [d]		X	X	X	X	X	X then Q2M (± 2 weeks)	7.1.1.3
PRO (e-device) and health economic measurements								
EORTC QLQ-C30	X	X	X	Every visit until RECIST 1.1-defined radiological disease progression (for participants who discontinued due to other reason) or start of subsequent anticancer therapy (whichever occurs first)				8.1.4.1
EORTC H&N35	X	X	X					8.1.4.2
CCI [redacted]								
Other assessment								
SPFQ (optional)	X							8.9

Table 2 Schedule of Activities – Follow-up Period for Participants Who Discontinued Study Intervention Due to Disease Progression or Other Reason

Procedure	End of treatment	Follow-up period						For details see Section
Month (post last dose IMP)	1	2	3	4	6	9	12+	
Window	± 1 week	± 1 week	± 1 week	± 1 week	± 1 week	± 1 week	± 1 week	

[a] WHO/ECOG PS should also be collected at other site visits, if appropriate site staff are available. In addition, WHO/ECOG performance status should be provided when subsequent anticancer therapy information is collected, where possible.

[b] Details of any treatment for SCCHN (including surgery) post the last dose of study intervention must be recorded in the eCRF. At minimum, collect the start date and description of the subsequent anticancer therapy.

[c] Free T4 or/and free T3 (per local standard clinical practice) will only be measured if TSH is abnormal or if there is clinical suspicion of an adverse event related to the endocrine system.

[d] Participants may be contacted in the week following data cutoffs to confirm survival status. Details of any treatment for SCCHN (including surgery) post the last dose of study intervention must be recorded in the eCRF.

ADA = antidrug antibody; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EORTC = European Organisation for Research and Treatment of Cancer; CCI [redacted]; iv = intravenous; MRI = magnetic resonance imaging; CCI [redacted]; PK = pharmacokinetic; CCI [redacted]; PS = performance status; Q2M = every 2 months; Q6M = every 6 months; QLQ-C30 = 30-item Core Quality of Life Questionnaire; QLQ-H&N35= Quality of Life Questionnaire Head and Neck Module; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; SAE = serious adverse event; SCCHN = squamous cell carcinoma of the head and neck; SPFQ = Study Participant Feedback Questionnaire; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WHO = World Health Organization; wk = week; WOCBP = women of childbearing potential.

2 INTRODUCTION

Monalizumab is a first-in-class ICI targeting NKG2A. It is a non-depleting humanized IgG4 mAb that binds with high affinity and specificity to, and blocks the inhibitory activity of the CD94/NKG2A receptor resulting in the stimulation of the cytolytic activity of CD94/NKG2A-expressing NK cells and CD8+ T cells. Monalizumab is being developed for the treatment of various cancers, including solid tumors and hematologic malignancies either as monotherapy or in combination.

2.1 Study Rationale

The aim of the study is to assess the efficacy and safety of monalizumab and cetuximab, compared to placebo and cetuximab in participants with R/M SCCHN after receiving an ICI.

In addition to blocking the CD94/NKG2A receptor, monalizumab enhances human NK cell ADCC mediated by cetuximab. While monalizumab monotherapy has shown limited clinical activity, encouraging antitumor results have been observed following monalizumab and cetuximab combination therapy in patients with R/M SCCHN who have received prior platinum-based chemotherapy, including patients who have also received prior therapy with an ICI. This dual targeting could therefore provide greater antitumor activity than cetuximab alone. The combination of monalizumab and cetuximab could be a key option to improve clinical outcomes in patients with R/M SCCHN after receiving an ICI.

2.2 Background

Overall, outcomes in patients with R/M SCCHN remain poor and most patients will ultimately experience disease progression and eventually die of the disease.

For 1L treatment of R/M SCCHN, the combination therapy of cetuximab plus platinum (either cisplatin or carboplatin) and 5-FU followed by cetuximab until progression or intolerance (EXTREME regimen) has been the standard of care in the European Union and the USA per the ESMO and NCCN guidelines, respectively (Gregoire et al 2010, NCCN 2021). In clinical practice, other single agents or doublet combinations, such as a taxane or cisplatin plus cetuximab, are also sometimes used as 1L treatment for R/M SCCHN when patients are not fit enough for the EXTREME regimen (Argiris et al 2017).

Squamous cell carcinoma of the head and neck tumors, like many other malignancies, create a highly immunosuppressive environment and are amenable to therapeutic intervention with immune-modulating agents (Curry et al 2014, Moy et al 2017). Recently, the PD-1 inhibitor pembrolizumab (KEYTRUDA®) received US FDA approval as: (i) a single agent for the 1L treatment of patients with metastatic or with unresectable, recurrent SCCHN whose tumors express PD-L1 (combined positive score ≥ 1, as determined by a US FDA-approved test) or (ii) in combination with platinum and 5-FU for the 1L treatment of patients with metastatic or

with unresectable, recurrent SCCHN (Keytruda 2021). The NCCN recommend pembrolizumab as a category 1 of evidence and consensus in the 1L R/M setting (NCCN 2021).

Patients who progress or are intolerant to 1L therapy are typically treated with single-agent cetuximab, single-agent chemotherapy (eg, taxanes, methotrexate), or since recently with PD-1 inhibitors. Cetuximab was approved by the US FDA in 2006 and for a decade remained the only drug indicated for the treatment of patients with R/M SCCHN progressing after platinum-based therapy (Erbitux PI 2021). Cetuximab continues as one of the recommended treatment options in the NCCN guideline (NCCN 2021); the ESMO guideline notes that single-agent cetuximab has activity comparable to single-agent methotrexate with a favorable safety profile (Gregoire et al 2010). In 2016, the US FDA granted approval to pembrolizumab (under accelerated approval) and another PD-1 inhibitor nivolumab (OPDIVO®) in patients with R/M SCCHN with disease progression on or after platinum therapy (Keytruda 2021, Opdivo 2021).

Treatment for patients with R/M SCCHN who progress after receiving a PD-1 inhibitor, such as pembrolizumab/nivolumab monotherapy or pembrolizumab in combination with platinum-based chemotherapy, in the 1L or second-line setting is not clearly defined. A re-challenge with PD-(L)1 inhibitors is not currently recommended. As no treatment strategies in the immunotherapy-refractory disease setting are currently approved or uniformly adopted by the medical community, a suggested approach is to enroll a patient with R/M SCCHN into a clinical study assessing combination immunotherapy (Cohen et al 2019a).

Human leukocyte antigen E, a nonclassical major histocompatibility complex class I molecule, is expressed on tumor cells in 78% to 86% of patients with SCCHN (Andre et al 2018, Nasman et al 2013, Silva et al 2011). Human leukocyte antigen E is the ligand of the inhibitory CD94/NKG2A receptors that are found on NK cells and intratumoral CD8+ T cells in a variety of tumor types, including SCCHN (Braud et al 1998, Gooden et al 2011, Katou et al 2007, Lee et al 1998). The interaction of HLA-E with CD94/NKG2A receptor results in the inhibition of NK cell and cytotoxic T lymphocyte-dependent tumor lysis and may represent a significant immune-escape mechanism by tumor cells (Borrego et al 1998, Braud et al 1998, van Montfoort et al 2018). Monalizumab is a humanized mAb of the IgG4 subtype that specifically binds and blocks the function of CD94/NKG2A.

Cetuximab is a chimeric monoclonal IgG1 antibody that is specifically directed against the EGFR. The EGFR is an important regulator of cell growth and differentiation. Upon ligand binding, EGFR homodimerizes or interacts with other HER members, ie, HER2 and HER3, to form heterodimers. This results in activation of downstream signaling cascades such as the RAS ERK pathway and PI3K/Akt pathway, thereby controlling many biological processes. These pathways play a pivotal role in multiple tumor types, including head and neck cancers,

and are frequently dysregulated via overexpression or autocrine stimulation. Targeting EGFR, eg, with an anti-EGFR mAb like cetuximab, is an important treatment modality for head and neck cancers. Several studies have suggested that ADCC activity is important for cetuximab clinical efficacy and is dependent on tumor cell surface EGFR expression (Kol et al 2017).

It has been previously demonstrated in nonclinical studies that high expression of HLA-E and CD94/NKG2A on tumor cells and effector lymphocytes, respectively, impaired ADCC activity and reduced cetuximab clinical efficacy (Levy et al 2009). NKG2A blockade with monalizumab has been shown to increase cetuximab-dependent ADCC activity, which may translate into increased clinical benefit for the use of cetuximab. Additionally, nonclinical studies have shown increased cetuximab-dependent NK cell-mediated ADCC in SCCHN cell lines expressing HLA-E and EGFR when exposed to monalizumab (Andre et al 2018). As CD94/NKG2A inhibits the effector function of NK cells in the presence of HLA-E, it is expected that blocking of this inhibitory signaling pathway with monalizumab will increase cetuximab-dependent NK cell-mediated ADCC activity, which could subsequently lead to increased clinical benefit.

A detailed description of the chemistry, pharmacology, mechanism of action, efficacy, and safety of monalizumab and cetuximab is provided in the Monalizumab IB and cetuximab (ERBITUX®) current US PI or local label (where available).

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of monalizumab and cetuximab may be found in the Monalizumab IB and current cetuximab US PI or local label (where available).

2.3.1 Risk Assessment

Potential risks for monalizumab are related to hypersensitivity, including anaphylaxis, serious allergic reactions, and immune complex disease. Administration of any therapeutic immunoglobulin antibody/protein is associated with the potential to induce infusion-related and/or hypersensitivity reactions. Infusion-related reaction is an identified risk with monalizumab. Immune-mediated adverse events are considered important potential risks for monalizumab. Activation of NK cells and subsets of T cells through blockade of inhibitory receptors may potentially lead to imAEs.

For cetuximab, skin reactions, hypomagnesemia, and infusion-related reactions are listed as very common (frequency of ≥ 10%) in the US PI or EU SmPC. Skin reaction is the most frequent side effect of cetuximab and may develop in more than 80% of patients.

Current data suggest no change to the safety profile of either product when monalizumab is given in combination with cetuximab.

Monalizumab monotherapy

Study IND.221 (NCT0259301) is a completed Phase 1/2 externally-sponsored, open-label, dose-ranging, cohort-expansion, single-agent, multicenter study of monalizumab in adult participants with R/M gynecologic malignancies who had received prior platinum-based therapy. In the dose-ranging part, up to 18 participants (6/dose level) were to be randomized to receive monalizumab 1.0, 4.0, or 10 mg/kg iv Q2W. In the cohort-expansion part, up to 40 participants were to receive monalizumab 10 mg/kg iv Q2W.

Study EORTC-1159 (NCT03088059/EudraCT 2017-000086-74) is an ongoing externally-sponsored, biomarker-driven platform study in participants with R/M SCCHN who progressed after 1L platinum-based chemotherapy. In the closed immunotherapy cohort 1, participants were to receive monalizumab 10 mg/kg iv Q2W.

In Study IND.221, Grade 3 monalizumab-related AEs were reported for Study IND.221 in 3/18 participants in the Phase 1b dose-ranging part: Grade 3 nausea, vomiting, dehydration (one participant each), and fatigue (2 participants); and in 2/40 participants in the cohort-expansion part: Grade 3 anorexia, nausea, dyspnea (one participant), and proctitis (one participant). No treatment-related Grade 4 AEs were reported. In Study EORTC-1159, none of the participants in immunotherapy cohort 1 had a Grade 3 or 4 monalizumab-related AE.

Monalizumab in combination with cetuximab

CCI

CCI

2.3.2 Benefit Assessment

While monalizumab monotherapy has shown limited clinical activity in participants with R/M SCCHN or gynecological malignancies (Tinker et al 2019a, 2019b), encouraging antitumor results have been observed following monalizumab and cetuximab combination therapy in participants with R/M SCCHN who have received prior platinum-based chemotherapy, including participants who have also received prior therapy with an ICI.

The combination of monalizumab and cetuximab demonstrated preliminary efficacy in participants with R/M SCCHN who had received prior platinum therapy (Cohen et al 2019c) (Table 3). In Cohorts 1 and 2 of Study 203 (see Section 2.3.1), participants may have received up to 2 prior systemic therapies, including platinum-based chemotherapy. Additionally, subjects in Cohort 2 were to have received prior anti-PD-(L)1 therapy. As of the DCO date of 30 April 2019, Cohort 1 completed enrollment of 40 participants with a median duration of 17 months follow-up. Of these participants, 53% were considered resistant to platinum therapy (ie, progressive disease on treatment or within 6 months after end of treatment), 53% had received more than one prior systemic regimen, and 43% had received prior PD-(L)1 inhibitor therapy (PD-[L]1 pretreated). The overall ORR per RECIST 1.1 was 27.5% (11/40 participants; 95% CI: 16%, 43%), with one CR. This represents an approximate doubling of the ORR of cetuximab monotherapy reported as 13% in participants with R/M SCCHN participants who had progressed on 2 to 6 cycles of platinum therapy (Erbitux PI 2021, Vermorken et al 2007). Median OS was 8.5 months. In PD-(L)1-pretreated participants, the ORR per RECIST 1.1 was 16.7% (3/18 participants with partial response [PR]; 95% CI: 6%, 39%), with a median OS of 14.1 months. In participants who had not received prior therapy with a PD-(L)1 inhibitor (PD-[L]1 naive), the ORR was 36.4% (8/22 participants; 95% CI: 20%, 57%), with one CR, and a median OS of 7.8 months. Preliminary data based on a recent data snapshot of 04 September 2019 from ongoing Cohort 2 in participants who had received prior platinum and prior PD-(L)1 therapy, showed an ORR of 24% (5/21 participants with PR; 95% CI: 11%, 45%). These results are consistent with the response rate seen in Cohort 1 PD-(L)1-pretreated participants.

Table 3 Preliminary Efficacy, Cohort 1 - Expansion Phase (Monalizumab + Cetuximab), All Subjects Treated (Study IPH2201-203)

Parameter	Total (N = 40)	PD-(L)1 pre-treated (N = 18)	PD-(L)1 naive (N = 22)
ORR, % (95% CI)	27.5 (16, 43)	16.7 (6, 39)	36.4 (20, 57)
Complete response	1 (2.5)	0	1 (4.5)
Partial response	10 (25.0)	3 (16.7)	7 (31.8)
Median PFS	4.5 (3.5, 5.8)	5.1 (3.5, 8.8)	3.9 (3.5, 6.9)
Median OS	8.5 (7.5, 16.4)	14.1 (8.0, NR)	7.8 (6.9, 15.8)

Participants received monalizumab 10 mg/kg iv Q2W + cetuximab at the approved dosage of 400 mg/m^2 iv initial dose followed by subsequent weekly doses of 250 mg/m^2 iv.
CI = confidence interval; NR = not reached; ORR = objective response rate; OS = overall survival; PD-(L)1 = programmed cell death-1 or programmed cell death ligand-1; PFS = progression-free survival; Q2W = every 2 weeks; iv = intravenous.
Based on a data snapshot date of 30 April 2019.

With regards to cetuximab, single-agent cetuximab is active in the treatment of participants with R/M SCCHN who progressed on platinum therapy with an ORR of approximately 13% (Vermorken et al 2007), and is listed as a recommended treatment option for SCCHN patients in the R/M setting in the latest NCCN and ESMO guidelines (Gregoire et al 2010, NCCN 2021) and SITC recommendations (Cohen et al 2019a). In the USA, the use of single-agent cetuximab is approved for R/M SCCHN progressing after platinum-based therapy (Erbitux PI 2021).

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures to minimize risk to participants in this study, the potential risks identified in association with monalizumab and cetuximab are justified by the anticipated benefits to participants with R/M SCCHN who have been previously treated with platinum-based chemotherapy and an ICI.

3 OBJECTIVES AND ENDPOINTS

Table 4 Objectives and Endpoints

Objective	Estimand [a] Description/Endpoint
Primary	
To compare the effect of monalizumab and cetuximab (Arm A) relative to placebo and cetuximab (Arm B) by assessment of OS in HPV-unrelated participants	• Population: The HPV-unrelated Analysis Set which will include all randomized participants who are either OPC HPV negative or non-OPC regardless of HPV status • Endpoint: OS, which is defined as time from randomization until the date of death due to any cause • Intercurrent events: If a participant is lost to follow-up or withdraws consent, OS will be censored based on the last recorded date on which the participant was known to be alive • Summary measure: p-value of treatment comparison using a stratified log rank test and hazard ratio of Arm A relative to Arm B with its confidence interval using a stratified Cox Proportional Hazards model
Secondary	
To compare the effect of monalizumab and cetuximab (Arm A) relative to placebo and cetuximab (Arm B) by assessment of OS in all randomized participants	• Population: The FAS which will include all randomized participants • Endpoint: OS, which is defined as time from randomization until the date of death due to any cause • Intercurrent events: If a participant is lost to follow-up or withdraws consent, OS will be censored based on the last recorded date on which the participant was known to be alive • Summary measure: p-value of treatment comparison using a stratified log rank test and hazard ratio of Arm A relative to Arm B with its confidence interval using a stratified Cox Proportional Hazards model
To compare the effect of monalizumab and cetuximab (Arm A) relative to placebo and cetuximab (Arm B) by assessment of PFS, ORR, and DoR in participants who are HPV-unrelated and in all randomized participants	• PFS is defined as time from randomization until disease progression, per RECIST 1.1 as assessed by the investigator at local site or death due to any cause, whichever occurs first. • ORR is defined as the proportion of participants with measurable disease who have a confirmed CR or PR, as determined by the investigator at local site per RECIST 1.1. • DoR is defined as the time from the date of first documented response until date of documented disease progression or death in the absence of disease progression.

Table 4 Objectives and Endpoints

Objective	Estimand [a] Description/Endpoint
To assess disease-related symptoms, functioning, and HRQoL in participants treated with monalizumab and cetuximab (Arm A) compared to placebo and cetuximab (Arm B) using the EORTC QLQ-C30 and the EORTC QLQ-H&N35 questionnaires in participants who are HPV-unrelated and in all randomized participants	Symptoms, functioning, and global health status/QoL scale/item scores of the EORTC QLQ-C30 & EORTC QLQ-H&N35 • Change from baseline scores across visits • Time to clinically meaningful deterioration in scores
To assess the PK of monalizumab	Concentration of monalizumab in blood and PK parameters (such as C_{max}, C_{trough}, as data allow; sparse sampling)
To investigate the immunogenicity of monalizumab	Presence of ADAs for monalizumab (confirmatory results: positive or negative, titers)
To characterize the association between clinical outcome and protein expression in the tumor microenvironment in participants treated with monalizumab and cetuximab (Arm A) or placebo and cetuximab (Arm B) in participants who are HPV-unrelated and in all randomized participants	HLA-E and NKp46+ expression in pre-treatment and post-treatment tumor biopsies
Secondary safety	
To assess the safety and tolerability of monalizumab and cetuximab (Arm A) compared to placebo and cetuximab (Arm B) in participants with R/M SCCHN previously treated with ICI	AEs, vital signs, clinical laboratory results, ECGs
Exploratory	
CCI [redacted]	

Table 4 Objectives and Endpoints

CCI

[redacted]

[a] Estimand is the target of estimation to address the scientific question of interest posed by the primary objective. Attributes of an estimand include the population of interest, the variable (or endpoint) of interest, the specification of how intercurrent events are reflected in the scientific question of interest, and the population-level summary for the variable.

ADA = antidrug antibodies; AE = adverse event; C_{max} = maximum serum concentration; CR = complete response; CCI [redacted]; C_{trough} = trough serum concentration; DoR = duration of response; ECG = electrocardiogram; EORTC = European Organisation for Research and Treatment of Cancer; CCI [redacted]; FAS = full analysis set; HLA-E = human leukocyte antigen E; CCI [redacted]; CCI [redacted]; HRQoL = health-related quality of life; ICI = immune checkpoint inhibitor; NK = natural killer; OPC = oropharyngeal cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; CCI [redacted]; CCI [redacted]; CCI [redacted]; PK = pharmacokinetic(s); PR = partial response; CCI [redacted]; QLQ-C30 = 30-item Core Quality of Life Questionnaire; QLQ-H&N35 = Quality of Life Questionnaire Head and Neck Module; RECIST 1.1 = Response Evaluation Criteria for Solid Tumors version 1.1; R/M = recurrent or metastatic; SCCHN = squamous cell carcinoma of the head and neck; CCI [redacted].

4 STUDY DESIGN

4.1 Overall Design

Study D7310C00001 is a Phase 3, randomized, double-blind, multicenter, global study assessing efficacy and safety of monalizumab and cetuximab compared to placebo and cetuximab in participants with R/M SCCHN previously treated with platinum-based chemotherapy and an ICI, regardless of the sequence of these therapies.

Approximately 624 eligible participants will be randomized in a 2:1 ratio to one of the following treatment arms.

- Arm A (n = 416): monalizumab and cetuximab
  Monalizumab CCI and cetuximab 400 mg/m^2 iv initial dose followed by 250 mg/m^2 iv Q1W, as per label
- Arm B (n = 208): placebo and cetuximab
  Placebo iv Q2W and cetuximab 400 mg/m^2 iv initial dose followed by 250 mg/m^2 iv Q1W, as per label

Participants will be stratified by the following (see Section 6.3.1 for more detail):

- Human papillomavirus status (OPC HPV positive or HPV-unrelated),
  - The number of OPC HPV-positive participants will be closely monitored throughout the study and is planned to be capped at approximately 20% of the total sample size.
- World Health Organization/ECOG PS (0 or 1), and
- Number of prior lines of therapy in the R/M setting (1 or 2)
  - The number of participants in each stratum (1 or 2 prior lines of therapy in the R/M setting) will be closely monitored throughout the study. If a disproportionate number of participants are enrolled in a single stratum (eg, > 75% of the total sample size), the Sponsor may elect to close further recruitment into that stratum.

Participants will be treated until RECIST 1.1-defined radiological disease progression per investigator, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Crossover between treatment arms will not be permitted.

An IDMC will review safety data regularly and make recommendations regarding further study conduct (see Appendix A 5). For both IAs, the IDMC will review unblinded interim data and inform the Sponsor whether the interim boundaries specified in Section 9.5 are met.

After discontinuation of study intervention, all participants will have a 3-month safety follow-up (see Section 7.1.1). Participants who have discontinued study intervention in the absence of RECIST 1.1-defined radiological disease progression per investigator will continue with scheduled tumor assessments until RECIST 1.1-defined disease progression or death. Additionally, all participants will be followed for survival status, subsequent anticancer therapy, and CCI, withdrawal of consent, or the end of the study.

An overview of the study design is presented in Figure 1. Details on the efficacy and safety endpoints are provided in Section 3.

Section 6.7 presents treatment options after the final DCO and database closure.

4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with GCP, and minimize risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent/re-consent for the mitigation procedures (note, in the case of verbal consent/re-consent, the ICF should be signed at the participant's next contact with the study site).
- Rescreening: additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The investigator should confirm this with the designated Study Clinical Lead.
- Telemedicine or Remote visit (where applicable): remote contact with the participants using telecommunications technology including phone calls and virtual or video visits.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix C.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Study Design and Participant Population

The primary aim of this study is to assess the efficacy of monalizumab and cetuximab compared to cetuximab and placebo in terms of OS. It is a double-blind, randomized study CCI [redacted]; unblinded Pharmacists and unblinded Study Monitors will be used in order to maintain the blind.

Preliminary data show that the combination monalizumab and cetuximab is well tolerated (Cohen et al 2017, Cohen et al 2018a, Cohen et al 2018b) and has promising activity. As the estimated percentage of patients with cancer eligible for ICI (including but not limited to

anti-PD-(L)1 antibodies) in the course of their disease is increasing, it is crucial to confirm the activity seen with monalizumab administered in combination with cetuximab in population of patients who have previously received ICI.

Participants enrolled in this study will have R/M SCCHN arising in the oropharynx regardless of HPV status, hypopharynx, larynx (supraglottis, glottis, and subglottis) or oral cavity; must have progressed on or after previous systemic cancer therapy (up 2 prior systemic regimens in the R/M setting); are not amenable to further therapy having curative intent; and must have received prior treatment with platinum-based chemotherapy and a systemic PD-(L)1 inhibitor in any setting, regardless of the sequence of these therapies (see inclusion criteria in Section 5.1).

Since HPV-positive OPC represents a biologically distinct disease (Taberna et al 2017), the study design proposed is considered the best approach to evaluate the contribution of monalizumab to cetuximab because the combination therapy will be compared directly to single-agent cetuximab in HPV-unrelated participants. Cetuximab is a valid treatment option for the study population per the revised NCCN and current ESMO guidelines (Gregoire et al 2010, NCCN 2021) and SITC recommendations (Cohen et al 2019a).

4.2.2 Rationale of Study Endpoints

Rationale for primary endpoint and other efficacy endpoints

The primary endpoint of the proposed study will be OS, defined as the time from the date of randomization until death due to any cause. Overall survival is considered the most reliable cancer endpoint supported by the US FDA and EMA guidelines (EMA 2017, FDA 2018a).

Rationale for other efficacy endpoints

The secondary efficacy endpoints will include PFS, ORR, DoR, and PRO measures. All tumor-related endpoints will be assessed by the investigator according to RECIST 1.1.

Target engagement of monalizumab will be assessed through HLA-E and NKp46+ expression in the TME and association with the participant's radiologic response.

In addition to assessing OS and other clinical endpoints in oncology studies, it is important to assess the impact of the disease and its treatment on cancer symptoms, functioning, and HRQoL of the patient, to aid understanding of how clinical benefit relates to patient wellbeing, and for consideration in making risk-benefit evaluations. Moreover, PROs assist in the documentation of symptoms and specifically what symptoms and impacts are most important to patients and how these relate to clinical outcomes. In this study, general cancer symptoms, functioning and HRQoL will be assessed with the EORTC QLQ-C30 while SCCHN-specific symptoms will be evaluated using the EORTC QLQ-H&N35. CCI

[redacted] The rationale for selecting the EORTC QLQ-C30 and QLQ-H&N35 and other PRO instruments is primarily because they have good coverage of the symptoms and impacts most important to SCCHN patients (Degboe et al 2018). These PRO questionnaires are also well established in oncology clinical studies for directly assessing patients' experience of cancer as well as the treatment impact.

4.3 Justification for Dose

4.3.1 Rationale for Monalizumab Dose

Existing PK and pharmacodynamic data, modeling and simulation, and clinical data have been utilized to guide the regimen selection for the combination of monalizumab [redacted] plus cetuximab at 400 mg/m^2 initial dose followed by 250 mg/m^2 Q1W. See the Monalizumab IB for more detail on monalizumab PK, pharmacodynamics, immunogenicity, and clinical activity.

Available PK/pharmacodynamic data were analyzed from ongoing Phase 1/2 Study D419NC00001 for monalizumab doses ranging from [redacted] to [redacted] or [redacted] in combination with durvalumab 1500 mg Q4W. An approximate dose-proportional increase in PK exposure (C_{max} and area under the serum drug concentration-time curve from time 0 to Day 28 post-dose) was observed with increasing doses of monalizumab ([redacted], and [redacted]). Full suppression of the target on NK cell in the periphery was observed over the dose range studied, consistent with engagement of monalizumab with NKG2a.

Pharmacokinetic data from the dose-escalation cohort in ongoing Phase 1b/2 Study IPH2201-203 (Study 203) of monalizumab [redacted] to [redacted] in combination with cetuximab 400 mg/m^2 initial dose followed by 250 mg/m^2 Q1W showed an approximate dose-proportional increase in monalizumab C_{max} over the dose range for the first dosing cycle. These data were consistent with the predicted monotherapy PK data (5th, 50th, and 95th percentiles) for a Q2W regimen.

Antidrug antibody analyses of serum samples from treated participants in Study D419NC00001 and Study 203, showed a low ADA signal, close to the screening cut point, for all ADA-positive samples, suggesting either false positive result or low ADA concentration. PK profiles for participants with ADA-positive samples were not modified, indicating that ADA did not impact monalizumab exposure.

Clinical data

A tolerable safety profile was observed for participants in Study 203 Cohorts 1 and 2 treated with monalizumab [redacted] or [redacted] respectively, plus cetuximab 400 mg/m^2

initial dose followed by 250 mg/m^2 Q1W. Promising clinical activity was observed in Cohort 1, with consistent preliminary results from ongoing Cohort 2.

Based on these data, the combination of monalizumab [redacted] plus cetuximab 400 mg/m^2 initial dose followed by 250 mg/m^2 Q1W was selected for further development. This dose is expected to achieve complete target saturation in the majority of participants and account for anticipated variability in PK, pharmacodynamics, and clinical activity in SCCHN populations.

Rationale for fixed-dose of monalizumab

Current ongoing studies with the combination of monalizumab and cetuximab administer monalizumab using either weight-based dosing (ie, monalizumab [redacted]; Study 203 Cohort 1) or [redacted] dosing (ie, monalizumab [redacted]; Study 203 Cohort 2 and Study D419NC00001).

Comparison of the observed monalizumab exposure between [redacted] and [redacted] showed similar preliminary PK exposure (C_{max} and C_{trough}) after the first monalizumab dose for the [redacted] dosage (monalizumab in combination with cetuximab, Study 203 Cohort 1) and the [redacted] dosage (monalizumab in combination with durvalumab, Study D419NC00001). The observed PK of monalizumab when administered in combination with cetuximab is within the range of monalizumab monotherapy PK.

A population PK model was developed for monalizumab using PK data from Study 203 and Study D419NC00001 in participants with solid tumors, including SCCHN, microsatellite-stable colorectal cancer, ovarian cancer, endometrial cancer, non-small cell lung cancer, cervical cancer, or pancreatic cancer. At the time of analysis, a total of 95 evaluable participants treated with monalizumab [redacted] or [redacted] in combination with cetuximab (N = 30; Study 203) or monalizumab [redacted], or [redacted] or [redacted] [redacted] in combination with durvalumab (N = 65; Study D419NC00001) were used for building the preliminary population PK model. To determine the impact of body weight-based ([redacted]) or [redacted] dosing ([redacted]) on monalizumab PK exposure, simulations were conducted (N = 500 participants/cohort with a body-weight distribution of 40 to 120 kg) and predicted steady state concentrations were compared. A [redacted] dose of [redacted] was selected to approximate [redacted] based on the median body weight of 75 kg. Simulation results demonstrated that body weight-based and [redacted]-dosing regimens yield similar steady-state PK concentrations with similar overall between-participant variability. The predicted similarity of exposure following either of the dosing regimen is consistent with literature showing that an exponent of the covariate model for body weight of approximately 0.5 is expected to yield similar median PK profiles without following either [redacted] or body weight-based dosing (Wang et al 2009). Therefore, based on an average body weight of 75 kg, a [redacted] dose of [redacted] monalizumab is equivalent to [redacted] respectively.

The proposed Phase 3 study of monalizumab in combination with cetuximab, will use the CC dose of monalizumab CCI This dosing regimen is aligned with the standard CC dosing of monalizumab CCI being investigated in the multiple ongoing monalizumab clinical studies (see Monalizumab IB).

4.3.2 Rationale for Cetuximab Dose

The dose regimen for cetuximab in this study (400 mg/m^2 initial dose followed by 250 mg/m^2 Q1W starting on Day 8) is per the cetuximab US PI (Erbitux PI 2021).

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the SoA (Section 1.3). Participants will be followed for survival status until death, withdrawal of consent, or the end of the study.

The end of the study is defined as the date of the last visit of the last participant in the study globally.

The study may be stopped if, in the judgment of the Sponsor, participants are placed at undue risk because of clinically significant findings.

See Section 6.7 for details on participant management following the final DCO as well as following study completion.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1 Participant must be ≥ 18 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 Histologically or cytologically confirmed R/M SCCHN of the oral cavity, oropharynx, hypopharynx, or larynx who have progressed on or after previous systemic cancer therapy and are not amenable to curative therapy

3 Must have received prior treatment with a systemic PD-(L)1 inhibitor (in any setting)

4 Prior platinum failure as defined by either:

- Disease progression during or after treatment with a platinum-containing regimen for R/M disease or
- Recurrence/progression within 6 months of the last dose of platinum as part of multimodal therapy for LA disease

5 Received 1 or 2 prior systemic regimens for R/M SCCHN (see Section 6.3.1 for additional detail on prior lines of therapy)

6 At least one lesion that qualifies as a RECIST 1.1 TL at baseline (see Appendix G). Tumor assessment by CT scan or MRI must be performed within 28 days prior to randomization.

7 Provide fresh or recently acquired tumor tissue (≤ 3 months prior to screening) for the purpose of biomarker testing. Tumor tissue collected when previous treatments were still ongoing is not acceptable.

- Tumor tissue beyond the 3-month window and up to 6 months old may be considered with Sponsor consultation provided that no intervening systemic regimen was ongoing at the time of sample collection (see Laboratory Manual for more information).

8 For participants with OPC only: known HPV status prior to randomization (see Section 6.3.1)

9 WHO/ECOG PS of 0 or 1 at enrollment

10 Adequate organ function, defined as:

(a) Hemoglobin ≥ 9.0 g/dL

(b) Absolute neutrophil count ≥ 1500/mm^3

(c) Platelets ≥ 75,000/mm^3

(d) Total bilirubin ≤ 1.5 × institutional ULN. This will not apply to participants with confirmed Gilbert's syndrome, who will be allowed in consultation with their physician.

(e) Aspartate aminotransferase and ALT ≤ 2.5 × institutional ULN; for participants with hepatic metastases, ALT and AST ≤ 5 × ULN

(f) Measured CrCL ≥ 30 mL/min or calculated CrCL ≥ 30 mL/min as determined by Cockcroft-Gault (using actual body weight)

- Males:

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

- Females:

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

11 Minimum life expectancy of 12 weeks

Weight

12 Body weight > 30 kg

Sex

13 Male and/or female

Reproduction

14 Negative pregnancy test ("highly effective" urine or serum test) for female participants of childbearing potential.

15 Female participants must be one year post-menopausal, surgically sterile, or using an acceptable method of contraception (see Appendix H) for the duration of the study (from the time they sign consent) and for 4 months after the last dose of study intervention to prevent pregnancy.

16 Male participants must be surgically sterile or using an acceptable method of contraception (see Appendix H) for the duration of the study (from the time they sign consent) and for 4 months after the last dose of study intervention to prevent pregnancy in a female partner. Male participants must not donate or bank sperm during the same time period.

Informed Consent

17 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this protocol

18 Provision of signed and dated, written ICF prior to any mandatory study specific procedures, sampling, and analyses

CCI

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

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 participants with squamous cell carcinoma of unknown primary or non-squamous histologies (eg, nasopharynx or salivary gland)

2 Prior cetuximab therapy (unless it was administered in curative LA setting with radiotherapy and no disease progression for at least 6 months following the last cetuximab dose)

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

- Participants with irreversible toxicity not reasonably expected to be exacerbated by treatment with monalizumab and cetuximab may be included only after consultation with the Study Clinical Lead.

4 Has carcinomatous meningitis and/or untreated central nervous system metastases identified either on the baseline brain imaging (see Appendix G) obtained during the screening period or identified prior to signing the ICF. Participants with a history of brain metastases or with suspected brain metastases at screening must have an MRI (preferred) or CT each preferably with iv contrast of the brain prior to study entry. Participants whose brain metastases have been treated may participate provided they show radiographic stability (defined as 2 brain images, both of which are obtained after treatment to the brain metastases. These imaging scans should both be obtained at least 4 weeks apart and show no evidence of intracranial progression). In addition, any neurologic symptoms that developed either as a result of the brain metastases or their treatment must have resolved or be stable either, without the use of steroids, or are stable on a steroid dose of ≤ 10 mg/day of prednisone or its equivalent and anticonvulsants for at least 14 days prior to the start of treatment. Brain metastases will not be recorded as RECIST 1.1 TL at baseline.

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

6 History of allogeneic organ transplantation

7 History of allergic reactions or hypersensitivity attributed to compounds of similar chemical or biologic composition to cetuximab and monalizumab or any of their excipients

8 History of active primary immunodeficiency

9 Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:
   - Participants with vitiligo or alopecia
   - Participants with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement
   - Any chronic skin condition that does not require systemic therapy
   - Participants without active disease in the last 5 years may be included but only after consultation with the Study Clinical Lead
   - Participants with celiac disease controlled by diet alone

10 Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), **hepatitis B** (known positive HBV surface antigen [HBsAg] result), **hepatitis C** (HCV), or **human immunodeficiency virus** (positive HIV 1/2 antibodies). Participants with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Participants positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

11 Uncontrolled intercurrent illness, including but not limited to: ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, uncontrolled cardiac arrhythmia, active interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the participant to give written informed consent

12 History of another primary malignancy except for:
   - Malignancy treated with curative intent and with no known active disease ≥ 5 years before the first dose of study treatment and of low potential risk for recurrence
   - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
   - Adequately treated carcinoma in situ without evidence of disease
   - Participants with a history of prostate cancer (tumor/node/metastasis stage) of Stage ≤ T2cN0M0 without biochemical recurrence or progression and who in the opinion of the investigator are not deemed to require active intervention

13 Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥ 500 ms calculated from 3 ECGs (see Section 8.2.3)

Prior/Concomitant Therapy

14 Any concurrent anticancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is allowed.

15 Receipt of the last dose of anticancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, mAbs, or investigational agents) or radiotherapy with curative intent (to more than 30% of the bone marrow or with a wide field of radiation) ≤ 28 days prior to the first dose of study intervention. If sufficient wash-out time has not occurred due to the schedule or PK properties of an anticancer agent, a longer wash-out period will be required, as agreed by the Sponsor and the investigator.

16 Current or prior use of immunosuppressive medication within 14 days before the first dose of study intervention. The following are exceptions to this criterion (see also Table 6):

- 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 premedication for hypersensitivity reactions (eg, CT scan premedication)

17 Receipt of live attenuated vaccine within 30 days prior to the first dose of study intervention.
Note: Participants, if enrolled, should not receive live vaccine whilst receiving study intervention and up to 30 days after the last dose of study intervention.

Prior/Concurrent Clinical Study Experience

18 Participation in another clinical study with an investigational product administered in the last 28 days prior to randomization or concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study

19 Prior treatment with monalizumab

Other Exclusions

20 Involvement in the planning and/or conduct of the study (applies to both Sponsor staff and/or staff at the study site).

21 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions and requirements.

22 Previous study intervention assignment in the present study.

23 For women only - currently pregnant (confirmed with positive pregnancy test) or breast-feeding.

24 Genetics research study (optional):

Exclusion criteria for participation in the optional (DNA) genetics research component of the study include:

- Previous allogeneic bone marrow transplant
- Transfusion of non-leukocyte-depleted blood or blood components within 120 days of genetic sample collection

5.3 Lifestyle Considerations

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

1 Participants must follow the contraception requirements outlined in Appendix H.

2 Participants should not donate blood or blood components while participating in this study and through 4 months after the last dose of study intervention.

3 Women must not breastfeed during the study, and for 4 months after the last dose of study intervention.

Restrictions relating to concomitant medications are described in Section 6.5.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but do not fulfill the eligibility criteria, and therefore must not be randomized. These participants should have the reason for study withdrawal recorded as “eligibility criteria not fulfilled” (ie, participant does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (ie, not randomized participants).

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE. If a pre-screened tissue and/or whole blood/serum/plasma sample has already been procured prior to screen failure, a biomarker evaluation will be conducted if feasible (consistent with the ICF).

Individuals who do not meet the criteria for participation in this study (screen failure) may be

rescreened a single time, but they may not be re-randomized. Rescreened participants should be assigned the same E-code as for the initial screening. Participants will reconfirm their consent to participate in the study by re-signing and dating their original ICF(s), next to their original signature and date, or according to local or site-specific procedures. All assessments must be repeated for rescreening unless they are within 28 days of randomization.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Interventions Administered

6.1.1 Investigational Medicinal Products

Table 5 Investigational Medicinal Products

Intervention name	Monalizumab	Cetuximab	Placebo
Type	Biologic	Biologic	Drug
Dose formulation	CCI	As sourced by AstraZeneca, cetuximab will be supplied as a liquid solution containing 5 mg/mL cetuximab, sodium chloride, glycine, polysorbate 80, citric acid monohydrate, sodium hydroxide, and WFI. If cetuximab is sourced locally it will be as the approved commercial product.	CCI
Unit dose strength(s)		500 mg (nominal) cetuximab per vial as sourced by AstraZeneca. Cetuximab will be locally sourced as the approved commercial product.	

Table 5 Investigational Medicinal Products

Intervention name	Monalizumab	Cetuximab	Placebo
Dosage level(s)	CCI [redacted]	Initial dose: 400 mg/m2 Subsequent doses: 250 mg/m2 Q1W	CCI [redacted]
Route of administration	[redacted]	iv infusion	[redacted]
Use	Experimental	Experimental/Active comparator	Placebo
IMP and NIMP	IMP	IMP	IMP
Sourcing	AstraZeneca	AstraZeneca source centrally or locally sourced where feasible	Sourced locally by site
Packaging and labelling	CCI [redacted]	Each vial will be labelled in accordance with GMP Annex 13 and per country regulatory requirement.	CCI [redacted]
Current/Former name(s) or alias(es)	IPH2201	Erbitux®	Not applicable

CCI [redacted]; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; CCI [redacted].

6.1.2 Dosing Instructions

A physician must be present at the site or immediately available to respond to emergencies during all administrations of IMP. Fully functional resuscitation facilities should be available. As with any mAb, allergic reactions to dose administration are possible. Therefore, 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. See Section 6.6 and Section 8.3.15 for dose modification and management of IMP-related toxicities, respectively.

Section 6.2.1 describes dose preparation and administration.

Permissible medications prior to administration of monalizumab or cetuximab are described in Section 6.5.1. No premedication is required prior to monalizumab administration, unless a participant has experienced an infusion-related AE in the previous cycle. For cetuximab, participants should be premedicated per US PI (antihistamine iv 30 to 60 minutes prior to the

first infusion or subsequent infusions of cetuximab as deemed necessary) or local label (where available). Premedication may also be based on institutional guidance for management of infusion-related reactions.

Dosing regimen

The dosing regimen for Arm A and Arm B is presented in Figure 2 (see also SoA Table 1).

CCI

CCI

CCI

CCI

CCI

6.1.3 Duration of Treatment

All study intervention will be administered beginning on Day 1. Participants in Arm A or Arm B will remain on study intervention until RECIST 1.1-defined radiological disease progression (refer to Appendix G) unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. See Section 7.1 for information on discontinuation of study intervention for individual participants.

A follow-up scan is to be collected after the initial RECIST 1.1-defined disease progression, preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of disease progression (Eisenhauer et al 2009). This follow-up scan is evaluated using the Confirmation of Radiological Progression criteria outlined in Appendix G.

6.2 Preparation/Handling/Storage/Accountability of Interventions

1 The investigator or designee (eg, unblinded pharmacist) must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are to be reported and resolved before use of the study intervention.

2 Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

3 The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

4 Further guidance and information for the final disposition of unused study interventions will be provided to the sites.

All IMPs should be stored in a secure and dry place. Vials of IMP for parenteral administration should be stored at 2 °C to 8 °C (36 °F to 46 °F; refrigerated) and must not be frozen. IMP must be kept in original packaging until use to prevent prolonged light exposure.

Placebo will be locally sourced by the study site and cetuximab will either be locally sourced by the study site or centrally supplied by the Sponsor. When centrally supplied, cetuximab will be labeled with local language translated text in accordance with regulatory guidelines.

6.2.1 Dose Preparation and Administration

6.2.1.1 Monalizumab

The dose of monalizumab for administration must be prepared by the investigator's or site's

designated IMP manager using aseptic technique. CCI [redacted]

CCI [redacted]

CCI [redacted]

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

The iv line will be flushed according to local practices to ensure the full dose is administered. Infusion time does not include the final flush time.

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

6.2.1.2 Cetuximab

The dose of cetuximab for administration must be prepared by the investigator's or site's designated IMP manager using aseptic technique. See the Pharmacy Manual for guidance on

cetuximab storage conditions, dose preparation, and dose administration. See Section 6.1.2 for the cetuximab dosing regimen.

6.2.1.3 Placebo

CCI

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

The iv line will be flushed according to local practices to ensure the full dose is administered. Infusion time does not include the final flush time.

If either preparation time or infusion time exceeds the time limits, a new placebo dose must be prepared.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Participant Enrollment and Randomization

Participants will be randomized in a 2:1 ratio to Arm A or Arm B.

Randomization will be stratified by

- Human papillomavirus status (OPC HPV positive or HPV-unrelated),
  - The number of OPC HPV-positive participants will be closely monitored throughout the study and is planned to be capped at approximately 20% of the total sample size.
- World Health Organization/ECOG PS (0 or 1), and
- Number of prior lines of therapy in the R/M setting (1 or 2)
  - The number of participants in each stratum (1 or 2 prior lines of therapy in the R/M setting) will be closely monitored throughout the study. If a disproportionate number of participants are enrolled in a single stratum (eg, > 75% of the total sample size), the Sponsor may elect to close further recruitment into that stratum.

All participants will be centrally assigned to randomized study intervention using an IRT. Before the study is initiated, user guides, the log in information, and directions for the IRT will be provided to each site.

If participants withdraw from the study, then their randomization codes cannot be reused. Withdrawn participants will not be replaced.

Investigators should keep a record (ie, the participant screening log) of participants who entered screening.

At screening/baseline (Days -28 to -1), the investigators or suitably trained delegate will:

- Obtain signed informed consent before any study-specific procedures are performed. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the participants. However, all screening laboratory and imaging results must have been obtained within 28 days of randomization.
- Have participants identified to the IRT per country regulations. A unique 7-digit enrollment number (E-code) will be obtained, through the IRT in the following format (ECCNNXXX: CC being the country code, NN being the center number, and XXX being the participant enrollment code at the center). This number is the participant's unique identifier and is used to identify the participant on the eCRFs.
- Obtain a tumor tissue sample for determination of HLA-E and NKp46 expression (see Section 8.6.1).
- Determine participant eligibility (see Section 5.1 and Section 5.2).
- Determine HPV status (positive or negative) for participants with OPC for purposes of stratification. HPV status will be assessed using local testing by IHC analysis with CINtec® Histology p16 assay. Positive p16 IHC expression is defined as 70% or more of cytoplasmatic and nuclear staining of the tumor cells. Should the CINtec Histology assay not be available at a local institution, a tumor tissue sample should be submitted to the central laboratory for HPV assessment (details are provided in the Laboratory Manual).
- Determine WHO/ECOG PS (0 or 1)
- Determine the number of prior lines of therapy in the R/M setting (1 or 2) for stratification purposes.
  - For participants with LA disease previously treated with platinum (cisplatin/carboplatin) as part of multimodality therapy and progressed during or within 6 months after the last platinum dose, this will be considered as one line of therapy in the R/M setting.
- CCI [redacted] Participants who decide CCI to sign CCI , CCI the general study ICF, are eligible for study enrollment and all other study procedures.

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

- Obtain a randomized treatment arm via the IRT. Randomization codes will be assigned strictly sequentially within each stratum and site/country/region as participant become eligible for randomization. The system will randomize the eligible participant to one of the 2 treatment arms.

If the participant is ineligible and not randomized, the IRT should be accessed to terminate the participant in the system.

Participants will begin treatment on Day 1. Every effort should be made to minimize the time between randomization and starting study intervention. It is strongly recommended that participants commence study intervention on the same day as randomization by IRT. If same-day treatment is not possible, then study intervention must occur within 2 days of randomization. Participants must not be randomized and treated unless all eligibility criteria have been met.

6.3.2 Procedures for Handling Incorrectly Enrolled or Randomized Participants

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

Where a participant does not meet all the eligibility criteria but is randomized in error, or incorrectly started on study treatment, the investigator should inform the Study Clinical Lead immediately, and a discussion should occur between the Study Clinical Lead and the investigator regarding whether to continue or discontinue the participant from study intervention. The Study Clinical Lead must ensure all decisions are appropriately documented and that the potential benefit/risk profile remains positive for the participant.

6.3.3 Methods for Assigning Treatment Arms

The actual treatment given to participants will be determined by the randomization scheme in the IRT. 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 randomization will be balanced within the IRT at the site/country/region/central level.

Randomization codes will be assigned strictly sequentially, within each stratum, as participants become eligible for randomization. The IRT will provide the kit identification number for centrally supplied IMP to be allocated to the participant at the randomization visit and subsequent treatment visits.

6.3.4 Methods for Ensuring Blinding

The study will be conducted in a double-blind manner.

Monalizumab placebo CCI [redacted] will be prepared by the unblinded pharmacist. The participant, the investigator, and study center staff will be blinded to treatment arm allocation and will remain blinded to each participant's assigned study treatment throughout the course of the study. To maintain this blind, an otherwise uninvolved third party (ie, the unblinded pharmacist) will be unblinded to treatment allocation and will prepare monalizumab or placebo for a participant as specified by the randomization scheme and IRT (the unblinded pharmacist will be the only member of investigator site staff to know the randomization/treatment allocation details).

The IRT will provide to the investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit. Pharmacists will be given specific instructions for monalizumab/placebo preparation and will note if the double-blind conditions have been compromised or the blind has been broken. Lot numbers of monalizumab dispensed will be recorded by the pharmacist and monitored by an unblinded monitor. Other blinded study center staff and monitors will not be given access to lot number information. Blinded and unblinded access and notifications will be controlled using the IRT.

Routines for this will be described in the IRT user manual that will be provided to each center.

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization. The investigator documents and reports the action to the Sponsor, without revealing the treatment given to the participant to the Sponsor staff.

The Sponsor retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IMP and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

No member of the extended study team at the Sponsor, at the investigational centers, or any blinded CRO handling data will have access to the randomization scheme until the time of the final analysis or any IA data where a decision is made to unblind the study. At such time, the Sponsor and any CRO handling data will have access to the randomization scheme. Exceptions are relevant persons within the Pharmaceutical Development Supply Chain at AstraZeneca or their designee, where the information is needed to package the study intervention; the drug safety departments at AstraZeneca; and the pharmacists required to dispense the study intervention at the study site. Investigators will be unblinded to treatment allocation only in cases of medical emergency. Additionally, at the request of the investigator,

at progression of disease, the participant can be unblinded.

The treatment codes and results will be kept strictly within AstraZeneca to safeguard the integrity of the blind and hence to minimize any possible bias in data handling.

In the event that the treatment allocation for a participant becomes known to the investigator or other study staff involved in the management of study participants, or needs to be known to treat an individual participant for an AE, the Sponsor must be notified promptly by the investigator and, if possible, before unblinding.

The IRT will be programmed with blind-breaking instructions. The blind may be broken if, in the opinion of the investigator, it is in the participant's best interest for the investigator to know the study treatment assignment. The Sponsor must be notified before the blind is broken unless identification of the study intervention is required for a medical emergency in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition (eg, antidote available). In this case, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable. Study unblinding should occur after database lock, once all decisions on the evaluability of the data from each individual participant have been made and documented.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. This information, plus drug accountability for all study interventions at every visit, will be used to assess compliance. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Any change from the dosing schedule, dose delays/interruptions, and dose discontinuations should be recorded in the eCRF. Dose modifications for monalizumab/placebo and cetuximab are permitted per the guidelines described in Section 6.6.

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

The Investigator Product Storage Manager is responsible for managing the IMP from receipt by the study site until destruction of all unused IMP.

6.5 Concomitant Therapy

Any concomitant treatment, procedure, or medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the participant is receiving

according to the schedule in the SoA (Section 1.3) must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Study Clinical Lead should be contacted if there are any questions regarding concomitant or prior therapy.

If any concomitant therapy is administered due to new or unresolved AE, it should be recorded.

Participants must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

Prohibited and permitted concomitant medications/therapies are described in Table 6 and Table 7, respectively. Refer also to the guidelines for management of IMP-related toxicities in Section 8.3.15. For cetuximab, refer to the local label (where available) with regard to warnings, precautions, and contraindications.

Table 6 Prohibited Concomitant Medication/Therapy

Type of medication/treatment	Timeline/Instructions
Any investigational therapy other than those under investigation in this study	Until end of study treatment.
Any concurrent chemotherapy, radiotherapy, immunotherapy (including other monoclonal antibodies), or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Until end of study treatment. Concurrent use of hormones for non-cancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable (eg, by local surgery or radiotherapy)

Table 6 Prohibited Concomitant Medication/Therapy

Type of medication/treatment	Timeline/Instructions
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly or used for premedication prior to the infusions of IMP. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IMP-related adverse events or infusion-related reactions • Short-term premedication for cetuximab where the local label requires the use of steroids • Short-term premedication for monalizumab/placebo following > Grade 2 infusion-related reaction at the previous cycle (see monalizumab TMG) • Use in participants with contrast allergies • Use of inhaled, topical, and intranasal corticosteroids A temporary period of steroid use will be permitted if clinically indicated and considered to be essential for the management of non-immunotherapy-related events experienced by the participant (eg, chronic obstructive pulmonary disease, radiation, nausea, etc).
Live attenuated vaccines	Within 30 days prior to the first dose of IMP, whilst receiving IMP and up to 30 days after the last dose of IMP.
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the Sponsor

IMP = investigational medicinal product.

Table 7 Permitted Concomitant Medication/Therapy

Type of medication/treatment	Timeline/Instructions
All necessary supportive care in the form of treatment or prophylaxis as clinically indicated eg, transfusion of blood products, antibiotics, anti-histamines, analgesics	Throughout the study
Vaccines limited to non-live attenuated preparations (eg, influenza vaccine) See Appendix C for vaccination against COVID-19	Throughout the study

COVID-19 = coronavirus disease 2019.

6.5.1 Permitted Medication Prior to Study Intervention

Monalizumab

No premedication is required prior to monalizumab administration. However, from Cycle 2, premedication with acetaminophen and/or an antihistamine drug might be prescribed, at the investigator's discretion, if the participant experienced any Grade 1 to 3 infusion-related AE at

the previous cycle (see monalizumab TMG provided as a supplement to the CSP).

Cetuximab

Participants should be premedicated per US PI (antihistamine iv 30 to 60 minutes prior to the first infusion or subsequent infusions of cetuximab as deemed necessary) or local label (where available). Premedication may also be based on institutional guidance for management of infusion-related reactions.

6.5.2 Drug-drug Interactions

No formal drug-drug interaction studies have been conducted with monalizumab. Monalizumab and cetuximab are immunoglobulins and the primary elimination pathways are protein catabolism via reticuloendothelial system or target mediated disposition. Therefore, there are no anticipated drug-drug interactions between monalizumab and cetuximab based on the elimination pathway when monalizumab and cetuximab are administered in combination. Moreover, monalizumab and cetuximab are not expected to induce or inhibit the major drug metabolizing cytochrome P450 pathways.

Based on available non-compartment analysis data, the observed PK of monalizumab when administered in combination with cetuximab is within the range of monalizumab monotherapy PK (see Monalizumab IB, Section 5.1 for further details).

6.5.3 Rescue Medication

Fully functional resuscitation facilities should be available at each site during infusion of the study interventions. Please see recommendations regarding rescue treatment (Section 6.1.2) and management of IMP-related toxicities (Section 8.3.15). The date of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.6 Dose Modification

It is important to keep the day on which monalizumab/placebo and cetuximab are administered as Day 1 of each 2-week cycle (except if one of the study interventions is permanently discontinued). If a participant does not meet monalizumab/placebo dosing criteria on Day 1 of any cycle, both monalizumab/placebo and cetuximab administration should be postponed for a week. If dosing criteria are not met after a week delay, suspension of study intervention will be extended for an additional week. In the absence of resolution after a 2-week delay, the investigator should contact the Sponsor for guidance on further dosing. If dosing delay is due to treatment-related toxicity, TMGs for monalizumab and local prescribing information for cetuximab should be followed (see Section 8.3.15).

For guidance on dose modification in relation to the novel coronavirus (COVID-19) outbreak,

see Appendix C.

Monalizumab/placebo

Dose delays are permitted for monalizumab/placebo (see management of monalizumab-related toxicities in Section 8.3.15.1). However, dose reduction is not permitted.

The duration between each monalizumab/placebo infusion should be at least 14 days (see Table 1 for administration schedule, including acceptable window).

In the event that monalizumab/placebo is discontinued due to monalizumab/placebo-related toxicity, treatment with cetuximab may continue at the investigator's discretion when toxicity resolves to ≤ Grade 1. Note: If the investigator determines that a participant is ready to restart treatment prior to the toxicity resolving to ≤ Grade 1, the Sponsor should be consulted for an exception to this rule.

Cetuximab

Cetuximab dose modification for the management of cetuximab-related toxicities should follow local standard clinical practice (see Section 8.3.15.2). For specific information, refer to the local label (where available) for cetuximab.

The duration between each cetuximab infusion should be at least 7 days (see Table 1 for administration schedule, including acceptable window). If dosing of cetuximab is delayed on Day 1 of a cycle (ie, when monalizumab/placebo is also due to be given) then dosing of monalizumab/placebo should also be delayed (see above). If cetuximab is delayed due to toxicity on Day 8 of a cycle (ie, when single-dose cetuximab is due to be given), the dose of cetuximab will be omitted and the next cycle can continue as usual.

In the event that cetuximab is discontinued due to cetuximab-related toxicity, treatment with monalizumab/placebo may continue at the investigator's discretion when the cetuximab-related toxicity resolves to ≤ Grade 2. Note: If the investigator determines that a participant is ready to restart treatment prior to the cetuximab-related toxicity resolving to ≤ Grade 2, the Sponsor should be consulted for an exception to this rule.

6.7 Intervention After the End of the Study

As described in Section 4.4, the study will remain open until all participants have discontinued study intervention and completed their last expected visit/contact.

After the final DCO and database closure, the Sponsor will supply open-label IMP to participants who are receiving benefit from their assigned treatment, for as long as they and their physician considers they are gaining clinical benefit. See Section 8 for a description of

the assessments to be conducted for these participants.

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, participants 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 visit assessments per its protocol. Any participant who would be proposed to move to such a study would be given a new ICF.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Participants will be discontinued from study intervention in the following situations.

- RECIST 1.1-defined radiological disease progression (refer to Section 6.1.3, Section 8.1.1, and Appendix G)
- Investigator determination that the participant is no longer benefiting from study intervention
- An AE that, in the opinion of the investigator or the Sponsor, contraindicates further dosing
- Any AE that meets criteria for discontinuation defined in the guidelines for management of IMP-related toxicities (see Section 8.3.15) or as defined in the local label (where available) for cetuximab
- Participant decision. The participant is at any time free to discontinue study intervention, without prejudice to further treatment. A participant who discontinues study intervention is normally expected to continue to participate in the study (eg, for safety and survival follow-up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 7.3).
- Severe non-compliance with the CSP as judged by the investigator or the Sponsor
- For females of childbearing potential, pregnancy or intent to become pregnant
- Initiation of subsequent anticancer therapy, including another investigational agent

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

See the SoA (Section 1.3) for data to be collected at the time of study intervention discontinuation and follow-up for safety and other assessments.

If a participant discontinues treatment with one of the combination agents due to toxicity, they may continue with monalizumab/placebo or cetuximab in monotherapy within the study as

long as they are continuing to show clinical benefit, as judged by the investigator and in the absence of discontinuation criteria.

7.1.1 Procedures for Discontinuation of Study Intervention

The EOT visit should be performed and conducted one month after the participant permanently discontinues from study intervention. The assessments to be conducted at the EOT visit are specified in the SoA (Table 2). The reason for discontinuation should be documented in the source document and the appropriate section of the eCRF.

Participants who have permanently discontinued from further receipt of study intervention will need to be discontinued from the IRT.

The date of last intake of study intervention should be documented in the eCRF. Discontinuation of study intervention, for any reason, does not impact on the participant's participation in the study. The participant should continue attending subsequent study visits and data collection should continue according to the study protocol. If the participant does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information including new AEs, follow-up on any ongoing AEs and concomitant medications, and subsequent anticancer therapy. This could be a telephone contact with the participant at one month (+ 3 days) after study intervention is discontinued, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A participant that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

The investigator should instruct the participant to contact the site before or at the time when study intervention is stopped. A participant that decides to discontinue study intervention will always be asked about the reason(s) and the presence of any AEs.

7.1.1.1 Tumor Assessment Post Discontinuation of Study Intervention

Participants who have discontinued study intervention prior to objective RECIST 1.1-defined radiological disease progression, regardless of whether they have commenced subsequent anticancer therapy will continue on their regular scan schedule (see SoA, Table 2) until RECIST 1.1-defined radiological disease progression or death, unless they have withdrawn all consent to study-related assessments.

7.1.1.2 [redacted]

[redacted]

CCI

[redacted]

7.1.1.3 Follow-up for Survival

Participants will be followed for survival status as indicated in the SoA (Table 2) until death, withdrawal of consent, or the end of the study. Survival information may be obtained via telephone contact with the participant or the participant's family, or by contact with the participant's current physician. Additional assessments to be performed at the time of survival follow-up are detailed in the SoA (Table 2).

Participants on treatment or in survival follow-up will be contacted following each DCO to provide complete survival data. These contacts should generally occur within 7 days after the DCO.

7.2 Participant Withdrawal From the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- Upon withdrawal from the study, an EOT visit should be conducted, if possible. See SoA (Section 1.3) for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she is still agrees for samples to be used (see Section A 3). He/she may request destruction of any samples taken, and the investigator must document this in the site study records.
- The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.
- The Sponsor or its delegate will request investigators to collect information on participants' vital status (dead or alive; date of death when applicable) during survival follow-up from publicly available sources, in accordance with local regulations. Knowledge of the vital status at study end in all participants is crucial for the integrity of the study.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site by the time the study is completed (see Section 4.4), such that there is insufficient information to determine the participant's status at that time.

Participants who decline to continue 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 participants throughout the study period. If contact with a missing participant is re-established, the participant should not be considered lost to follow-up and evaluations should resume according to the protocol.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant or next of kin by, eg, repeat telephone calls, certified letter to the participant's last known mailing address, or local equivalent methods. These contact attempts should be documented in the participant's medical record.
- Efforts to reach the participant should continue until the end of the study. Should the participant be unreachable at the end of the study, he/she will be considered lost to follow-up with unknown vital status at the end of the study and censored at latest follow-up contact.

In order to support key efficacy endpoints of OS, PFS, and CCI [redacted], the survival status of all participants in the FAS and the SAF should be re-checked; this includes those participants who withdrew consent or are classified as "lost to follow-up."

- Lost to follow-up – Site personnel should check hospital records and a publicly available death registry (if available), as well as checking with the participants' current physician, to obtain a current survival status. (The applicable eCRF modules will be updated.)
- In the event that the participant has actively withdrawn consent to the processing of their personal data, the survival status of the participant 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.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (see Section 1.3). Protocol waivers or exemptions are not allowed. Assessments following final DCO and database closure until the end of the study are described in Section 8.3.11.

- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Efficacy Assessments

8.1.1 Imaging Tumor Assessments

This study will evaluate a primary endpoint of OS and secondary endpoints of PFS, ORR, and DoR for Arm A vs Arm B. CCI . With the exclusion of OS, efficacy will be derived (by the Sponsor) using investigator RECIST 1.1 assessments.

Tumor assessments use images from iv contrast-enhanced CT (preferred) of the neck (including the base of skull), chest, and abdomen (including the entire liver) collected during screening/baseline and at regular (follow-up) intervals during study intervention. Any other areas of disease involvement should be additionally imaged at screening based on known metastasis sites or by the signs and symptoms of individual participants. MRI with iv contrast is acceptable if CT is contraindicated. The imaging modality (CT/MRI) used for baseline tumor assessments should be kept the same consistently at each subsequent follow-up assessment throughout the study if possible. It is important to follow the tumor assessment schedule as closely as possible (refer to the SoA [Section 1.3]) relative to randomization. Screening/baseline imaging should be performed no more than 28 days before randomization and ideally should be performed as close as possible to randomization. Scanning/tumor

assessments will continue throughout intervention until RECIST 1.1-defined radiological disease progression by investigator assessment (see Section 6.1.3). If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the participant has not progressed, every attempt should be made to perform the subsequent assessments at the next scheduled visit.

Tumor assessment by RECIST 1.1 guidelines are provided in Appendix G.

8.1.2 CCI

CCI

8.1.3 Overall Survival

Assessments for survival will be conducted according to the SoA (Table 2) following objective disease progression or treatment discontinuation. Survival information may be obtained via telephone contact with the participant, participant's family, by contact with the participant's current physician, or local death registries as described in Section 7.2.

8.1.4 Clinical Outcome Assessments

A COA is an assessment of a clinical outcome reported by a clinician, a patient, or a non-clinician observer, or through a performance-based assessment (FDA 2018b). A COA may be used in clinical studies to provide either direct or indirect evidence of treatment benefit. It is important to examine the impact of therapy on disease-related symptoms, physical function, and other HRQoL of the patient to aid understanding of how clinical benefit relates to patient well-being and for consideration in making benefit-risk evaluations. Patient-reported outcome is one type of clinical outcome assessment and is a general term referring to all outcomes and symptoms that are directly reported by the patient. Moreover, PROs assist in the documentation of symptoms and specifically what symptoms and impacts are most important to patients and how these relate to clinical outcomes. Patient-reported outcomes have become important in evaluating effectiveness of study treatments in clinical studies and will aid in understanding of the benefit-risk evaluation (Kluetz et al 2018). The following

PROs will be administered in this study: EORTC QLQ-C30, EORTC QLQ-H&N35, CCI [redacted] See questionnaires in Appendix I. Patient-reported outcomes will be administered according to the SoA during the treatment and follow-up periods (see Section 1.3). Patient-reported outcomes will be translated into the language of the country being administered, CCI [redacted]

8.1.4.1 EORTC QLQ-C30

The EORTC QLQ-C30 was developed by the EORTC Quality of Life Group 1993 (see Appendix I 1). It consists of 30 items and measures symptoms, functioning, and global health status/QoL (Aaronson et al 1993) for all cancer types. Questions are grouped into 5 multi-item functional scales (physical, role, emotional, cognitive, and social); 3 multi-item symptom scales (fatigue, pain, and nausea/vomiting); a 2-item global QoL scale; 5 single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation, and diarrhea), and one item on the financial impact of the disease. The EORTC QLQ-C30 is a valid and reliable PRO instrument in this patient population.

8.1.4.2 EORTC QLQ-H&N35

The EORTC QLQ-H&N35 module is a 35-item self-administered questionnaire (see Appendix I 2). 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.

8.1.4.3 CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI

8.1.4.4 CCI

CCI

CCI

CCI

8.1.4.5 CCI

CCI

8.1.4.6 CCI

CCI

8.1.4.7 Administration of Electronic PRO Questionnaires

Participants will complete the PRO assessments using an electronic tablet (ePRO) during clinic visits at the time points indicated in the SoA (see Section 1.3). It is important that the ePRO device is charged and set up for the participant prior to their arrival at the site for their

baseline PRO assessments (close to when the participant will be randomized), to ensure it is functioning properly and ready for use, in accordance with device training. The participant should be trained on the use of the device, including the importance of completing the PRO questionnaires throughout the study in accordance with the SoA.

The below instructions should be followed when collecting PRO data via an electronic device:

- Patient-reported outcome questionnaires must be completed prior to treatment administration and ideally before any discussions of health status to avoid biasing the participant's responses to the questions. As feasible, site staff should also ensure PRO questionnaires are completed prior to other study procedures, such as collection of laboratory samples, to further minimize bias.
- When each instrument is due to be completed, the following order is observed; EORTC QLQ-C30 should be administered first followed by EORTC QLQ-H&N35, CCI
- Patient-reported outcome questionnaires should be completed by the participant in a quiet and private location.
- The participant should be given sufficient time to complete the questionnaires at their own speed.
- The research nurse or appointed site staff must explain to participants the value and relevance of ePRO participation so they are motivated to comply with questionnaire completion. Inform the participant that these questions are being asked to find out, directly from them, how they feel.
- The research nurse or appointed site staff should stress that the information is not routinely shared with study staff. Therefore, if the participant has any medical problems, they should discuss them with the doctor or research nurse separately from the ePRO assessment.
- The research nurse or appointed site staff must train the participant on how to use the ePRO device, using the materials and training provided by the ePRO vendor.
- All PRO questionnaires are to be completed using the ePRO device. If technical or other device-related issues prohibit completion on the device, an appropriate backup option may be considered with prior approval from AstraZeneca.
- The research nurse or appointed site staff must remind participants that there are no right or wrong answers, and avoid introducing bias by not clarifying items for the participant.
- The participant should not receive help from relatives, friends, or clinic staff to decide on answers to the ePRO questionnaires. The responses are the participant's alone.
- On completion of the questionnaire at the site, it should be handed back to the designated responsible person, who should check that all questionnaires were completed.

- If a participant needs visual aids (eg, spectacles or contact lenses) for reading and does not have them when he or she attends the clinic, the participant will be exempted from completing the ePROs at that clinic visit.
- Site staff must not read the ePRO questionnaires on behalf of the participant. If the participant is unable to read the questionnaire (eg, is blind or illiterate, or not fluent in the available language), that participant is exempted from completing PRO questionnaires but may still participate in the study. If the participant cannot complete the ePRO questionnaires due to reasons other than being blind, illiterate, or fluent in language, the AstraZeneca study team must be contacted to determine if they can be exempted. Participants exempted in this regard should be flagged appropriately by the site staff in the source documents and in the REVPRDI eCRF.
- Questions must not be translated from an available language in the device into the language the participant speaks.
- It is vital that the ePRO reporting is initiated at Cycle 1 Day 1 dosing visit (baseline) as specified in the SoA to capture the effect of study treatment. The ePRO device must be charged and fully functional at the beginning of the baseline visit to ensure that the PROs can be completed at the start of the visit.
- Finally, the research nurse or appointed site staff will review the completion status of questionnaires during site visits and document the reason(s) why a participant could not complete assessments in the designated eCRF.

The research nurse or appointed site staff must monitor compliance since 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 the site receives an email notification regarding the participant's compliance, appropriate action should be taken (eg, discussion with participant to improve compliance, a check in call from the site to ask the participant if they have any difficulties in completing questionnaires on schedule, etc). A solution to enhance/resolve compliance should be discussed with the participant. Discussions and compliance review should be reflected in source documents.

8.1.4.8 WHO/ECOG PS

World Health Organization/ECOG PS will be assessed at the time points specified in the SoA (Section 1.3) based on the following:

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

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

2 Ambulatory and capable of self-care, but unable to carry out any work activities; up and about more than 50% of waking hours

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

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

5 Dead

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

The ECOG status collected at screening must be reported in IRT and not re-assessed.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical Examinations

Physical examination, as well as assessment of height and weight, will be performed at time points specified in the SoA (Section 1.3).

- A full physical examination will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. In addition, targeted physical examinations, eg, urogenital, are to be performed by the investigator based on clinical observations and symptomatology.
- Targeted physical examinations are to be performed by the investigator on the basis of clinical observations and symptomatology.

Situations in which physical examination results should be reported as AEs are described in Section 8.3.5.

8.2.2 Vital Signs

Vital signs will be performed at time points specified in the SoA (Section 1.3).

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Vital signs will be measured after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate.

First infusion

On the first infusion day, participants will be monitored and vital signs collected/recorded in eCRF prior to, during, and after infusion of monalizumab/placebo as presented in the bulleted list below.

Blood pressure and pulse will be collected from participants before, during, and after each monalizumab/placebo infusion 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 infusion (**halfway** through infusion)
- At the end of the infusion (approximately 60 minutes ± 5 minutes)

If the monalizumab/placebo infusion takes longer than 60 minutes, then blood pressure and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. A one-hour observation period is recommended after the first infusion of monalizumab/placebo.

Vital signs will be collected in all participants before cetuximab dosing (approximately 30 minutes before up to 0 minutes) and as clinically indicated during and after dosing, as per the local label and institutional standard. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs eCRF.

Subsequent infusions

Blood pressure, pulse, and other vital signs should be measured (approximately 30 minutes before up to 0 minutes), collected/recorded in the eCRF prior to the start of the infusions of monalizumab/placebo and cetuximab. Participants should be carefully monitored, and blood pressure and other vital signs should be measured during and post infusions as per institutional standard and as clinically indicated (and in line with the local label for cetuximab). Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs eCRF.

Situations in which vital signs results should be reported as AEs are described in Section 8.3.5. For any AEs of infusion reactions, the vital signs values should be entered into eCRF.

8.2.3 Electrocardiograms

Triplicate 12-lead ECGs will be recorded at scheduled visits and as clinically indicated per the SoA (Section 1.3). An ECG will be obtained after the participant has been resting semi-recumbent or supine for at least 5 minutes and recorded while the participant remains in that position using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals.

Three individual ECG tracings should be obtained in succession, no more than 2 minutes apart. The full set of triplicates should be completed within 5 minutes. The machine-derived

QTc must be manually verified and interpreted by the investigator. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal.

Situations in which ECG results should be reported as AEs are described in Section 8.3.5.

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the visits indicated in the SoA (Section 1.3). Samples for determination of coagulation parameters are to be collected at baseline on Day 1 (unless all screening laboratory hematology assessments are performed within 3 days prior to Day 1), and then as clinically indicated. 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.

Clinical laboratory safety tests, including serum pregnancy tests, will be performed at a licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. Pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

Table 8 presents the laboratory variables to be measured. Other safety tests to be performed at screening include assessments for hepatitis B surface antigen, hepatitis C antibodies, and HIV antibodies.

Table 8 Laboratory Safety Variables

Hematology/Hemostasis (whole blood)	Clinical chemistry (serum or plasma)
Hb	Creatinine [a]
Platelet count	Bilirubin, total [b]
Absolute neutrophil count [c]	ALP [b]
Absolute lymphocyte count [c]	AST [b]
Total WBC count	ALT [b]
Coagulation [d]	Albumin
aPTT, fibrinogen, and INR	Potassium
	Calcium, total
Urinalysis [e]	Sodium
Bilirubin	Magnesium
Blood	Phosphate
Protein/Albumin	Amylase [f]
Glucose	Lipase [f]
Color and appearance	Gamma-glutamyl transferase
Ketones	Glucose
Specific gravity	Bicarbonate (where available)

Table 8 Laboratory Safety Variables

Hematology/Hemostasis (whole blood)	Clinical chemistry (serum or plasma)
pH	Chloride
	LDH
	Protein, total
	TSH [g]
	free T4 [h]
	free T3 [h]
	Urea or blood urea nitrogen, depending on local practice

[a] Creatinine clearance will be calculated by the site using Cockcroft-Gault (using actual body weight).
[b] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥ 2 × ULN (and no evidence of Gilbert's syndrome), then fractionate into direct and indirect bilirubin.
[c] Can be recorded as absolute counts or as percentages, except at screening when absolute neutrophil count must be recorded. Total WBC count therefore has to be provided.
[d] Coagulation parameters are to be assessed at baseline on Day 1 (unless all screening laboratory hematology assessments are performed within 3 days prior to Day 1), and then as clinically indicated.
[e] Urinalysis should be done at baseline (screening) and then as clinically indicated.
[f] It is preferable that both amylase and lipase parameters are assessed. For sites where only one of these parameters is routinely measured, either lipase or amylase is acceptable.
[g] If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at Day 1.
[h] Free T4 or/and free T3 (per local standard clinical practice) will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

ALP = alkaline phosphate; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; INR = International Normalized Ratio; LDH = lactate dehydrogenase; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; ULN = upper limit of normal; WBC = white blood cell count.

In case a participant shows an AST **or** ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN, please refer to Appendix F (Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law) for further instructions.

8.3 Adverse Events and Serious Adverse Events

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

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

For guidance in relation to the novel coronavirus (COVID-19) outbreak, see Appendix C.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from time of signature of the ICF until 90 days after the last dose of study intervention (see SoA, Section 1.3). Collection and reporting of AEs and SAEs

after the final DCO is described in Section 8.3.11.

Serious adverse events will be recorded from the time of signing of ICF.

If the investigator becomes aware of an SAE with a suspected causal relationship to the IMP that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the Sponsor.

8.3.2 Follow-up of AEs and SAEs

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

Adverse event variables

The following variables will be collected for each AE;

- Adverse event (verbatim)
- The date when the AE started and stopped
- Select the appropriate as required:
  - The maximum CTCAE grade reported
  - Changes in CTCAE grade (report only the maximum CTCAE grade for a calendar day)
- Whether the AE is serious or not
- Investigator causality rating against the IMP(s) (yes or no)
- Action taken with regard to IMP(s)
- Administration of treatment for the AE
- Outcome

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

- Date AE met criteria for serious AE
- Date investigator became aware of serious AE
- Adverse event is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death

- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication

The grading scales found in the NCI CTCAE, Version 5.0 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 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

8.3.3 Causality Collection

The investigator should assess causal relationship between IMP 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 should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: '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.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the CSP-mandated laboratory tests and vital signs will be summarized in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, and ECGs should therefore only be reported as an AE if it fulfills any of the SAE criteria, is the reason for discontinuation of treatment with the IMP, or is considered to be clinically relevant as judged by the investigator (this may include but is not limited to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting investigator uses the clinical, rather than the laboratory term (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 AE(s).

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.6 Hy's Law

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

8.3.7 Disease Progression

Disease progression can be considered as a worsening of a participant's condition attributable to the disease for which the IMP 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.

8.3.8 New Cancers

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

8.3.9 Deaths

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

- Death clearly resulting from disease progression should be documented in the eCRF in the Statement of Death page. 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 as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co-involvement of disease progression, if appropriate, and should assign the main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE and documented in the Statement of Death page in the eCRF, but every effort should be made to determine a cause of death. 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 Patient Safety or its representative within the usual time frames.

Deaths occurring after the protocol-defined follow-up period after the administration of the last dose of study intervention should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the defined follow-up period and the event is considered to be due to a late-onset toxicity to study treatment, then it should also be reported as an SAE.

8.3.10 Adverse Events of Special Interest

Adverse events of special interest are events of scientific and medical interest specific to the further understanding of study intervention safety profile and require close monitoring and rapid communication by the investigators to the Sponsor. An AESI can be serious or non-serious. All AESIs will be recorded in the eCRF. Serious AESIs will be recorded and reported as per Section 8.3.12.

Adverse events of special interest for monalizumab include events with a potential immune-mediated inflammatory mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants, and/or hormone replacement therapy. An imAE 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 imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxic, or other etiologic causes of the imAE.

If the investigator has any questions in regard to an event being an imAE, the investigator should promptly contact the Study Clinical Lead.

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

Further information on these risks (eg, presenting symptoms) can be found in the current version of the monalizumab IB. More specific guidelines for their evaluation and treatment

are described in detail in the monalizumab TMG (see Section 8.3.15).

8.3.11 Safety Data to be Collected Following the Final DCO of the Study

For participants continuing to receive open-label IMP after the final DCO and database closure (see Section 6.7), it is recommended that the participant continue the scheduled site visits and investigators monitor the participant's safety laboratory results prior to and periodically during treatment with IMP in order to manage AEs in accordance with toxicity-management guidelines (see Section 8.3.15). All data post the final DCO and database closure will be recorded in the participant notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

All SAEs that occur in participants still receiving IMP (or within the 90 days following the last dose of IMP) post the final DCO and database closure must be reported as detailed in Section 8.3.12.

8.3.12 Reporting of Serious Adverse Events

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

If any SAE occurs in the course of the study, then investigators or other site personnel inform the appropriate Sponsor representatives within one day ie, immediately but **no later than 24 hours** of when they become aware of it.

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

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

Once the investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated Sponsor representative.

If the EDC system is not available, then the investigator or other study site staff reports an SAE to the appropriate Sponsor representative by telephone.

The Sponsor representative will advise the investigator/study site staff how to proceed.

The reference documents for definition of expectedness/listedness are the IB for monalizumab

and the appropriate label for cetuximab.

8.3.13 Pregnancy

All pregnancies and outcomes of pregnancy with conception dates following the first date of study intervention, including pregnancy in the partner of male participants, should be reported to AstraZeneca except if the pregnancy is discovered before the study participant has received any study intervention.

8.3.13.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, IMP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/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 anomaly) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate Sponsor representatives within one day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative works with the investigator to ensure that all relevant information is provided to the Sponsor Patient Safety data entry site within one or 5 calendar days for SAEs (see Section 8.3.12) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy.

8.3.13.2 Paternal Exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 4 months after the last dose of study intervention.

Pregnancy of the participant'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 anomaly) occurring from the date of the first dose of study intervention until 4 months after the last dose of study intervention should, if possible, be followed up and documented in the Pregnancy Report Form. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the investigator must obtain the consent of the participant's partner. The local study team should adopt the Master Pregnant Partner Form in line with local procedures/requirements and submit it to the relevant Regulatory Authority/IRB/IEC prior to use.

8.3.14 Medication Error

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate Sponsor representatives within one day, ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated Sponsor representative works with the investigator to ensure that all relevant information is completed on the specific medication error eCRF within one (initial fatal/life-threatening or follow up fatal/life-threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error (see Section 8.3.1) and within 30 days for all other medication errors.

The definition of a medication error can be found in Appendix B.

8.3.15 Management of IMP-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 IMP 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 IMP 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.

See Section 6.6, and Sections 8.3.15.1 and Section 8.3.15.2 below for dose modification guidance.

All toxicities will be graded according to NCI CTCAE, Version 5.0.

8.3.15.1 Monalizumab

The monalizumab TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune mediated reactions that may be observed with monalizumab, with specific instructions for dose modifications (omissions and discontinuations) and treatment interventions. The most current version of the TMGs is provided to the investigative site as a supplement to the CSP and is maintained within the Site Master File.

Participants should be thoroughly evaluated, and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxic, or other etiologic causes of the suspected 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 monalizumab should be permanently discontinued (see Section 7.1 and the monalizumab TMGs). Following the first dose of monalizumab, subsequent administration of monalizumab can be modified based on toxicities observed as described in the TMGs. These guidelines have been prepared by the Sponsor to assist the investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to monalizumab regimen by the reporting investigator.

Dose reductions are not permitted. In case of doubt, the investigator should consult with the Study Clinical Lead.

8.3.15.2 Cetuximab

Please refer to the local label (where available) for the management of AEs with cetuximab.

In case of infusion-related reactions to cetuximab, manage as per local label (where available) for cetuximab and institutional guidance on management of infusion-related reactions.

For management of AEs with cetuximab, refer to the local label.

8.4 Overdose

Use of monalizumab or cetuximab in doses exceeding those specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of overdose of monalizumab, and possible symptoms of overdose are not established. If an overdose of cetuximab occurs, please refer to the local label (where available).

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module

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

The designated Sponsor representative works with the investigator to ensure that all relevant information is provided to the Sponsor Patient Safety data entry site within 1 or 5 calendar days for overdoses associated with an SAE (see Section 8.3.12) and within 30 days for all

other overdoses.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Sample see Appendix D.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - Pharmacokinetic samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterization of any ADAs, confirmation and/or requalification of the assay, as well as additional assay development work. The results from future analysis will not be reported in the CSR.

8.5.1 Pharmacokinetics

- Blood samples will be collected for measurement of serum concentrations of monalizumab as specified in the SoA.
- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the Sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.
- Serum samples will be used to analyze the PK of monalizumab. Samples collected for analyses of monalizumab serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentration in serum will be assayed by bioanalytical test sites operated by or on behalf of the Sponsor, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel [until the study has been unblinded].

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

8.5.2 Immunogenicity Assessments

Blood samples for determination of ADA in serum will be assayed by bioanalytical test sites operated by or on behalf of the Sponsor, using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate report.

Antidrug antibody samples may also be further tested for characterization of the ADA response.

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

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

Samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA (Section 1.3). Details for sample collection, processing, and testing are provided in the Laboratory Manual.

At screening, all participants will be asked to provide formalin-fixed paraffin-embedded samples from archival or fresh tumor biopsy (acquired ≤ 3 months prior to screening). Tumor tissue beyond the 3-month window and up to 6 months old may be considered upon Sponsor consultation, provided that no intervening systemic regimen was ongoing at the time of sample collection (see the Laboratory Manual for more information). Archival tumor biopsies older than 6 months (> 6 months) or collected when previous treatments were still ongoing are not acceptable. Participants whose archival tumor tissue is unavailable or unsuitable for use will be asked to provide a fresh tumor biopsy. Fresh tumor biopsy should not be collected from lesions in proximity to cardiopulmonary, visceral, or vital neurovascular structures that could make the collection procedure high risk.

The screening tumor biopsy will be evaluated for the expression of HLA-E and NKp46 in the

TME by IHC. Associations between HLA-E and NKp46 expression and the participant's radiologic response (RECIST 1.1) will be assessed. CCI

CCI

8.6.2 Collection of Optional Biomarker Samples

Optional samples may be collected for biomarker research as listed in the SoA (Section 1.3).

All participants will be asked to provide consent for collection of tumor biopsies once during treatment and at time of progression. CCI

8.6.3 Other Study-related Biomarker Research

CCI

8.7 CCI

CCI

CCI

CCI

CCI

CCI

8.8 Medical Resource Utilization and Health Economics

For economic evaluation for payer submissions, it is necessary to capture healthcare resource utilization related to the intervention and the underlying disease. Within this study, the following will be captured:

- CCI
- Treatment-related to AEs (including the method of delivery of the treatment) captured in AE/SAE assessment module
- Treatment not related to the study obtained in Concomitant Medications eCRF

8.9 Study Participant Feedback Questionnaire

Participants will have the option to complete the anonymized SPFQ assessing their clinical study experience (see Appendix J; assessment schedule is presented in Section 1.3). Participants who do not wish to complete this questionnaire may still participate in the study. Individual participant-level responses will not be reviewed by investigators. Responses would be used by the Sponsor to understand where improvements can be made in the clinical study process. This questionnaire does not collect data about the participant's disease, symptoms, treatment effect, or AEs and therefore would not be study data.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The formal statistical analysis will be performed to test the following main hypotheses for monalizumab plus cetuximab (Arm A) or placebo plus cetuximab (Arm B):

- H0: No difference between Arm A and Arm B
- H1: Difference between Arm A and Arm B

9.2 Sample Size Determination

Approximately 624 participants will be randomized 2:1 to monalizumab plus cetuximab (Arm A) or placebo plus cetuximab (Arm B). Randomization will be stratified by HPV status (OPC HPV positive or HPV-unrelated), WHO/ECOG PS (0 or 1), or number of prior lines of

therapy in the R/M setting (1 or 2).

The study is powered to demonstrate superiority in the OS benefit of Arm A vs Arm B in HPV-unrelated participants with R/M SCCHN previously treated with an ICI.

There will be two planned IAs and one FA for the study.

Interim Analysis 1 (IA1): Futility in OS will be evaluated when approximately 99 OS events have occurred across Arm A and Arm B in HPV-unrelated participants (25% information fraction) and randomized at least 2 months before the DCO for the futility analysis (ie, with a minimum follow-up of 2 months).

Interim Analysis 2 (IA 2): A hypothesis of monalizumab plus cetuximab (Arm A) prolongs OS compared to placebo plus cetuximab (Arm B) will be tested at IA2 when approximately 278 OS events have occurred across Arm A and Arm B in HPV-unrelated participants (approximately 70% information fraction, 56% maturity).

Final Analysis (FA): A hypothesis of improved OS will be tested at the final analysis when approximately 397 OS events have occurred across Arm A and Arm B in HPV-unrelated participants (approximately 80% maturity).

If the true OS HR is 0.72, corresponding to an approximate 3-month improvement in median OS compared to Arm B of 7.7 months, approximately 397 OS events in HPV-unrelated participants will provide approximately 86.5% power to demonstrate statistical significance at the 5% level (using a 2-sided test) for the FA. The 5% (2-sided) alpha for the OS analysis will be controlled at the IA2 and FA time points by using the Lan-DeMets (Lan and DeMets 1983) spending function that approximates the O'Brien-Fleming approach, where the significance level applied depends upon the proportion of information (ie, information fraction) available at time of IA2. For example, if the information fraction for OS at IA2 is 70% then the two-sided significance levels of 1.48% and 4.55% will be applied to IA2 and FA for OS, respectively. The smallest detectable treatment difference in HR, ie, critical value, that could be statistically significant at the FA is 0.81. With a planned recruitment period of 30 months, it is expected that a total of 498 HPV-unrelated participants are needed in order to achieve 397 OS events with a follow-up period of approximately 12 months. The 278 OS events for the IA2 are expected to be reached approximately 30.5 months after the randomization of the first participant.

The number of OPC HPV-positive participants will be closely monitored throughout the study and are planned to be capped at approximately 20%of the total sample size. With the assumption of 20% OPC HPV-positive participants in the overall participants, approximately 624 randomized participants will be needed in overall population. Under the same assumption of effect size in HR and median OS stated above, approximately 498 OS events are expected

in all participants which will provide approximately 93.0% power to demonstrate statistical significance at the 5% level (using a 2-sided test) for the FA.

9.3 Populations for Analyses

Definitions of the analysis sets for each endpoint are provided in Table 9.

Table 9 Summary of Outcome Variables and Analysis Populations

Endpoint	Population
Efficacy data	
OS	HPV-unrelated Analysis Set and Full Analysis Set
PFS	HPV-unrelated Analysis Set and Full Analysis Set
ORR [a], DoR, and PRO [b] endpoints	HPV-unrelated Analysis Set and Full Analysis Set
Demography and other baseline characteristics	HPV-unrelated Analysis Set and Full Analysis Set
PK data	
PK data	PK Analysis Set
Biomarker data	
Biomarker data	HPV-unrelated Analysis Set and Full Analysis Set
Safety data	
Exposure	Safety Analysis Set
AEs	Safety Analysis Set
Laboratory measurements	Safety Analysis Set
Vital signs and other safety	Safety Analysis Set
ADA data	ADA Analysis Set

[a] ORR: measurable disease at baseline.
[b] PRO: evaluable PRO measurements
ADA = antidrug antibody; AE = adverse event; DoR = duration of response; HPV = human papillomavirus; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic(s); PRO = patient-reported outcome.

9.3.1 HPV-unrelated Analysis Set

The primary population is the HPV-unrelated Analysis Set which will include all randomized participants who are either OPC HPV negative or non-OPC regardless of the HPV status. The HPV status will be determined by HPV status in the CRF and not the IVRS value. The HPV-unrelated Analysis Set will be used for summarizing baseline characteristics, all efficacy analyses, including PROs and biomarker analyses. Treatment arms will be compared on the basis of randomized study intervention, regardless of the intervention actually received. Participants who were randomized but did not subsequently go on to receive study intervention are included in the analysis in the treatment arm to which they were randomized.

Analysis for ORR will be based on participants in the FAS who had measurable disease at baseline. Analysis of DoR will be based on participants in the FAS who achieved objective response.

9.3.2 Full Analysis Set

The FAS will include all randomized participants. The FAS will be used for summarizing baseline characteristics, all efficacy endpoints (including PROs) and biomarker analyses as secondary analyses. Treatment arms will be compared on the basis of randomized study intervention, regardless of the intervention actually received. Participants who were randomized but did not subsequently go on to receive study intervention are included in the analysis in the treatment arm to which they were randomized.

9.3.3 Safety Analysis Set

The SAF will consist of all participants who received any amount of study treatment. Safety data will not be formally analyzed but summarized descriptively using the SAF according to the intervention received; that is, erroneously-treated participants (eg, those randomized to Arm A but actually given Arm B intervention) will be summarized according to the study intervention they actually received.

9.3.4 Pharmacokinetic Analysis Set

All participants who receive at least one dose of CCI per the protocol for whom there is at least one reportable PK concentration and who do not violate or deviate from the protocol in ways that would significantly affect the PK analyses will be included in the PK Analysis Set. The population will be defined by the Study Clinical Lead, pharmacokineticist, and statistician prior to any PK analyses being performed.

9.3.5 ADA Analysis Set

The ADA Analysis Set will include all participants who have non-missing baseline ADA and at least one non-missing post-baseline ADA results. All major ADA analyses will be based on the ADA Analysis Set.

9.4 Statistical Analyses

Analyses will be performed by the Sponsor or its representatives. A comprehensive SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the CSR.

9.4.1 General Considerations

A hypothesis of improved OS will be tested at IA2 when approximately 278 OS events have

occurred across Arm A and Arm B in HPV-unrelated participants (approximately 56% maturity; IA2).

A hypothesis of improved OS will be tested at the final analysis when approximately 397 OS events have occurred across Arm A and Arm B in HPV-unrelated participants (approximately 80% maturity; FA).

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 IMP, except for efficacy variables. For efficacy variables, baseline is defined as the last visit prior to randomization.

All data collected will be listed. Efficacy and PRO data will be summarized and analyzed based on the HPV-unrelated Analysis Set and will be repeated for FAS as a secondary analysis. PK data will be summarized and analyzed based on the PK Analysis Set. Safety data will be summarized on the SAF. Antidrug antibody data will be summarized on the ADA Analysis Set.

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

The following table details which endpoints are to be subjected to formal statistical analysis, together with pre-planned sensitivity analyses, making it clear which analysis is regarded as primary for that endpoint.

Table 10 Pre-planned Statistical and Sensitivity Analyses to be Conducted for Efficacy and COA Endpoints

Endpoints analyzed	Notes
Overall survival (Primary) in HPV-unrelated Analysis Set	Primary confirmatory analysis Stratified log-rank test adjusting for, WHO/ECOG PS and number of prior lines of therapy in the R/M setting for primary comparison of survival between randomized treatment arms Sensitivity and supplemental analysis Assessment of assumption of proportionality and stratified max combo test Subgroup analysis using Cox model

Table 10 Pre-planned Statistical and Sensitivity Analyses to be Conducted for Efficacy and COA Endpoints

Endpoints analyzed	Notes
Overall survival (Secondary) in FAS	Secondary confirmatory analysis Stratified log-rank test adjusting for HPV status, WHO/ECOG PS, number of prior lines of therapy in the R/M setting Sensitivity and supplemental analysis Subgroup analysis using Cox model
Progression-free survival (Secondary) in HPV-unrelated Analysis Set and FAS	PFS according to RECIST 1.1 based on investigator assessments will be analyzed as a secondary variable. Secondary confirmatory analysis For HPV-unrelated Analysis Set, stratified log-rank tests adjusting for WHO/ECOG PS and number of prior lines of therapy in R/M setting, using PFS according to RECIST 1.1 based on investigator assessments For FAS, stratified log-rank tests adjusting for HPV status, WHO/ECOG PS, number of prior lines of therapy in R/M setting, using PFS according to RECIST 1.1 based on investigator assessments Sensitivity and supplemental analysis Analysis using alternative censoring rules – attrition bias Subgroup analysis using Cox proportional hazards model
Objective response rate (Secondary) in HPV-unrelated Analysis Set and FAS	For HPV-unrelated Analysis Set, logistic regression adjusted for WHO/ECOG PS, number or prior lines of therapy in the R/M setting, using tumor data according to RECIST 1.1 based on investigator assessment For FAS, logistic regression adjusted HPV status, WHO/ECOG PS, number or prior lines of therapy in the R/M setting, using tumor data according to RECIST 1.1 based on investigator assessment
Duration of response (Secondary) in HPV-unrelated Analysis Set and FAS	KM plots based on the tumor data using investigator assessment of RECIST 1.1. Median DoR calculated from the KM curve.
CCI [redacted]	
Each scale/item of EORTC QLQ-C30 and QLQ-H&N35 (Secondary) in HPV-unrelated Analysis Set and FAS	Summary and descriptive statistics Unadjusted change from baseline
Key symptoms, functions, global health status/QoL of EORTC QLQ-C30 and QLQ-H&N35 (Secondary) in HPV-unrelated Analysis Set and FAS	MMRM analysis (overall and by each visit)

Table 10 Pre-planned Statistical and Sensitivity Analyses to be Conducted for Efficacy and COA Endpoints

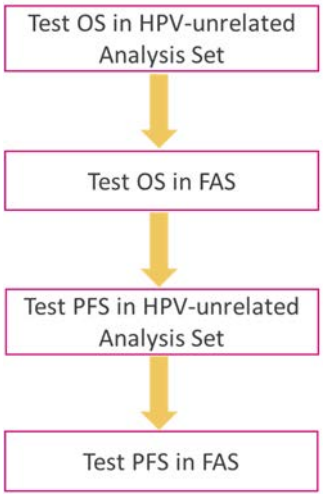
Endpoints analyzed	Notes
Time to symptom, function, or HRQoL deterioration of key COA endpoints using EORTC QLQ-C30 and QLQ-H&N35 (Secondary) in HPV-unrelated Analysis Set and FAS	Stratified log-rank test
CCI	

COA = clinical outcome assessment; CR = complete response; DCR = disease control rate; DoR = duration of response; EORTC = European Organisation for Research and Treatment of Cancer; CCI ; FAS = Full Analysis Set; HPV = human papillomavirus; HR = hazard ratio; HRQoL = health related quality of life; KM = Kaplan Meier; MMRM = mixed-effect model repeated measure; OS = overall survival; PFS = progression-free survival; CCI ; CCI ; PR = partial response; CCI ; PS = performance status; QLQ-C30 = 30-item Core Quality of Life Questionnaire; QLQ-H&N35 = 35-Item Head and Neck Cancer Quality of Life Questionnaire; QoL = quality of life; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; R/M = recurrent/metastatic; SAP = statistical analysis plan; SD = stable disease; WHO/ECOG = World Health Organization/Eastern Cooperative Oncology Group.

9.4.1.1 Methods for Multiplicity Control

Strong control of the FWER at 5% level (2 sided) across the testing of OS and PFS endpoints will be achieved through a combined approach of alpha allocation to the OS analyses (IA2 and the FA) via alpha spending function and a hierarchical testing procedure; that is, OS in FAS will be tested only if OS in HPV-unrelated analysis set met significance at IA2 or FA; PFS will be tested only if OS met statistical significance at IA2 or FA and PFS in FAS will be tested only if PFS in HPV-unrelated analysis set met statistical significance at IA2 or FA (Glimm et al 2010) (Figure 3). The IA2 for OS will be conducted when approximately 278 of the 397 expected OS events (ie, 70% information fraction) have occurred in HPV-unrelated participants. Using the Lan-DeMets spending function approximating O'Brien-Fleming boundaries, 2-sided significance levels of 0.0148 and 0.0455 will be applied to OS IA2 and FA, respectively (Lan and DeMets 1983).

Figure 3 Graphical Presentation of the Propose Multiple-Testing Procedure at IA2 and FA



FA = final analysis; FAS = full analysis set; HPV = human papillomavirus; IA2 = interim analysis 2; OS = overall survival; PFS = progression-free survival.
Notes: At each analysis (IA2 and FA), PFS will be formally tested only if OS meets statistical significance.

Each statistical test will be performed only if the preceding test is statistically positive. At the time of OS IA2, the PFS data will be mature given its expected short median of 2.3 months in this population (Cohen et al 2019b, Ferris et al 2016, Rischin et al 2019) and it will be tested at 5% significance level.

9.4.2 Efficacy

9.4.2.1 Primary Endpoint

Derivation of primary endpoint

The primary endpoint OS is defined as the time from the date of randomization until date of death due to any cause. Any participant not known to have died at the time of analysis will be censored based on the last recorded date on which the participant was known to be alive.

Note: Survival calls will be made following the date of DCO for the IAs or FA (these contacts should generally occur within 7 days of the DCO). If participants are confirmed to be alive or if the death date is post the DCO date, these participants will be censored at the date of DCO. Death dates may be found by checking publicly available death registries.

Primary analysis

Overall survival in the HPV-unrelated Analysis Set will be analyzed using a stratified log-rank test, adjusting for WHO/ECOG PS (0 or 1) and number of lines of prior therapy in the R/M setting (1 or 2). The HR and its CI will be estimated from a stratified Cox Proportional Hazards model. The effect in Arm A vs Arm B will be estimated by the HR together with its

corresponding CI and p-value (from stratified log-rank test). Kaplan-Meier plots will be presented by treatment arm. Summaries of the numbers and percentages of participants 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 arm.

Sensitivity analysis

The assumption of proportionality will be assessed first by examining the plots of complementary log-log (event times) versus log (time) and, if these raise concerns, by fitting a time-dependent covariate to assess the extent to which this represents random variation. If a lack of proportionality is evident, a stratified max-combo test will be used as a sensitivity analysis with the same stratification factors as the primary analysis. The max-combo test is based on an adaptive procedure, optimizing test statistics among log rank test ($FH^{0,0}$) and the FH weighted log-rank test (Harrington and Fleming 1982) ($FH^{0,1}$ and $FH^{1,1}$) with alpha correction (Karrison 2016). It is a more robust and powerful test under NPH when compared to the log-rank test and is recommended by the Cross-Pharma Non-proportional Hazard Working Group in presence of NPH (Lin et al 2020). The variation in treatment effect will be described by presenting piecewise HR calculated over distinct time-periods. In such circumstances, the HR can still be meaningfully interpreted as an average HR over time unless there is extensive crossing of the survival curves. If lack of proportionality is found, this may be a result of treatment-by-covariate interactions, which will be investigated. In addition, the KM curve along with landmark analyses (eg, one-year OS rate) will also help in understanding the treatment benefit.

Analysis of OS in FAS

Overall survival in the FAS will be analyzed similarly except that the stratified log-rank test will be adjusted for HPV status (OPC HPV positive or HPV-unrelated), WHO/ECOG PS (0 or 1), and number of lines of prior therapy in the R/M setting (1 or 2).

Subgroup analysis

Subgroup analyses will be conducted comparing OS between Arm A vs Arm B in the following subgroups of the HPV-unrelated Analysis Set and FAS (but not limited to):

- Sex (male vs female)
- Age at randomization (< 65 vs ≥ 65 years of age)
- Human papillomavirus status (OPC HPV positive or HPV-unrelated) (applicable to FAS only)
- WHO/ECOG PS (0 or 1)
- Number of prior lines of therapy in the R/M setting (1 or 2)
- Race/ethnicity data (Asian vs non-Asian)

Other baseline variables may also be assessed if there is clinical justification or 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. Forest plots will be presented.

Additionally, for each subgroup, the HR (Arm A:Arm B) and 95% CI will be calculated from a Cox proportional hazards model with treatment as the only covariate. These will be presented on a forest plot including the HR and 95% CI from the overall population.

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 and PFS.

9.4.2.2 Secondary Endpoints

The analysis of the secondary efficacy endpoints, PFS, ORR, and DoR, will be primarily based on the site investigator assessments using RECIST 1.1.

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

At each visit, participants 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 28 days prior to enrollment. If a participant has had a tumor assessment that cannot be evaluated, then the participant will be assigned a visit response of NE (unless there is evidence of progression in which case the response will be assigned as PD).

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

9.4.2.2.1 Progression-free Survival

Derivation of PFS

The secondary endpoint PFS will be defined as the time from randomization until progression, per RECIST 1.1 as assessed by the investigator at local site or death due to any cause, whichever occurs first, regardless of whether the participant withdraws from study intervention or receives another anticancer therapy prior to progression (ie, date of event or censoring – date of randomization + 1). Participants 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 participant progresses or dies after 2 or more consecutively missed visits, the participant will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits. If the participant 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 on 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 assessment/scan dates of the component that indicates progression.
- When censoring a participant for PFS, the participant will be censored at the latest of the scan dates contributing to a particular overall visit assessment.

Analysis of PFS

The secondary endpoint PFS analysis will also be based on the programmatically derived RECIST 1.1 using the investigator tumor assessments. The analysis will be performed in both the HPV-unrelated Analysis Set and FAS using a stratified log-rank test, adjusting for HPV status (for FAS only), WHO/ECOG PS, and number of prior lines of therapy in the R/M setting. The effect of Arm A vs Arm B will be estimated by the HR together with its corresponding 95% CI and p-value.

Kaplan Meier plots of PFS will be presented by treatment arm. Summaries of the number and percentage of participants experiencing a PFS event and the type of event (RECIST 1.1 or death) will be provided along with median PFS for each treatment arm.

Sensitivity analysis of PFS

Sensitivity analyses will be performed to assess attrition bias by repeating the PFS analysis except that the actual PFS event times, rather than the censored times, of participants who progressed or died in the absence of progression immediately following 2 or more non-evaluable tumor assessments will be included. In addition, participants who take subsequent therapy prior to progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy. This analysis will be supported by a KM plot of the time to censoring where the censoring indicator of the PFS analysis is reversed.

Further sensitivity analysis may be documented in the SAP.

Subgroup analysis

Subgroup analyses will be conducted comparing PFS (per RECIST 1.1 using investigator assessments) between Arm A and Arm B in the subgroups, as specified in Section 9.4.2.1.

9.4.2.2.2 Objective Response Rate

Derivation of ORR

ORR is defined as the proportion of participants with measurable disease who have a confirmed CR or PR, as determined by the investigator at local site per RECIST 1.1. Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Participants who discontinue study intervention without progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR.

Analysis of ORR

Objective response rate will be based on the programmatically-derived RECIST using the investigator tumor data. ORR will be compared between Arm A and Arm B using a logistic regression model, adjusting for the same factors as the primary endpoint (HPV status [for FAS only], WHO/ECOG PS, number of prior lines of therapy in the R/M setting). The results of the analysis will be presented in terms of an odds ratio together with its associated profile likelihood 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 in the subset of participants in the HPV-unrelated Analysis Set who had measurable disease at baseline. This analysis will be repeated for the subset of participants in the FAS who had measurable disease at baseline.

Summaries will be produced that present the number and percentage of participants with a tumor response (CR/PR). Overall visit response data will be listed for all participants (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.

9.4.2.2.3 Duration of Response

Derivation of DoR

The secondary endpoint DoR (per RECIST 1.1 using investigator assessment) 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 participant does not progress following a response, then their DoR will be censored at the PFS censoring time. Duration of response will not be defined for those participants who do not have documented response.

Analysis of DoR

Kaplan Meier plots of DoR based on the investigator assessment of RECIST 1.1 will be

presented. Median DoR will also be summarized and calculated from the KM curve. Only participants who have a confirmed response will be included in this summary table. Swimmer plots that clearly show the profile of each participant who responds will also be produced.

9.4.2.2.4 Patient-reported Outcome: EORTC QLQ-C30

Scoring

The EORTC QLQ-C30 will be scored according to the EORTC QLQ-C30 Scoring Manual (Fayers et al 2001). An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales, each of the functional scales, and the global measure of health status scale in the EORTC QLQ-C30 according to the EORTC QLQ-C30 Scoring Manual. Higher scores on the global measure of health status and functional scales indicate better health status/function, but higher scores on symptom scales represent greater symptom severity. For each subscale, if < 50% of the subscale items are missing, then the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscales (Fayers et al 2001). If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded.

Analysis methods

A main PRO instrument identified in the secondary objectives are global health status/QoL, physical functioning, fatigue, pain, and appetite loss subscales of the EORTC QLQ-C30.

The primary assessment of global health status/QoL, physical functioning, or symptom will focus on comparing the mean change from baseline between treatment arms. The analysis population will be a subset of the HPV-unrelated Analysis Set, including all participants in the HPV-unrelated Analysis Set with an evaluable baseline assessment and at least one evaluable post-baseline assessment. Change from baseline will be analyzed using a mixed-model repeated measurements analysis of all the post-baseline scores. The model will include treatment arm, visit, and treatment by visit interaction as explanatory variables, and the baseline score and baseline score by visit as covariates. Adjusted mean change from baseline estimates per treatment arm and corresponding 95% CIs will be presented, along with an overall estimate of the treatment difference, 95% CI, and p-value.

Additional analyses will include time to deterioration.

The analysis will be repeated for a subset of the FAS, including all randomized participants with an evaluable baseline assessment and at least one evaluable post-baseline assessment.

Details of all statistical analyses and appropriate sensitivity analyses will be described in full in the SAP.

9.4.2.2.5 Patient-reported Outcome: EORTC QLQ-H&N35

Scoring

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.

Analysis methods

Another main PRO instrument identified in the secondary objectives are from the 4-symptom scales/items in the QLQ-H&N35 (pain, swallowing, senses, and speech).

The primary assessment of symptoms will focus on comparing the mean change from baseline between treatment arms. The analysis population will be a subset of the HPV-unrelated Analysis Set, including all participants in HPV-unrelated Analysis Set with an evaluable baseline assessment and at least one evaluable post-baseline assessment. Change from baseline will be analyzed using a mixed-model repeated measurements analysis of all the post-baseline scores. The model will include treatment arm, visit, and treatment by visit interaction as explanatory variables, and the baseline score and baseline score by visit as covariates. Adjusted mean change from baseline estimates per treatment arm and corresponding 95% CIs will be presented, along with an overall estimate of the treatment difference, 95% CI, and p-value.

Additional analyses will include time to deterioration.

The analysis will be repeated for a subset of the FAS, including all randomized participants with an evaluable baseline assessment and at least one evaluable post-baseline assessment.

Details of all statistical analyses and appropriate sensitivity analyses will be described in full in the SAP.

9.4.2.3 Exploratory Endpoints

9.4.2.3.1 CCI

CCI

CCI

CCI

CCI

CCI

9.4.2.3.2 CCI

CCI

9.4.2.3.3 CCI

CCI

CCI

CCI

9.4.2.3.4 CCI

CCI

CCI

9.4.3 Safety

9.4.3.1 Calculation or Derivation of Safety Variables

9.4.3.1.1 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 participants. 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 IMP (ie, the last dose of monalizumab, cetuximab, or placebo). For AEs, on-treatment (or treatment-emergent) AEs will be defined as any AEs that started after dosing or prior to dosing and which worsen following exposure to the study treatment.

Adverse events observed up until 90 days following discontinuation of the IMP or until the initiation of the first subsequent therapy following discontinuation of treatment (whichever occurs first) will be used for the reporting of the AE summary tables. This will more accurately depict AEs attributable to study treatment only, as a number of AEs up to 90 days following discontinuation of the IMP are likely to be attributable to subsequent therapy. However, to assess the longer-term toxicity profile, AE summaries will also be produced containing AEs observed up until 90 days following discontinuation of the IMP (ie, without taking subsequent therapy into account). Any events in this period that occur after a participant has received further therapy for cancer (following discontinuation of study treatment) will be flagged in the data listings.

The SAF will be used for reporting of safety data.

A separate data listing of AEs occurring > 90 days after discontinuation of IMP will be produced. These events will not be included in AE summaries.

9.4.3.1.2 Other 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 formula:

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

The denominator used in laboratory summaries will only include evaluable participants, 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 participants 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 participant need only have 1 post-dose value recorded.

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

9.4.3.2 Analysis of safety variables

All safety analyses will be performed on the SAF. Safety and tolerability data will be presented by treatment arm based on actual treatment received.

Data from all cycles of treatment will be combined in the presentation of safety data. Adverse events (both in terms of Medical Dictionary for Regulatory Activities preferred terms and CTCAE grade) will be listed individually by participant. The number of participants 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.

Other safety data will be assessed in terms of physical examination, clinical chemistry, hematology, vital signs, WHO ECOG/PS, and ECGs. Exposure to monalizumab plus cetuximab combination therapy and cetuximab will be summarized. Time on study, dose delays/dose modifications of monalizumab and cetuximab will also be summarized. At the end of the study, appropriate summaries of all safety data will be produced, as defined in the SAP.

9.4.4 Other Analyses

9.4.4.1 Healthcare Resource Use

The potential impact the disease and treatment have on healthcare resource use will be analyzed for the purposes of submissions to payers (eg, pricing and reimbursement agencies and health technology assessment bodies). Descriptive statistics (as appropriate, including means, median, counts and frequencies, standard deviation, interquartile range, skew, and range) will be provided for each treatment arm on the different types of hospital admissions, the length of stay for participants admitted to the hospital (eg, inpatient, emergency room, intensive care unit), as well as the participant's primary sign or symptom. To support submissions to payers, additional analyses may be undertaken and will be outlined in a separate Payer Analysis Plan.

9.4.4.2 Pharmacokinetic Data

Monalizumab serum concentration data will be listed for each participant with monalizumab treatment and each dosing day. Summary will be provided for PK Analysis Set.

9.4.4.3 Immunogenicity Data

Immunogenicity results will be listed by participant, and a summary will be provided by the number and percentage of participant who develop detectable CCI
The immunogenicity titer will be listed for samples confirmed positive for the presence of CCI

The effect of immunogenicity as well as the effect of its neutralizing properties on PK, pharmacodynamics, efficacy, and safety will be evaluated, if the data allow. A detailed plan will be written by the Sponsor Clinical Pharmacology group or designee.

9.4.4.4 Pharmacokinetic/Pharmacodynamic Relationships

If the data are suitable, the relationship between PK exposure and efficacy/safety parameters may be investigated graphically or using an appropriate data modeling approach.

9.4.4.5 Biomarker Data

CCI

9.5 Interim Analyses

Two IAs are planned as described below.

IA1: The first interim analysis will be performed when approximately 99 OS events have been observed in the HPV-unrelated participants (25% information fraction) in participants randomized at least 2 months before the DCO for the futility analysis (ie, with a minimum follow-up of 2 months). Based on enrollment assumptions, it is expected that this will occur approximately 19 months after randomization of the first participant. The objective of IA1 is to evaluate futility of the Arm A compared to Arm B in terms of OS in the HPV-unrelated participants.

OS will be analyzed using a stratified Cox Proportional Hazards model as described in Section 9.4.2.1 and HR with its CI will be reported. The futility criteria are determined as observed HR at IA1 >CCI which corresponds to CCI conditional power assuming future data is consistent with current IA trend.

IA2: The second interim analysis will be performed when approximately 278 OS events have been observed in the study (56% maturity or 70% information fraction) in the HPV-unrelated population. Based on enrollment assumptions, it is expected that this will occur approximately 30 months after randomization of the first participant.

The IA2 will evaluate the efficacy of Arm A compared to Arm B in terms of OS in the HPV-unrelated population (primary objective).

The SAP will describe the planned IAs in greater detail.

9.6 Data Monitoring Committee

For details on the Independent Data Monitoring Committee, refer to Appendix A 5

9.7 Impact of COVID-19 on Data

Depending on the extent of any impact, summaries of data relating to participants diagnosed with COVID-19, and impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued study treatments, and other protocol deviations) may be generated. More detail will be provided in the SAP.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulation
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Sponsor will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with the Sponsor.

Regulatory reporting requirements for SAEs

- Prompt notification by the investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the [IB or state other documents] and will notify the IRB/ IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- If a participant declines to participate in a voluntary exploratory genetic research component of the study, there will be no penalty or loss of benefit to the participant and he/she will not be excluded from other aspects of the study.
- If a participant's partner becomes pregnant during or within 90 days after the last dose of study intervention, the partner is asked to sign the "Adult Study Informed Consent Form for Pregnant Partners of Study Patients" and provide information about the pregnancy accordingly.

Participants who are rescreened will resign and date their original ICF(s), next to their original signature and date, or according to local or site-specific procedures.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the

samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

The safety of all Sponsor clinical studies is closely monitored on an on-going basis by Sponsor representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the CSP and letters to investigators.

An IDMC comprised of independent experts will be convened and will meet approximately 6 months after the study has started or after the first 60 participants have been randomized, whichever occurs first. The IDMC will review safety assessments and make recommendations to continue, amend, or stop the study based on safety findings. The committee will meet approximately every 6 months thereafter. For the IAs, the IDMC will review unblinded interim data and inform the Sponsor whether the interim boundaries specified in Section 9.5 are met. The IDMC will inform the Sponsor of its recommendation according to the IDMC Charter.

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

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the relevant study plans.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A 9 Study and Site Start and Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant(s) in the study and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

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

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

B 2 Definitions of Serious Adverse Event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, 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.
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

AEs for **malignant tumors** reported during a study should generally be assessed as **Serious** AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **Non-Serious** AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumor event in question is a new

malignant tumor (ie, it is *not* the tumor for which entry into the study is a criterion and that is being treated by the IMP under study and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumor.

Life threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the participant'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 participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical treatment

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 participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Intensity rating scale

The grading scales found in the revised NCI CTCAE, Version 5.0 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 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 Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 3 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 participant 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, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? The Sponsor 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 no available facts or arguments to suggest a causal relationship, 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.

B 4 Medication Error

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

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

Medication error includes situations where an error.

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

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

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT errors)

- Wrong drug administered to participant (excluding IRT errors)

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

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

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

Appendix C Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis, including COVID-19 Outbreak

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following agreement from the sponsor.

C 1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections C 2 to C 4. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

C 2 Rescreening of Participants to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened participants. The investigator should confirm this with the designated Study Clinical Lead.

In addition, during study disruption there may be a delay between confirming eligibility of a participants and either enrolment into the study or commencing of dosing with IMP. If this delay is outside the screening window specified in Section 6.3.1 the participant will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a participant in addition to that detailed in Section 5.4. The procedures detailed in Section 6.3.1 must be undertaken to confirm eligibility using the same randomization number as for the participant.

C 3 Telemedicine Visit to Replace On-site Visit (Where Applicable)

In this appendix the term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow AEs and concomitant medication to be reported and documented.

C 4 Data Capture During Telemedicine or Home/Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP from the study site or TPV service in the source documents, or by the participant themselves.

C 5 COVID-19 Risk Assessment

The safety of participants is of primary importance. Any potential risks of participating in the study, particularly with the added challenges due to COVID-19 outbreak, should be weighed against the anticipated benefit (see also Principle 2.2 of ICH GCP). Investigators are advised to use clinical judgment in determining infection prevention precautions for study participants.

The emergence of SARS-CoV-2 presents a potential safety risk for cancer patients. Participants enrolling in this study may require more frequent visits to the site for study treatment administration and for study assessments compared to participants receiving standard of care. Therefore, several risk mitigation factors have been implemented related to study conduct during the COVID-19 outbreak, for patient management in an event of COVID-19, and actions to be taken on study treatment (see Section C 8). With these measures in place, it is considered that the anticipated potential benefits for the participants enrolled in this study outweigh the potential risks. All implemented measures prioritize trial participant safety and data validity; in case these two conflict with each other, trial participant safety should always prevail (see also European Medicines Agency Guidance on the management of clinical trials during the COVID-19 [coronavirus] pandemic [EMA 2020]).

Notably, participants with active COVID-19 infection confirmed by local laboratory testing will not be eligible for study enrolment (see CSP Section 5.2, Exclusion Criterion 11).

C 6 Potential Risks during COVID-19

Every effort should be made to follow the CSP. Section C 9 provides a dose modification and management plan for participants with confirmed or suspected COVID-19 who are being treated with IMP (monalizumab/placebo and cetuximab). The risk-benefit assessment should be carefully considered for each participant enrolling in the study based on the known safety risks related to COVID-19, individual needs, and local guidelines and restrictions. Investigators must continue to use their best clinical judgment in determining the most optimal care for participants and utmost diligence in determining their eligibility for study participation, continued study treatment, and overall assessment of benefit/risk of study

treatment or participation.

The sponsor must be promptly notified of a site's inability to perform study activities due to COVID-19 outbreak in order to minimize any potential risks.

C 7 New Participant Enrolment

Study sites may continue to recruit new participants into the study provided the following activities to preserve study integrity can be met:

- Upon discussion with the site monitor, the study site has confirmed the ability to enroll and manage new participants effectively and in compliance with the protocol.
- Data will continue to be entered into the eCRF and queries resolved in a timely manner.

Per CSP Exclusion Criterion 11 (see CSP Section 5.2), participants with uncontrolled intercurrent illness, including but not limited to, ongoing or active infection are not eligible for the study participation and hence such participants (including those who have confirmed COVID-19) should not be included for study participation.

C 8 Study Treatment Administration

If an AE or SAE is associated with COVID-19, the investigator should determine whether the participants' treatment with investigational product should continue, be interrupted, or be discontinued in accordance with the CSP.

Adverse events, SAEs, cycle delays and/or treatment suspensions associated with COVID-19 along with logistical issues should be reported according to the eCRF Completion Guidelines.

For dosing discontinuations, where applicable, the dosing discontinuation guidelines should be followed, and the End of Treatment Form(s) completed

C 9 Ongoing Participants

Participants receiving study intervention should continue to undergo safety assessments prior to dosing in accordance with the CSP. In case it is not feasible to perform safety assessments, study intervention should be interrupted until such assessments can be completed.

C 9.1 If a Participant has an Event Suspected to be COVID-19

Delay or omit study intervention as appropriate and test for COVID-19 per local health authority or institutional guidance.

- Signs and symptoms of COVID-19 include but are not limited to new onset of fever, new or worsening cough, shortness of breath, difficulty breathing and sometimes

abnormal chest imaging and may be similar to those of an imAE. Toxicity management guidelines for imAEs should be considered if the symptoms are consistent with an imAE.

- In accordance with the CSP and the TMGs for imAEs, thorough evaluation should be performed to accurately identify the underlying pathology in case an AE is encountered for a participant.
- If COVID-19 is ruled out, study intervention may be resumed per the CSP and TMGs (if applicable).
- If COVID-19 **is confirmed or diagnosis still suspected after evaluation**, manage COVID-19 per local guidance until full recovery.

C 9.2 Participants with Confirmed COVID-19

Participants with confirmed COVID-19 (by local laboratory testing and/or combination of key symptoms) should have study intervention withheld and COVID-19 managed per local guidance.

In case of confirmed COVID-19 and a simultaneous imAE requiring treatment, investigators are advised to apply clinical judgement regarding the use of corticosteroids as per the monalizumab TMGs. This includes also the consideration of alternate immunosuppressive agents other than corticosteroids for imAE management, depending on the individual participant's presentation (Curigliano et al 2020).

C 9.3 Restarting Study Intervention

Study intervention must not be resumed until recovery from COVID-19 (eg, confirmed by imaging, lab testing and/or absence of symptoms) and COVID-19-specific treatment has been completed per local guidance.

The Study Clinical Lead should be contacted if any additional guidance or clarification is needed.

C 9.4 Vaccination Against COVID-19

Protocol restrictions applying to live attenuated vaccines are relevant for live attenuated COVID-19 vaccines as well. Investigators should apply their discretion assessing the risk-benefit of other types of COVID-19 vaccines for participants in clinical trials. Ideally, administration of the vaccine should be done on a different day other than the day of study drug administration to differentiate any potential AEs seen from the vaccine and study drug. The administration of the vaccine and any potential AEs associated with the vaccine are to be documented on the concomitant medication and AE eCRFs, respectively.

C 10 References

Curigliano et al 2020
Curigliano G, Banerjee S, Cervantes A, Garassino M, Garrido P, Girard N et al. Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. Ann Oncol 2020;31(10):1320-35.

EMA 2020
EMA, Clinical Trials Facilitation and Coordination Group, European Commission. Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic, Version 2, 27 March 2020. Available from: URL: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf. Cited date: 17 December 2020.

Appendix D Handling of Human Biological Samples

D 1 Chain of Custody

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

The investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

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

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

D 2 Withdrawal of Informed Consent for Donated Biological Samples

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

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the

withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action documented and study site notified.

D 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B, or Exempt

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. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900:

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, C, D, and E viruses. 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 - Substances that do not contain infectious substances or substances that are unlikely to cause disease in humans or animals are not subject to these regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

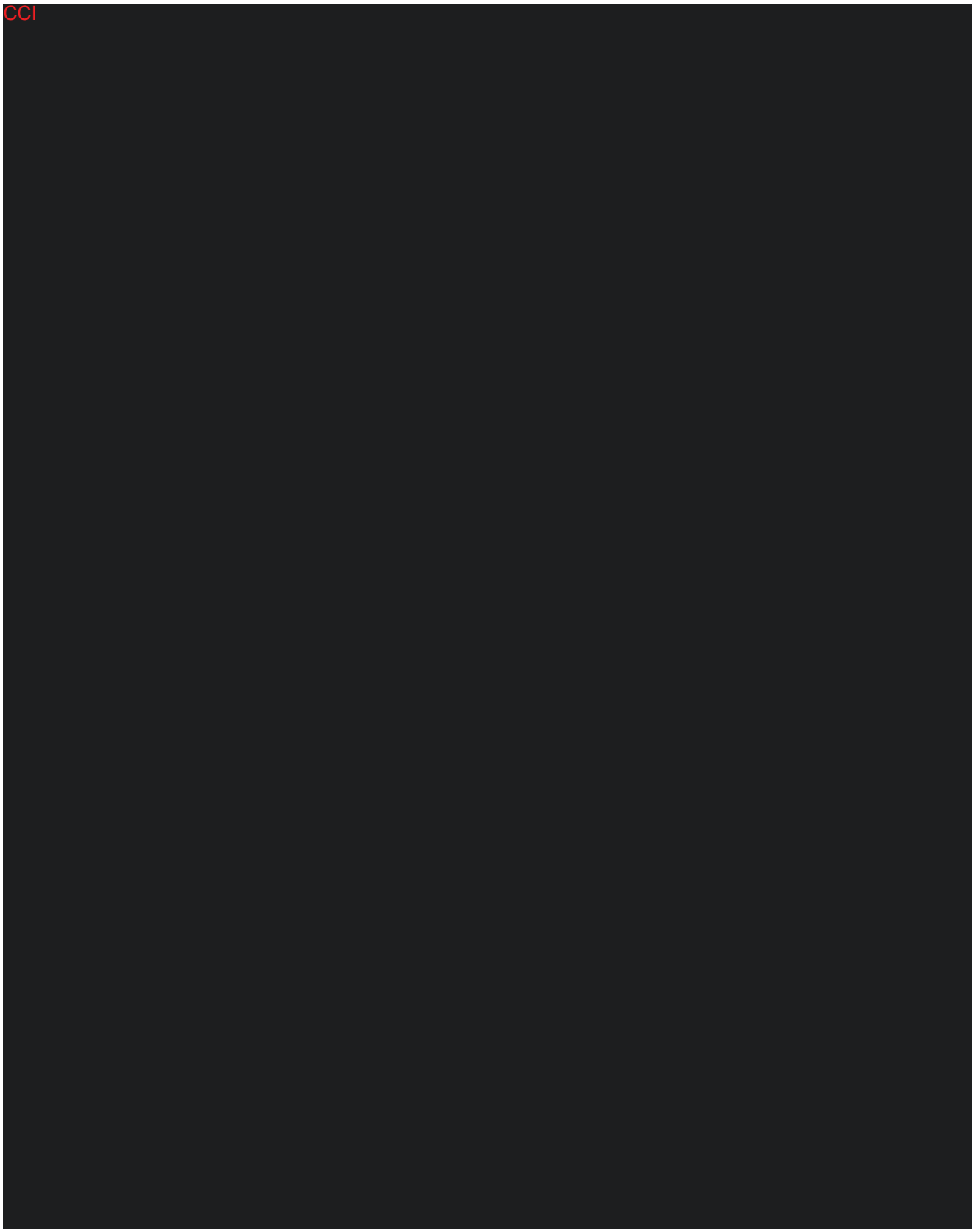
Appendix E CCI

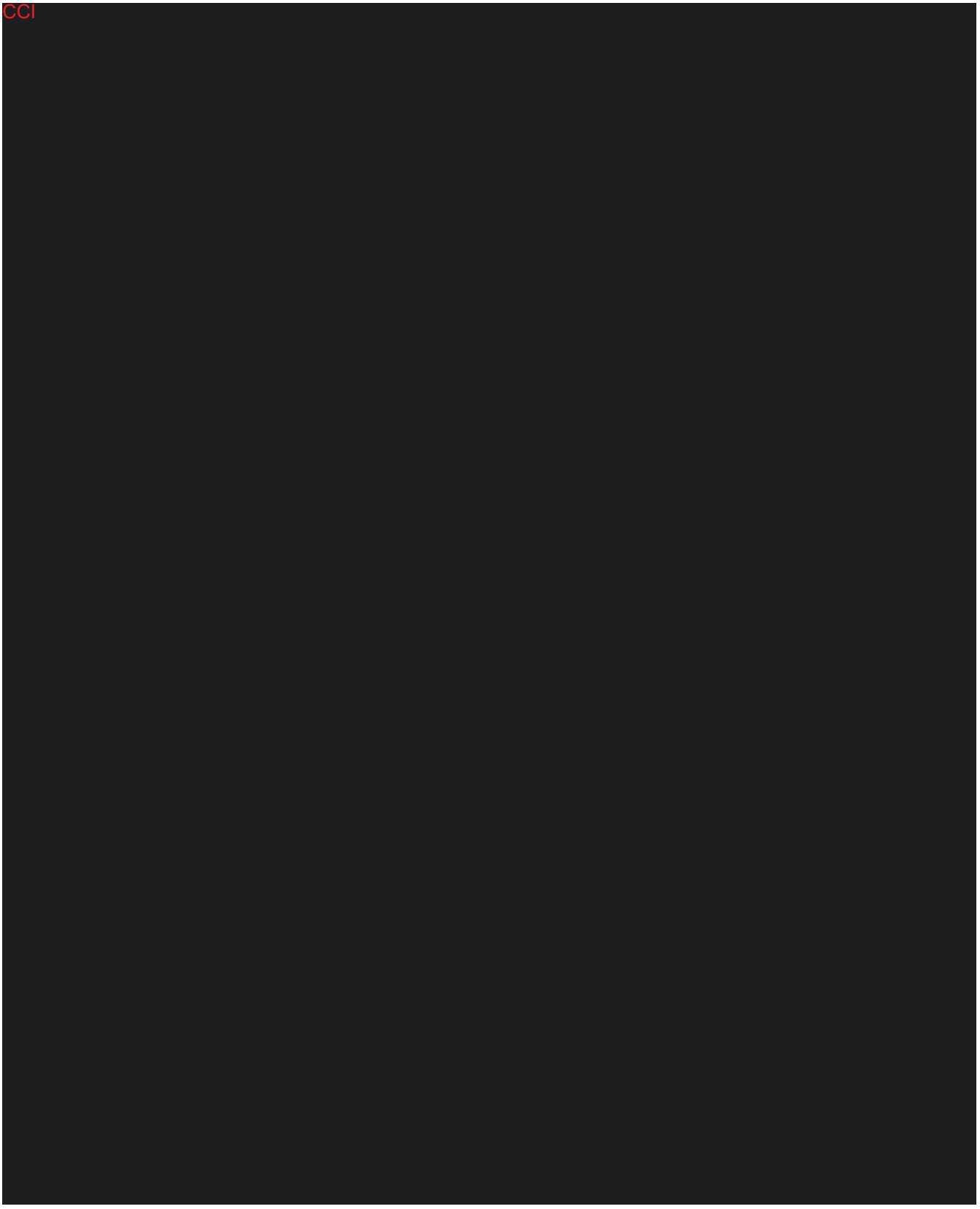
E 1 CCI

CCI

E 2 CCI

CCI


CCI


CCI

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

F 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with the Sponsor clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

F 2 Definitions

Potential Hy's Law
Aspartate aminotransferase or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law
Aspartate aminotransferase 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.

F 3 Identification of Potential Hy's Law Cases

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

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

Local laboratories being used:

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

Determine whether the participant meets PHL criteria (see Section F 2 Definitions within this appendix for definition) by reviewing laboratory reports from all previous visits

Promptly enter the laboratory data into the laboratory eCRF

F 4 Follow-up

F 4.1 Potential Hy's Law Criteria Not Met

If the participant does not meet PHL criteria the investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

F 4.2 Potential Hy's Law Criteria Met

If the participant does meet PHL criteria the investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Section F 6)
- Notify the Sponsor representative who will then inform the central study team
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of PHL; serious criteria 'important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.

- For participants that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change # in the participant's condition

- The Study Clinical Lead contacts the investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data

- Subsequent to this contact the investigator will:

  – Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  – Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Clinical Lead.
  – Complete the three Liver eCRF Modules as information becomes available

 # A 'significant' change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the Study Clinical Lead if there is any uncertainty.

F 5 Review and Assessment of Potential Hy's Law Cases

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

As soon as possible after the biochemistry abnormality was initially detected, the Study Clinical Lead 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, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The Sponsor Global Clinical Lead or equivalent 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.

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF

- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the Sponsor's 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:

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

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

F 6 Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment

This section is applicable to participants 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 participants' 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 Sponsor representative, who will inform the central Study Team, then follow the subsequent process described in Section F 4.2

F 7 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a participant 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 eg, chronic or progressing malignant disease, severe infection, or liver disease or did the participant meet PHL criteria prior to starting study treatment and at their first on-study treatment visit as described in Section F 6?

If **No**: follow the process described in Section F 4.2 for reporting PHL as an SAE.

If **Yes**: Determine if there has been a significant change in the participant's condition # compared with when PHL criteria were previously met.

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section F 4.2 for reporting PHL as an SAE

A 'significant' change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the Study Clinical Lead if there is any uncertainty.

F 8 Laboratory Tests

These are recommended laboratory tests to be performed in cases of PHL. Any test results need to be recorded in the eCRF.

Hy's Law Laboratory Tests

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA IgG anti-HCV HCV RNA [a] IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-liver/kidney microsomal Ab (Anti-LKM) Anti-smooth muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

[a] HCV RNA is only tested when IgG anti-HCV is positive or inconclusive.

F 9 References

Aithal et al, 2011
Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

FDA Guidance for Industry, July 2009
FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'. Available from; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

Appendix G 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 RECIST 1.1 guidelines (Eisenhauer et al 2009). Investigator assessments will use the RECIST 1.1 guidelines described in this appendix. Additional special guidance is provided for evaluation of scans collected after a RECIST 1.1-defined radiological progression.

Imaging Modalities and Acquisition Specifications for RECIST 1.1

A summary of the imaging modalities that can be used for tumor assessment of TLs, NTLs, and NLs is provided in Table 11.

Table 11 Summary of imaging modalities for tumor assessment

Target lesions	Non-target lesions	New lesions
CT MRI	CT MRI Plain X-ray Chest X-ray	CT MRI Plain X-ray Chest X-ray Bone scan (Scintigraphy) FDG-PET/CT

CT = computed tomography; FDG-PET/CT = ^{18}F-Fluoro-deoxyglucose positron emission tomography/CT; MRI = magnetic resonance imaging.

CT and MRI

Computed tomography with iv contrast is the preferred imaging modality (although MRI with iv contrast is acceptable if CT is contraindicated) to generate reproducible anatomical images for tumor assessments (ie, for measurement of TLs, assessment of NTLs, and identification of NLs). It is essential that the same correct imaging modality, image acquisition parameters (eg, anatomic coverage, imaging sequences, etc), imaging facility, tumor assessor (eg, radiologist), and method of tumor assessment (eg, RECIST 1.1) are used consistently for each participant throughout the study. The use of the same scanner for serial scans is recommended, if possible. It is important to follow the image collection/tumor assessment schedule as closely as possible (refer to the SoA; Section 1.3), and this on-study imaging schedule MUST be followed regardless of any delays in dosing or missed imaging visits. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the participant has not progressed, every attempt should be made to perform the subsequent scan acquisitions at the next scheduled imaging visit.

Due to its inherent rapid acquisition (seconds), CT is the imaging modality of choice. Body

scans should be performed with breath-hold scanning techniques, if possible. Therefore, CT of the chest is recommended over MRI due to significant motion artifacts (eg, heart, major blood vessels, breathing) associated with MRI. MRI has excellent contrast and spatial and temporal resolutions; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. In general, local oncology diagnostic imaging parameters are applied for scan acquisition. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases.

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

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

Required anatomical regions to be imaged for assessment of tumor burden (TLs and/or NTLs) at baseline and follow-up visits vary according to the study, and these time points are specified in the SoA (Section 1.3). Examples include the following:

- Intravenous contrast-enhanced CT of chest-abdomen (including the entire liver and both adrenal glands) (-pelvis)
- Non-contrast CT of chest and IV contrast-enhanced abdomen (including the entire liver and both adrenal glands) (-pelvis)
- Intravenous contrast-enhanced CT or MRI of the head and neck
- Intravenous contrast-enhanced MRI (preferred) or CT of the brain

For chest-abdomen (-pelvis) imaging, the following are scanning options in decreasing order of preference, with additional options (2 to 4) for consideration when participants have sensitivity to iv contrast or have compromised renal function:

1 Chest-abdomen (-pelvis) CT with iv CT contrast (most preferred)
2 Chest CT without iv contrast + abdomen (-pelvis) MRI with IV MRI contrast, if CT iv contrast (iodine based) is medically contraindicated at any time during the study

3 Chest-abdomen (-pelvis) CT without iv contrast, if both iv CT and MRI contrast are medically contraindicated or the participant has compromised renal function

4 Chest-abdomen (-pelvis) MRI with iv MRI contrast, if CT cannot be performed at any time during the study

b. Intravenous contrast administration: Optimal visualization and measurement of metastases in solid tumors require consistent administration (dose and rate) of iv contrast as well as timing of scanning. An adequate volume of a suitable contrast agent should be given so that the tumor lesions are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. Oral contrast is recommended to help visualize and differentiate structures in the abdomen and pelvis.

c. Slice thickness and reconstruction interval: It is recommended that CT or MRI scans be acquired/reconstructed as contiguous (no gap) slices with ≤ 5-mm thickness throughout the entire anatomic region of interest for optimal lesion measurements. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses > 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

For CT scans, all window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study.

Chest X-ray

Chest X-ray assessment will not be used for the assessment of TLs. Chest X-ray can, however, be used to assess NTLs and to identify the presence of NLs. However, there is preference that a higher resolution modality, such as CT, be used to confirm the presence of NLs.

Plain X-ray

Plain X-ray may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

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 NTLs and followed by the same method per baseline assessment (CT, MRI, or X-ray).

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 may be recorded in case positive hot-spots appear on a bone scan that were not present on a previous bone scan; however, a newly

observed equivocal hot-spot on a bone scan that cannot be verified with correlative imaging (CT, MRI, or X-ray) of the same anatomical region shall not be the only trigger for a PD assessment at that time point.

FDG-PET/CT

[1]FDG-PET/CT scans may be used as a method for identifying new lesions for RECIST 1.1 assessments according to the following algorithm: NLs will be recorded where there is positive FDG uptake[1] not present on baseline or prior FDG-PET scan or in a location corresponding to a NL on a companion CT/MRI collected close in time to the FDG-PET scan. The PET portion of the PET/CT introduces additional data that may bias an investigator if it is not routinely or serially performed. Therefore, if there is no baseline or prior FDG-PET scan available for comparison, and no evidence of NLs on companion CT/MRI scans, then follow-up CT/MRI assessments should continue as per the regular imaging schedule to verify the unequivocal presence of NLs.

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

Ultrasound

Ultrasound examination will not be used for RECIST 1.1 assessment of tumors as it is not a reproducible acquisition method (operator dependent), is subjective in interpretation, and may not provide an accurate assessment of the true tumor size. Tumors identified by ultrasound will need to be assessed by correlative CT or MRI anatomical scan.

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1 A positive FDG-PET scan lesion should be reported only when an uptake (eg, SUV) greater than twice that of the surrounding tissue or liver is observed.

Other Tumor Assessments

Clinical examination

Clinical examination of skin/surface lesions (by visual inspection or manual palpation) will not be used for RECIST 1.1 assessments. Tumors identified by clinical examination will need to be assessed by correlative CT or MRI anatomical scans.

Endoscopy and laparoscopy

Endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor assessment.

Histology and cytology

Histology or tumor markers on tumor biopsy samples will not be used as part of the tumor response assessment as per RECIST 1.1.

Results of cytological examination for the neoplastic origin of any effusion (eg, ascites, pericardial effusion, and pleural effusion) that appears or worsens during the study will not be used as part of the tumor response assessment as per RECIST 1.1.

Furthermore, an overall assessment of CR (all other disease disappears/reverts to normal) would be changed to PR if an effusion remains present radiologically.

Measurability of Tumor Lesions at Baseline

RECIST 1.1 measurable lesions at baseline

A tumor lesion that can be accurately measured at baseline as ≥ 10 mm in the longest diameter nor non-nodal lesions or ≥ 15 mm in short axis[2] diameter for lymph node lesions with iv contrast-enhanced CT or MRI and that is suitable for accurate repeated measurements.

Non-measurable lesions at baseline

- Truly non-measurable lesions include the following:
  - Bone lesions (see exception below for soft tissue component)
  - Leptomeningeal disease
  - Ascites, pleural effusion, or pericardial effusion
  - Inflammatory breast disease
  - Lymphangitic involvement of skin or lung
- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10-mm to < 15-mm short axis diameter at baseline[3])
- Previously irradiated lesions [4]
  This study allows a previously irradiated lesion as a TL if there has been demonstrated progression in the lesion and it meets reproducible measurability and minimum size requirements and if this is the only lesion available.
- Brain metastasis

Special considerations regarding lesion measurability at baseline

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[2] The short axis is defined as the longest in-plane axis perpendicular to the long axis.

[3] Lymph nodes with <10-mm short axis diameter are considered non-pathological and should not be recorded or followed as NTLs.

[4] Localized post-radiation changes that affect lesion size may occur. Therefore, lesions that have been previously irradiated are typically considered non-measurable and as NTL at baseline and followed up as part of the NTL assessment.

- Bone lesions
  - Bone scan, PET scan, or plain X-ray are not considered adequate imaging techniques to measure bone lesions; however, these techniques can be used to confirm the presence or disappearance of bone lesions.
  - 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 lesions thought to represent 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 participant, these should be selected over cystic lesions as TLs.

RECIST 1.1 TL selection at baseline

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 TLs at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis diameter 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 that can be measured reproducibly should be selected.

Lymph nodes, in any location (local/regional and distant), are collectively considered as a single organ, with a maximum of 2 lymph nodes as TLs. A bilateral organ (eg, adrenal glands), a segmented organ (eg, liver), or a multilobed organ (eg, lung) is each considered as a single organ.

The site and location of each TL should be documented, as well as the longest axis diameter for non-nodal lesions (or short axis diameter for lymph nodes). All measurements should be recorded in millimeters. At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits, the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

Special cases for TL assessment at baseline

- For TLs 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 diameter.

- When lymph nodes are coalesced and no longer separable in a conglomerate mass, the maximal short-axis diameter of the coalesced mass should be recorded. Non-nodal lesions that coalesce should similarly be assessed by the long-axis diameter.
- Tumor lesions selected for fresh screening biopsy should not be selected as TLs, unless imaging occurred at least approximately 2 weeks after biopsy, allowing time for healing.
- 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 diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as an NL.

RECIST 1.1 NTL selection at baseline

All other lesions, including non-measurable lesions and surplus measurable lesions, not recorded as TLs should be identified as NTLs at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Evaluation of Tumor Response and Progression

RECIST 1.1 TL assessment at follow-up

This section defines the criteria used to determine objective tumor visit response for RECIST 1.1-defined TLs. The imaging modality, location, and scan date of each TL identified previously at baseline should be documented at follow-up visits with the long axis diameter for non-nodal lesions or short axis diameter for lymph node lesions. All measurements should be recorded in whole millimeters. The sum of the diameters for all TLs at each follow-up visit will be compared to the baseline sum of diameters (for response or SD) or to the smallest prior (nadir) sum of diameters (for progression).

Special cases for TL assessment at follow-up:

- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as an NL.
- If a TL splits into 2 or more parts, the sum of the diameters of those parts should be recorded.
- If 2 or more TLs merge, then the sum of the diameters of the combined lesion should be recorded for 1 of the lesions and 0 mm recorded for the other lesion(s). If the merged TLs are non-nodal lesions, record the long axis diameter of the merged lesion. If pathologic lymph nodes coalesce and are no longer individually separable within a conglomerate mass, the maximal short axis diameter is recorded.
- 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. The choice of "Too large to measure" in the case report form will trigger an overall visit response of PD.
- When a TL has had an unscheduled, non-protocol intervention, the following apply:
  - Target lesion intervention may include radiotherapy, embolization, excisional biopsy, surgery, etc. that is not a part of study treatment and might adversely affect the size of that TL.
  - If an intervention on a TL is ticked in the eCRF, the diameter of the lesion is still recorded (0mm if no longer present) and is included in the sum of diameters.
  - If a TL intervention is ticked, the intervention must be reported for all subsequent assessments of that TL.
  - If a TL has an intervention, the only Overall Visit Responses allowed to be recorded by the investigator are NE or PD, with PD if the sum of diameters exceeds a 20% increase and at least a 5 mm absolute increase in the visit sum of diameters compared to the previous minimum (nadir) sum of diameters.
  - No visit with a recorded TL intervention can be used as the minimum (nadir) sum of diameters.

Table 12 RECIST 1.1 Evaluation of TLs

CR	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis diameter to < 10 mm.
PR	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters.
SD	Neither sufficient decrease in the sum of diameters to qualify for PR nor sufficient increase to qualify for PD.
PD	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest previous sum of diameters (nadir) - this includes the baseline sum if that is the smallest on study. In addition to the relative increase of 20%, the sum must demonstrate an absolute increase of at least 5 mm from nadir.
NE	Only relevant if any of the TLs at follow-up were not assessed or NE (eg, missing anatomy) or had a lesion intervention at this visit. Note: If the sum of diameters meets the PD criteria, PD overrides NE as a TL response.
NA	Only relevant if no TLs present at baseline.

CR = complete response; NA = not applicable; NE = not evaluable; PD = progression of disease; PR = partial response; SD = stable disease; TL = target lesion.

RECIST 1.1 NTL assessment at follow-up

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs 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.

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 SD or PR in TLs, the overall tumor burden has increased sufficiently to merit unequivocal progression by NTLs. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

Table 13 RECIST 1.1 Evaluation of NTLs

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 NTLs.
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.
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 participants 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.
NA	Only relevant if no NTLs present at baseline

CR = complete response; NA = not applicable; NTL = non-target lesion; PD = progression of disease; TL = target lesion.

RECIST 1.1 NL identification at follow-up

Details, including the imaging modality, the date of scan, and the location of any NLs will also be recorded in the case report form. The presence of one or more NLs is assessed as progression. The finding of a NL 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 NL is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the previously (pre-existing) new lesion has been assessed as unequivocal at a follow-up visit, and then the progression date should be declared using the date of the initial scan when the NL first appeared.

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

RECIST 1.1 evaluation of overall visit response at follow-up

Derivation of overall visit response as a result of the combined assessment of TLs, NTLs, and NLs uses the algorithm shown in Table 14.

Table 14 RECIST 1.1 Overall Visit Response

Target lesions	Non-target lesions	New lesions	Overall visit response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE or NA	No	PR
SD	Non PD or NE or NA	No	SD
NA	Non-CR/Non-PD	No	SD (non-CR/non-PD)
NE	Non PD or NE	No	NE
NA	NE	No	NE
NA	NA	No	NED
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note: An overall assessment of CR (all other disease disappears/reverts to normal) would be changed to PR if ascites remains present radiologically.
CR = complete response; NA = not applicable (only relevant if there were no non-target lesions at baseline), NE = not evaluable; NED = no evidence of diseases (only relevant if there were neither TLs nor NTLs at baseline); PD = progression of disease; PR = partial response; SD = stable disease; TL = target lesion.

The following overall visit responses are possible depending on the extent of tumor disease at baseline:

- For participants with TLs (at baseline): CR, PR, SD, progression of disease (PD), or NE
- For participants with NTLs only (at baseline): CR, Non-CR/Non-PD, PD, or NE
- For participants with no disease at baseline: NED (available as an option in the eCRF), PD, or NE

Evaluation of scans subsequent to RECIST 1.1-defined progression

A follow-up scan is requested at least 4 weeks later and no longer than the next regularly scheduled imaging visit. The follow-up scans provide additional information to the investigator for participant management and further treatment decisions, and since the published RECIST 1.1 (Eisenhauer et al 2009) do not provide guidance on how to assess

scans acquired after RECIST 1.1-defined PD, supplemental instructions for investigators on how to evaluate these follow-up scans are provided below. A subsequent follow-up scan would be considered as having progressive disease if any of the following criteria are met:

- Greater than or equal to 20% increase and at least a 5-mm increase in the sum of diameters of TLs compared with the nadir sum of diameters at 2 consecutive visits, and a further increase of ≥ 5 mm in the sum of diameters at the follow-up scan time point compared with the immediate prior time point
- Significant progression (worsening) of NTLs at the follow-up scan time point compared with the immediate prior time point
- Significant progression (worsening) of previous NLs (pre-existing NLs) at the follow-up scan time point compared with the immediate prior time point
- Additional brand-new unequivocal lesions at the follow-up scan time point

Appendix H Contraception Requirements

Contraception requirements for this study are as follows.

H 1 Female Participant of Child-bearing Potential

Please note, females of childbearing potential are defined as those who are post-menarche, not surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

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

Female participants of childbearing potential who are not totally sexually abstinent (ie, refraining from heterosexual intercourse during the entire period of risk associated with study treatments) and intend to be sexually active with a nonsterilized male partner must use at least one highly effective method of contraception (Table 15) from the time of screening throughout the total duration of the drug treatment and for 4 months after the last dose of study intervention. Non-sterilized male partners of a female participant of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence (eg, calendar, symptothermal, post-ovulation methods), the rhythm method, the withdrawal method (coitus interruptus), and lactational amenorrhea method are not acceptable methods of contraception. Female participants should refrain from breastfeeding throughout this period.

H 2 Male Participants With a Female Partner of Childbearing Potential

Non-sterilized male participants (including males sterilized by a method other than bilateral orchidectomy, eg, vasectomy) who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) from the time of screening throughout the total duration of the drug treatment and for 4 months after the last dose of study

intervention. Periodic abstinence (eg, calendar, symptothermal, post-ovulation methods), the rhythm method, the withdrawal method (coitus interruptus), and lactational amenorrhea method are not acceptable methods of contraception. Male participants should refrain from sperm donation throughout this period.

Vasectomized (ie, sterile) males are considered fertile and should still use a male condom plus spermicide as indicated above during the clinical study.

Even if the female partner is pregnant, male participants should still use a condom, as indicated above during the clinical study, if there is a concern about damaging the developing fetus from drug in ejaculate.

Female partners (of childbearing potential) of male participants must also use a highly effective method of contraception throughout this period (Table 15).

H 3 Highly Effective Methods of Contraception

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly, are described in Table 15.

Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; spermicide alone; female cap, diaphragm, or sponge with or without spermicide; non copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills (also known as progesterone-only or “mini-pill”) where inhibition of ovulation is not the primary mode of action [excluding Cerazette®/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 15 Highly Effective Methods of Contraception (< 1% Failure Rate)

Barrier/intrauterine methods	Hormonal methods [b]
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (eg, Mirena®) [a]	• Implants: Etonogestrel-releasing implants (eg, Implanon® or Norplant®) • Intravaginal devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®) • Injection: Medroxyprogesterone injection (eg, Depo-Provera®) • Combined pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Ortho Evra®) • Minipill: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based pill

[a] This is also considered a hormonal method.

[b] The brand names in this table are examples only and availability will vary by country.

Appendix I Patient-reported Outcomes

I 1 EORTC QLQ-C30

I 2 EORTC QLQ-H&N35

I 3 CCI [redacted]

I 4 CCI [redacted]

I 5 CCI [redacted]

I 6 CCI [redacted]

I 1 EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊⌋⌊⌋⌊⌋
Your birthdate (Day, Month, Year): ⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋
Today's date (Day, Month, Year): 31 ⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

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

I 2 EORTC QLQ-H&N35

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

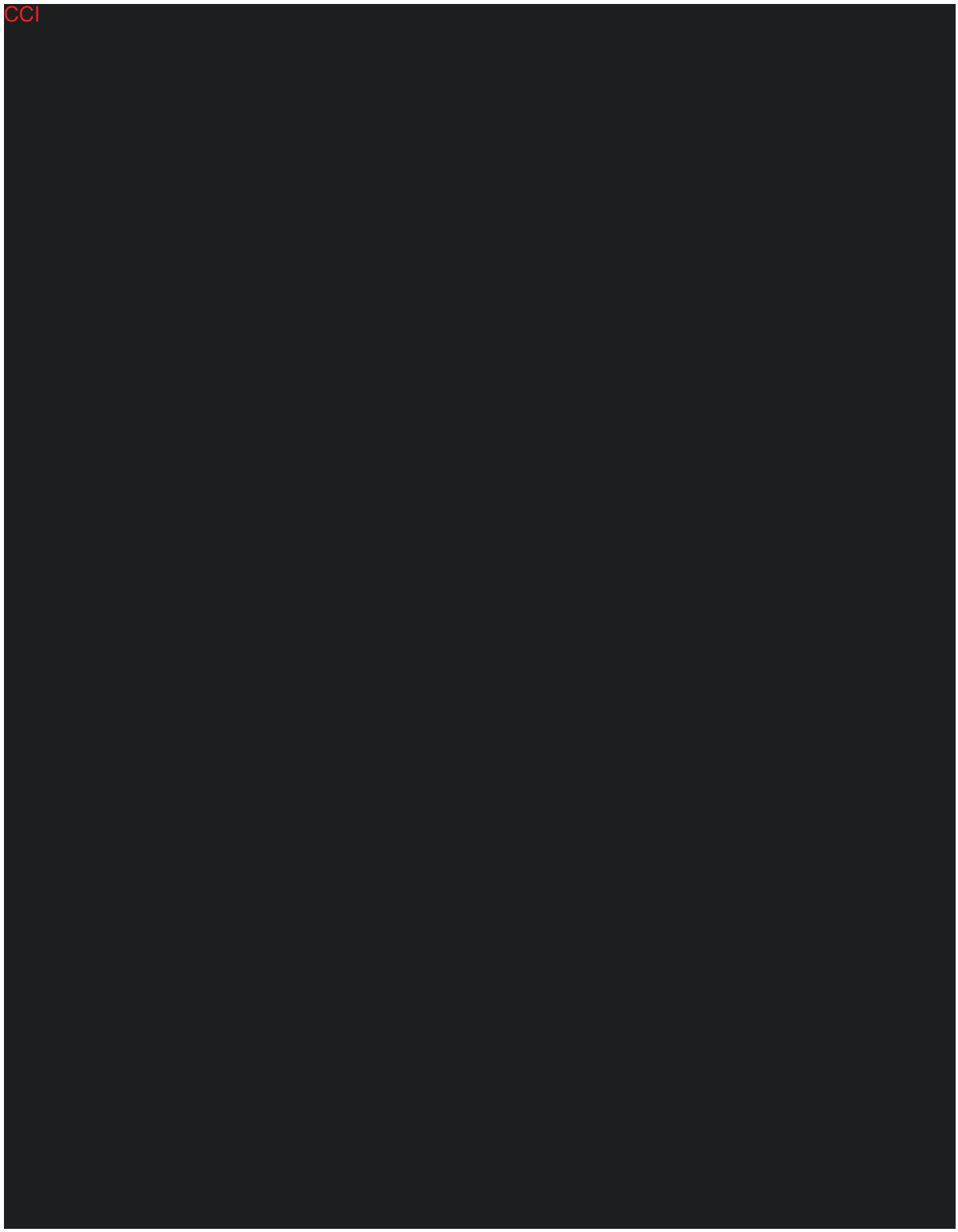
ENGLISH

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

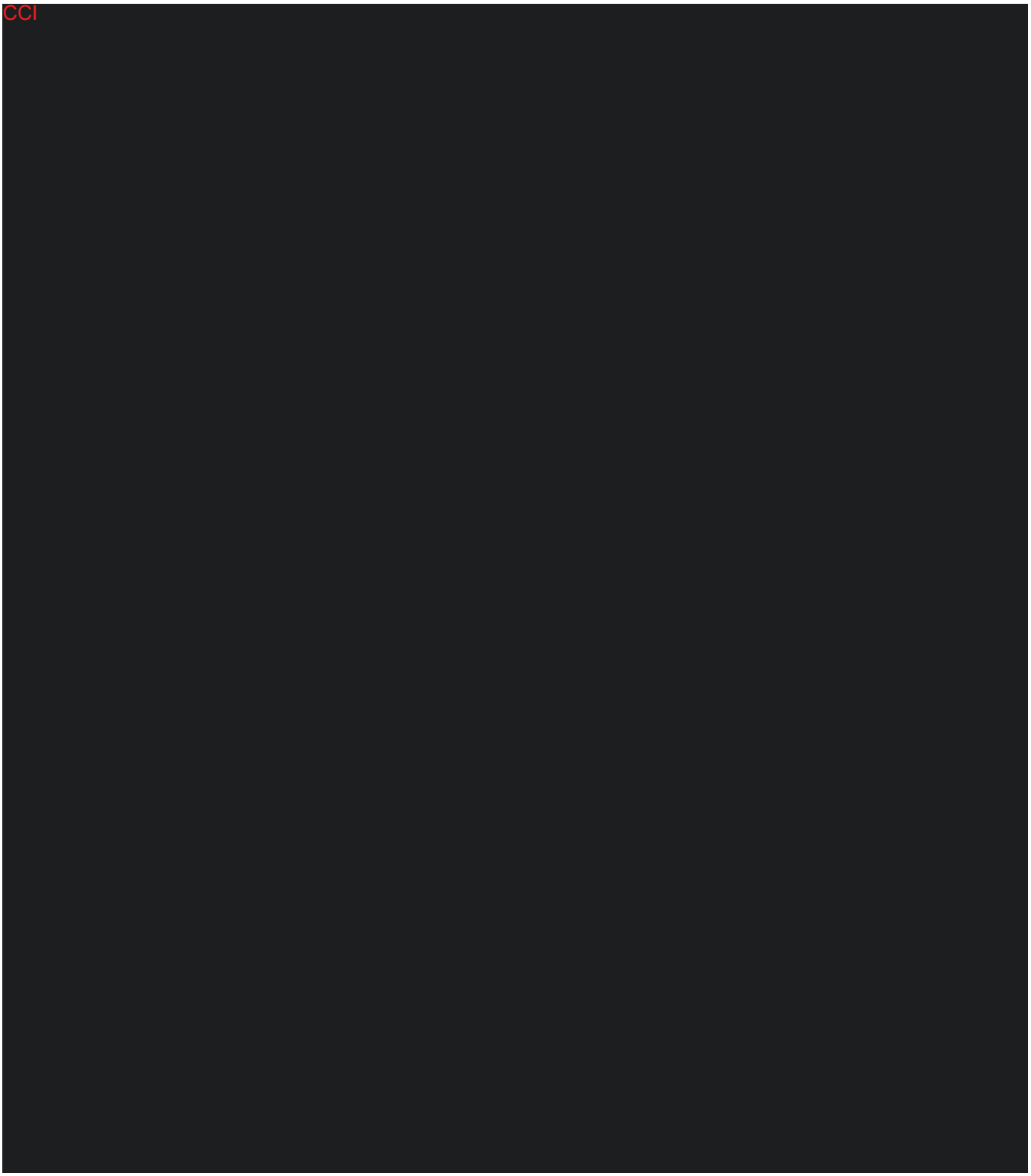
I 3 CCI

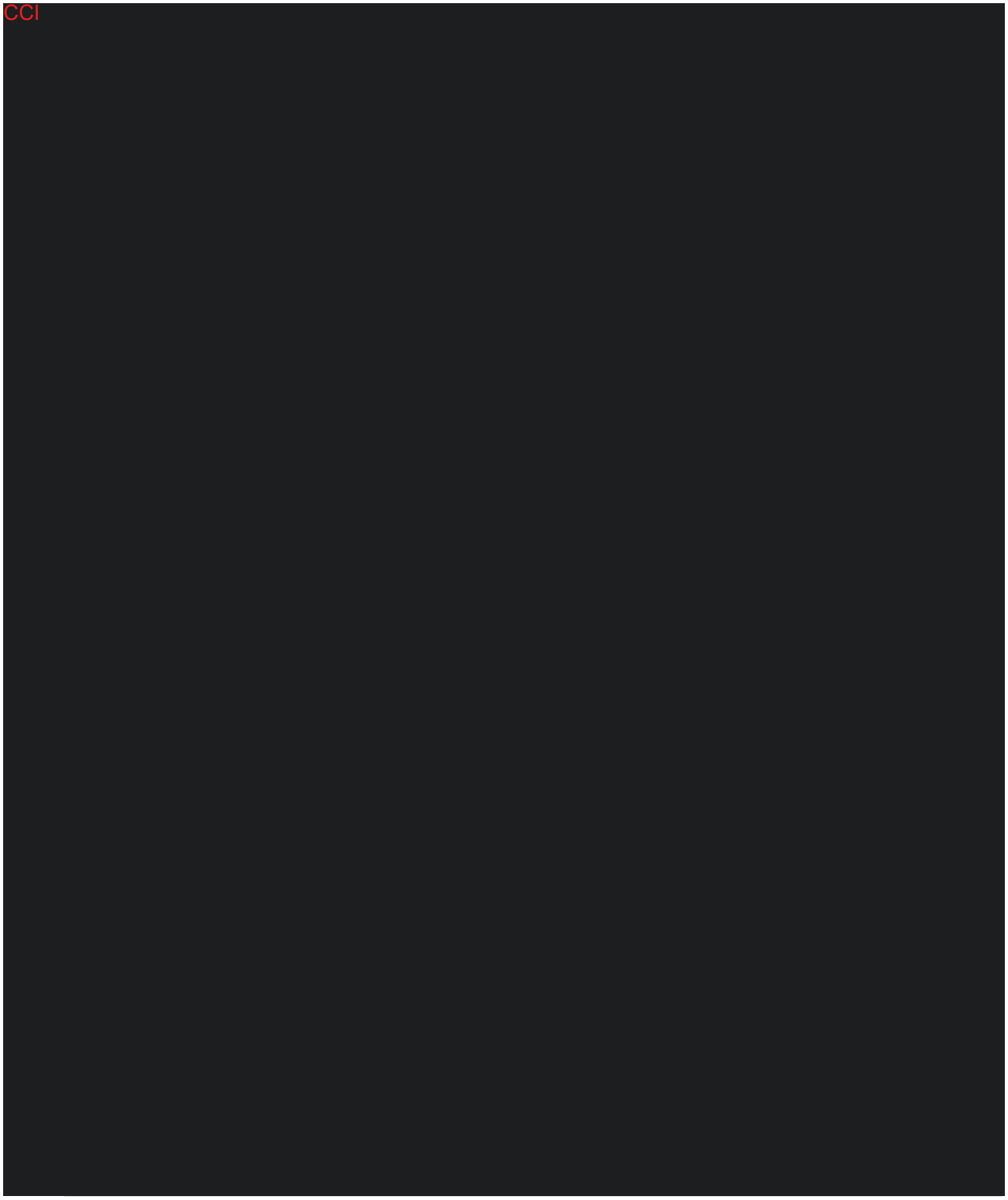
CCI

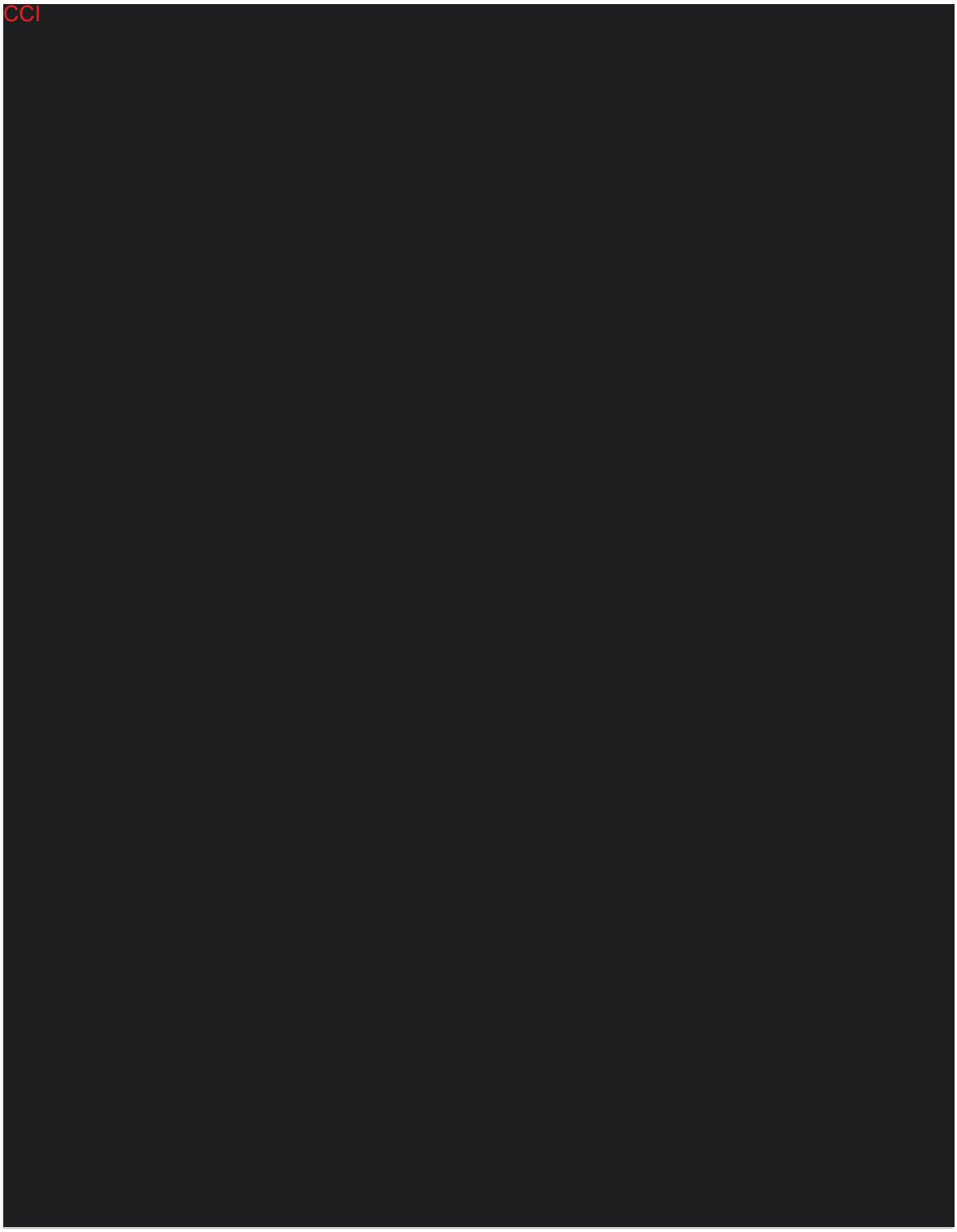


I 4 CCI

CCI




CCI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I 5 CCI

I 6 CCI

CCI

Appendix J Study Participant Feedback Questionnaire

TransCelerate BIOPHARMA INC.
ACCELERATING THE DEVELOPMENT OF NEW MEDICINES

Patient Experience Initiative

Study Participant Feedback Questionnaire (SPFQ)

Version 1.0

Prepared by:

TransCelerate Patient Experience Initiative Team

TransCelerate BIOPHARMA INC.

Study Participant Feedback Questionnaire (SPFQ)

Your experience before you started the study

Thank you for your participation. Your experiences in this trial are important to us and we would like to hear about them. Your answers will help us improve future trials. There are no right or wrong answers, and it will take approximately 15 minutes to complete. Your answers will be kept anonymous and will not impact your participation in this trial.

Please select **one** response for each item.	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1. I understand the treatment process in this trial (for example: when and how to take or use a treatment)	0	1	2	3	4
2 The information given to me before I joined the trial was everything I wanted to know (for example: visits and procedures, time commitment, who to contact with questions)					
3 The information given to me before I joined the trial was easy for me to understand (for example: visits and procedures, time commitment, who to contact with questions)					
4 I felt comfortable that I could ask any questions before I joined the trial					

TransCelerate BIOPHARMA INC.

Study Participant Feedback Questionnaire (SPFQ)

Your experience during the trial

Thank you for your participation. Your experiences in this trial are important to us and we would like to hear about them. Your answers will help us improve future trials. There are no right or wrong answers, and it will take approximately 15 minutes to complete. Your answers will be kept anonymous and will not impact your participation in this trial.

Please select one response for each item.	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1. Overall I am satisfied with the trial site (for example: comfort and privacy of treatment area, waiting area, parking, ease of access to the site)	0	1	2	3	4
2. My trial visits have been well organized					
3. My trial visits are scheduled at a convenient time for me					
4. The staff treats me with respect					
5. I feel comfortable that I can ask questions during the trial					
6. I am satisfied with the answers I have received to my questions during the trial					
	No		Yes		
7. The time taken to collect data is acceptable to me (for example: in person visits, questionnaires, forms)					
8. The impact the trial has on my daily activities is acceptable (for example: household chores, work commitments, eating)					

TransCelerate BIOPHARMA INC.

Study Participant Feedback Questionnaire (SPFQ)

Your experience at the end of the trial

Thank you for your participation. Your experiences in this trial are important to us and we would like to hear about them. Your answers will help us improve future trials. There are no right or wrong answers, and it will take approximately 15 minutes to complete. Your answers will be kept anonymous and will not impact your participation in this trial.

Please select **one** response for each item.

1 I was informed when I had completed the trial	No		Yes		
2 . I was informed of any future opportunities to access the overall trial results if I wanted to					
	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
3 . Overall, I was satisfied with the information I received about future support after the trial (for example: future treatment, follow-up contact details)	0	1	2	3	4
4 . Overall, I was satisfied with my trial experience					
	Much less than expected	Somewhat less than expected	Same as expected	Somewhat more than expected	Much more than expected
5 . Compared to when the trial started, the overall commitment required was similar to what I expected	0	1	2	3	4

3

Appendix K Abbreviations

Abbreviation or special term	Explanation
1L	first line
5-FU	5-fluorouracil
ADA	antidrug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BoR	best overall response
CI	confidence interval
C_{max}	maximum serum concentration
COA	clinical outcome assessment
COVID-19	coronavirus disease 2019
CR	complete response
CrCL	creatinine clearance
CRO	Contract Research Organization
CSP	clinical study protocol
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough serum concentration
DCO	data cutoff
DILI	drug induced liver injury
DNA	deoxyribonucleic acid
DoR	duration of response
ECG	electrocardiograms
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	Electronic Data Capture
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EOT	end of treatment

Abbreviation or special term	Explanation
ePRO	electronic patient-reported outcome (questionnaire)
CCI [redacted]	CCI [redacted]
ESMO	European Society of Medical Oncology
EU SmPC	European Union Summary of Product Characteristics
EXTREME regimen	cetuximab + platinum (cisplatin or carboplatin) + 5-fluorouracil followed by cetuximab until progression or intolerance
FA	final analysis
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG	^{18}F-Fluoro-deoxyglucose
FH	Fleming-Harrington
FWER	familywise error rate
GCP	Good Clinical Practice
HBsAg	HBV surface antigen
HBV	hepatitis B
HCV	hepatitis C
HER	human epidermal growth factor receptor
HIV	human immunodeficiency virus
HL	Hy's Law
HLA-E	human leukocyte antigen E
CCI [redacted]	CCI [redacted]
HPV	human papillomavirus
HPV-unrelated	randomized participants who are either OPC HPV negative or non-OPC
HR	hazard ratio
HRQoL	health-related quality of life
IA	interim analysis
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICI	immune checkpoint inhibitor
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG4	immunoglobulin G4
IHC	immunohistochemistry

Abbreviation or special term	Explanation
imAE	immune-mediated adverse event
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	Interactive Response Technology
iv	intravenous
IVRS	interactive voice response system
KM	Kaplan Meier
LA	locally advanced
mAb	monoclonal antibody
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Research
NCI	National Cancer Institute
NE	not evaluable
NED	no evidence of disease
NK	natural killer
NL	new lesion
NPH	non-proportional hazards
NTL	non-target lesion
OPC	oropharyngeal cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand-1
PD-(L)1	programmed cell death-1 or programmed cell death ligand-1
PET	positron emission tomography
PFS	progression-free survival
CCI	CCI [redacted]
CCI	[redacted]
[redacted]	CCI [redacted]
PHL	potential Hy's Law
PK	pharmacokinetic
PR	partial response

Abbreviation or special term	Explanation
PRO	patient-reported outcome
PS	performance status
Q1W	once weekly
Q2W	every 2 weeks
Q4W	every 4 weeks
QLQ-C30	30-item Core Quality-of-life Questionnaire
QLQ-H&N35	Quality of Life Questionnaire Head and Neck Module
QoL	quality of life
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
REVPRDI	Review of PRO/Questionnaire/Diary
R/M	recurrent or metastatic
SAE	serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome-coronavirus-2
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SITC	Society for Immunotherapy of Cancer
SoA	schedule of activities
SPFQ	Study Participant Feedback Questionnaire
TBL	total bilirubin
TL	target lesion
TME	tumor microenvironment
TMG	toxicity management guidelines
ULN	upper limit of normal
USA	United States of America
US FDA	United States Food and Drug Administration
US PI	United States Package Insert
WHO	World Health Organization
w/v	weight/volume

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