Statistical Analysis Plan	
Study Code	D7310C00001
Edition Number	4.0
Date	19 July 2022

A Phase 3 Randomized, Double-blind, Multicenter, Global Study of Monalizumab or Placebo in Combination With Cetuximab in Patients With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck Previously Treated With an Immune Checkpoint Inhibitor (INTERLINK-1)

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Global Product Statistician

PPD

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Study Statistician

PPD

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
AZ	AstraZeneca
BoR	Best objective response
BP	Blood pressure
CI	Confidence interval
CR	Complete response
Cl	Creatine clearance
CRO	Contract research organization
CRF	Case report form
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse event
CCI	[redacted]
CV	Coefficient of variation
DBL	Database lock
DCO	Data cut-off
CCI	[redacted]
DCR-24w	Percentage of patients who have a best objective response of CR or PR or who have SD for at least 24 weeks (±7 days), following start of treatment
DNA	deoxyribonucleic acid
DoR	Duration of response
d.p.	Decimal place
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviation or special term	Explanation
eCDF	Empirical cumulative distribution function
eCRF	Electronic case report form
EORTC	European Organization for Research and Treatment of Cancer
CCI	[redacted]
CCI	[redacted]
EQ-VAS	EuroQol visual analogue scale
FA	Final analysis
FAS	Full analysis set
FWER	Familywise error rate
HL	Hy's Law
HOSPAD	Hospital resource use module
HR	Hazard Ratio
HRQoL	Health-related quality of life
IA	Interim analysis
ICU	Intensive care unit
IDMC	Independent data monitoring committee
IHC	Immunohistochemistry
imAE	Immune-mediated adverse event
IMP	investigational medicinal product
IP	Investigational product
IPD	Important protocol deviation
IRC	Independent review charter
ITT	Intention to treat
iv	Intravenous
KM	Kaplan-Meier
LD	Longest diameter
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed model repeated measures
MRI	Magnetic resonance imaging
NA	Not applicable
nAB	Neutralizing antibody
NCI	National Cancer Institute
NE	Not evaluable
NTL	Non-target lesions

Abbreviation or special term	Explanation
OS	Overall survival
ORR	Objective response rate
PAP	Payer Analysis Plan
PDF	Probability density function
PD	Progressive disease
PFS	Progression free survival
CCI	[redacted]
CCI	[redacted]
CCI	[redacted]
PK	Pharmacokinetics
PR	Partial response
PRO	Patient reported outcome
CCI	[redacted]
PS	Performance status
PT	Preferred term
q2w	Every 2 weeks
QLQ-C30	30-Item Core Quality of Life Questionnaire
QLQ-H&N35	35-Item Quality of Life Questionnaire Head and Neck Questionnaire
QoL	Quality of Life
QTcF	QT interval corrected for heart rate using Friderica's formula
qXw	Every X weeks
RDI	Relative dose intensity
RECIST	Response evaluation criteria in solid tumors
REML	Restricted maximum likelihood
R/M	recurrent or metastatic
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SCCHN	squamous cell carcinoma of the head and neck
SD	Stable disease
SoC	Standard of care
TEAE	Treatment emergent adverse event
TL	Target lesion
TMB	Tumor mutation burden

Abbreviation or special term	Explanation
TSH	Thyroid stimulating hormone
TTD	Time to deterioration
ULN	Upper limit of normal
VAS	Visual analogue scale
WHO	World Health Organisation
WHO-DD	World Health Organisation drug dictionary
WOCBP	Women of childbearing potential

AMENDMENT HISTORY

Date	Brief description of change
21 October 2020	Version 1.0
07 January 2022	Version 2.0 with updates based on Protocol v2.0
24 May 2022	Version 3.0 with updates for clarification
19 July 2022	Version 4.0 with updates based on Protocol v3.0 and for clarification

Category: Change refers to	Date	Description of change	In line with CSP? Y (version) / N / NA	Rationale
List of abbreviations	24MAY2022	Removal of BICR: Blinded independent central review	Y (v2)	No BICR is planned on this study.
1.1 Study objectives, 3 Primary or secondary endpoints, 4.2.2 Statistical analysis method for the primary or secondary endpoints	05AUG2021	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). Added HPV-unrelated Analysis Set for secondary objectives.	Y (v2)	To align with CSP
1.1 Study objectives/Table 1	19JUL2022		Y (v3)	To align with CSP

1.2 Study design, **1.3 Number of subjects**	05AUG2021	The planned number of eligible participants was increased from 600 to 624. Text added to describe a cap on the number of OPC HPV-positive participants of approximately 20%.	Y (v2)	To align with CSP
2 ANALYSIS SETS / 2.1 Definition of analysis sets / Table 2: Summary of outcome variables and analysis populations	19JUL2022	Deaths summary and listing will be provided on Full analysis set	Y (v3)	For more clarity and align the table with the section 3.6 'Safety variables'
2 ANALYSIS SETS / 2.1 Definition of analysis sets / 2.1.4 Pharmacokinetics analysis set	19JUL2022	Removed 'or cetuximab' from 'The pharmacokinetics (PK) analysis set includes all subjects who receive at least one dose of monalizumab or cetuximab …'	Y (v3)	To align with CSP
2 ANALYSIS SETS / 2.1 Definition of analysis sets / 2.1.5 ADA analysis set	19JUL2022	Removed 'or cetuximab' from 'The ADA analysis set will include all subjects who have non-missing baseline ADA of monalizumab or	Y (v3)	To align with CSP

		cetuximab and at least 1 non-missing post-baseline monalizumab or cetuximab …'		
3 Primary and secondary variables / 3.1 Derivation of RECIST visit responses	24MAY2022	Reference to the CSP appendix where is detailed the RECIST version 1.1 updated from 'F' to 'G'	Y (v2)	Oblivion in previous update
3 Primary and secondary variables / 3.1 Derivation of RECIST visit responses / 3.1.1 Target lesions (TLs)	24MAY2022	In the 'TL visit responses subsequent to CR' paragraph: addition of specifications to the details into bracket of what could lead to assess 'not all lesions meet the CR criteria'. The following has been added: 'and an absolute increase of ≥5mm, taking as reference the smallest short axis for the same TL since treatment started including the baseline'	Y (v2)	To be more complete and specific
3 Primary and secondary variables / 3.1 Derivation of RECIST visit responses / 3.1.2 Non-target lesions (NTLs) and new lesions	24MAY2022	Removal of the paragraph: 'If the question 'Any new lesions since baseline' has not been answered with Yes or No and the new lesion details are blank this is not evidence that no new lesions are present but that the new lesion response should be treated as NE in the	Y (v2)	As per standards this is not applicable anymore. Only the presence or absence of a new lesion is assessed.

		derivation of the overall visit response.'		
3 Primary and secondary variables / 3.1 Derivation of RECIST visit responses / 3.1.3 Overall RECIST 1.1 visit response	24MAY2022	Addition of the combinations when the target lesions response is 'NA' to the table 5 'Overall visit responses'	Y (v2)	To be more complete and specific
3 Primary and secondary variables / 3.2 Primary and secondary efficacy variables / 3.2.2 Progression free survival (PFS)	24MAY2022	Modifications of the 2 missed visits definition paragraph. Time window for week 39 to week 47 has been updated from 'study days 274 to 330' to 'study days 274 to 329'. And the week when the scheduling changes to twelve-weekly assessments as be change from 'week 49' to 'week 47'. A summary table has been also added.	Y (v2)	To be more compliant with the schedule of assessment and more specific.
3 Primary and secondary variables / 3.2 Primary and secondary efficacy variables / 3.2.3 Objective response rate (ORR)	24MAY2022	Addition of the specification that the palliative radiotherapy is not considered a subsequent anti-cancer therapy. Before 'radiotherapy' only was mentioned without the specification that should be 'palliative'.	Y (v2)	To be more complete and specific

3 Primary and secondary variables / 3.2 Primary and secondary efficacy variables / 3.2.4 Duration of response (DoR)	24MAY2022	Addition of the 'time to response' variable as a supportive variable of the DoR.	Y (v2)	To be more complete and specific
3 Primary and secondary variables / 3.6 Safety variables/ 3.6.1 Exposure and dose delay/interruptions	24MAY2022	Addition of the following sentence for the calculation of the duration of monalizumab/placebo and cetuximab dose delay/interruption: If the calculation of the duration of dose delay/interruption results in a negative value because of out of scheduled subsequent doses, the duration of dose delay/interruption will be set to '0'.	Y (v2)	To be more complete and specific
3 Primary and secondary variables / 3.6 Safety variables/ 3.6.5 Laboratory measurements	24MAY2022	Addition of the following paragraph in case the creatinine clearance is not calculated/reported by the laboratory: If creatinine clearance (CrCL) is not calculated/reported by the laboratory, it will be derived during creation of the reporting database using the following formula: - Males: CrCL(mL/min) = Weight (kg) × (140 - age) / 72 × serum	Y (v2)	To be more complete and specific

		creatinine (mg/dL) - Females: CrCL(mL/min) = Weight (kg) × (140 - age) × 0.85 / 72 × serum creatinine (mg/dL)		
3 Primary and secondary variables / 3.6 Safety variables/ 3.6.10 General considerations for safety assessments/ 3.6.10.3 Handling of missing data	24MAY2022	For missing start dates for AEs, self-evident specification added in case of missing day, the following in bold has been added: • Missing day: Impute the 1st of the month unless month **and year are** the same as month **and year** of the first dose of study drug then impute first dose date.	Y (v2)	To be more complete and specific
3 Primary and secondary variables / 3.8 Immunogenicity variables	19JUL2022	To indicate the ADA sample analysis will be performed for Arm A only (for monalizumab only) and not on both arms as previously mentioned.	Y (v3)	To align with CSP
4 ANALYSIS METHODS	19JUL2022	Updated to indicate that there will be 3 DCO for this study.	Y (v3)	For clarity
4 ANALYSIS METHODS / 4.1 General principles	24MAY2022	The following has been added: 1) '(where applicable' after 'upper and lower quartiles' 2) For time variables provided in months, the time in days will be divided by 30.4375 days to obtain the time in months.	Y (v2)	1) Upper and lower quartiles are provided where applicable as per standards 2) To be more complete and specific

4 ANALYSIS METHODS / 4.2 Analysis methods	24MAY2022	Removal of 'BICR Blinded independent central review' from the footnotes of the 'Table 8: Formal statistical analysis to be conducted and pre-planned sensitivity analysis'	Y (v2)	No BICR is planned on this study.
4 ANALYSIS METHODS / 4.2 Analysis methods / 4.2.1 Multiplicity	05AUG2021	Updated Multiple-Testing Procedure to include both HPV-unrelated Analysis Set and FAS	Y (v2)	To align with CSP
4 ANALYSIS METHODS / 4.2 Analysis methods / 4.2.2 Primary efficacy endpoint overall survival (OS) / Subgroup analysis	19JUL2022	Addition of the following sentence: 'For subgroup analyses listed above, the human papillomavirus status, WHO/ECOG PS and number of prior lines of therapy in the R/M setting subgroups will be determined based on the data recorded in the CRF and not the stratification factor entered into the IxRS'	Y (v3)	To be more complete and specific
4 ANALYSIS METHODS / 4.2 Analysis methods / 4.2.2 Primary efficacy endpoint overall survival (OS) / 4.2.3 Secondary efficacy endpoints / 4.2.4 CCI [redacted] **/ 4.2.5 Patient**	05AUG2021	Updated Table 8 to align with CSP Updated analysis set for primary analysis to be HPV-unrelated Analysis Set Remove attrition bias for OS as not appropriate for this study	Y (v2)	To align with CSP and Adjustment to previous analysis

reported outcomes (PROs)		Added max combo test for OS Removed evaluation time bias for PFS as not necessary for this study Added sensitivity analysis censoring COVID deaths		
	24MAY2022	Presentation of the 25th and 75th percentiles have been added for the reporting of time to event endpoints. Time to response has been added as supportive endpoint of the DoR in the DoR paragraph.	Y (v2)	To be more complete and specific
4 ANALYSIS METHODS / 4.2 Analysis methods / 4.2.7 Safety data / 4.2.7.1 Adverse events	24MAY2022	Reporting of hemorrhages adverse events by Standardized MedDRA Query (SMQ) grouped term and PT has been added. Text addition to specify the overall summary is to be displayed by subject level and episode level.	Y (v2)	To be more complete and specific
	19JUL2022	The following sentence has been added to the deaths summary section: 'A summary of deaths will be also provided by HPV status recorded in CRF.'	Y (v3)	To be more complete and specific
4 ANALYSIS METHODS / 4.2 Analysis methods / 4.2.7 Safety data /	24MAY2022	Typo correction to go from 'Creatine' to 'Creatinine'.	Y (v2)	To be more complete and specific

4.2.7.4 Laboratory measurements		Addition of 'Creatinine clearance'.		
4 ANALYSIS METHODS / 4.2 Analysis methods / 4.2.11 Demographic, initial diagnosis and baseline characteristics data	24MAY2022	Addition of the of the following variables to the disease characteristics at baseline reporting: best response to first and last previous PD-1 or PD-L1 therapy, best response to immediate last line of therapy. Specification that the general medical history should be displayed as the disease related medical history is already displayed in the disease characteristic at baseline and TNM classification at diagnosis reporting. Addition of the disease related relevant surgical history and of the stratification factors recorded at randomization by IVRS and on eCRF reporting.	Y (v2)	To be more complete and specific
4 ANALYSIS METHODS / 4.2 Analysis methods / 4.2.12 Concomitant and other treatments	24MAY2022	1) Specification on the display of concomitant medications and procedures which are planned to be displayed by ATC classification (only one level) and preferred WHO name rather than by ATC level 2, ATC level 4 and preferred WHO name.	Y (v2)	1) As per standard coding the maximum ATC level for a medication/procedure will be reported 2) To be more complete and specific

		2) Addition of the definition of concomitant medications related to study drug dosing and of the mention the concomitant medications summary tables could present only the preferred WHO name.		
4.2.13 COVID-19	05AUG2021	Added description of summary for COVID-19 data	Y (v2)	To align with CSP
5 Interim Analysis	05AUG2021	Added IA1 (futility interim)	Y (v2)	To align with CSP
	19JUL2022	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.	Y (v3)	To align with CSP

1 STUDY DETAILS

This statistical analysis plan (SAP) contains a more detailed description of the analysis in the clinical study protocol (CSP). This SAP is based on version 3.0 of the CSP, dated 12th July 2022.

This is a Phase 3, randomized, double-blind, multi-center, global study assessing the safety and efficacy of monalizumab or placebo in combination with cetuximab in patients with recurrent/metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) not amenable to curative treatment previously treated with platinum-based chemotherapy and an immune checkpoint inhibitor (ICI), regardless of the sequence of these therapies.

Approximately 832 participants will be enrolled at up to approximately 190 sites to achieve approximately 624 eligible participants who will be randomized in a 2:1 ratio to one of the following treatment groups:

- Arm A: monalizumab and cetuximab
  Monalizumab CCI and cetuximab CCI initial dose followed by CCI
- Arm B: placebo and cetuximab
  Placebo iv Q2W and cetuximab CCI initial dose followed by CCI

Refer to the CSP for a detailed description of the rationale for this study as well as its inclusion/exclusion criteria.

1.1 Study objectives

Table 1: Study objective and corresponding Endpoint

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. • For participants who have a confirmed CR or PR, DoR is defined as the time from the date of first documented response (which is subsequently confirmed) until date of

Objective	Estimand [a] Description/Endpoint
	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 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	CCI [redacted] 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]	

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 CCI ; CCI ; FAS = full analysis set; CCI ; CCI ; HPV = human papillomavirus; HRQoL = health-related quality of life; ICI = immune checkpoint inhibitor; NK = natural killer; OPC = oropharyngeal cancer; ORR = objective response rate; OS = overall survival; CCI ; 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 .

1.2 Study 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 832 participants will be screened at up to approximately 190 sites to achieve approximately 624 eligible participants who will be randomized in a 2:1 ratio to one of the following treatment groups:

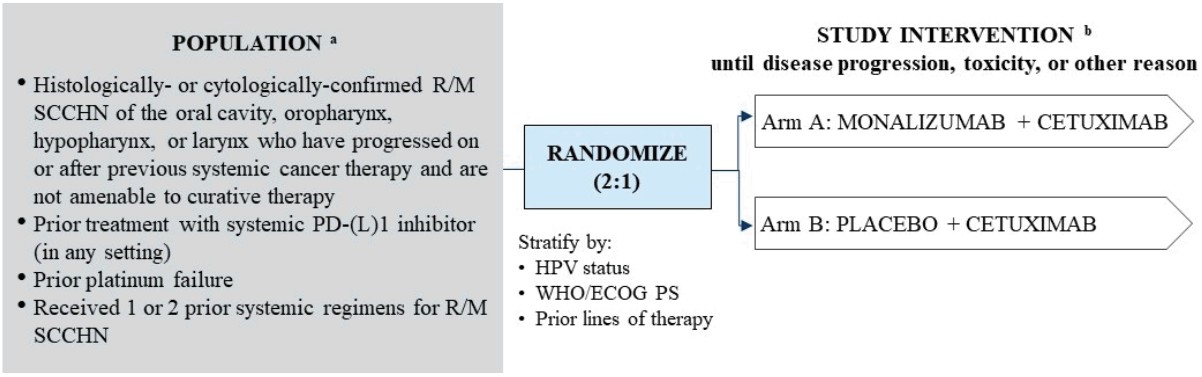
- Arm A (n = 416): monalizumab and cetuximab
  Monalizumab CCI and cetuximab CCI initial dose followed by CCI, as per label
- Arm B (n = 208): placebo and cetuximab
  Placebo iv Q2W and cetuximab CCI initial dose followed by CCI, as per label

Randomization will be stratified by the following:

- 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% (ie, ≤ 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.

Randomized patients 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 overview of the study design is shown in Figure 1 Study Design



[b] 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.

[c] CCI [redacted]

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; CCI [redacted]; R/M = recurrent/metastatic; SCCHN = squamous cell carcinoma of the head and neck.

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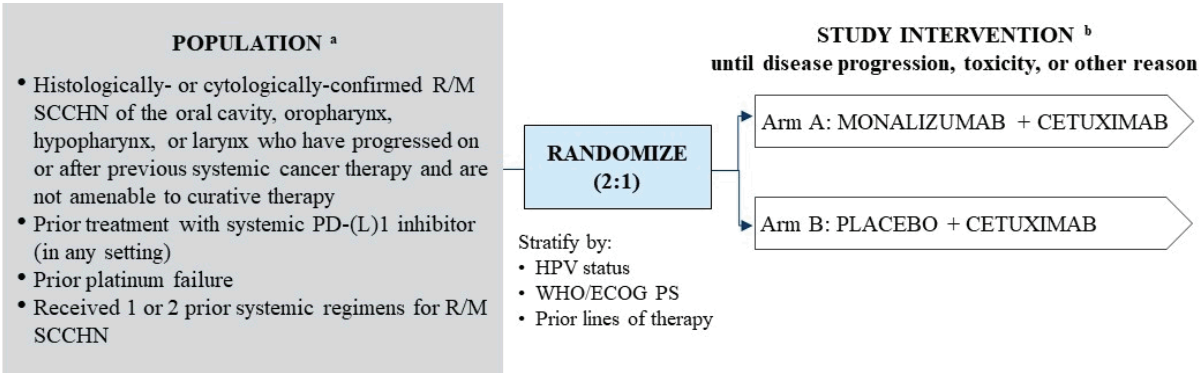
Figure 1 Study Design



[d] 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.

[e] CCI [redacted]

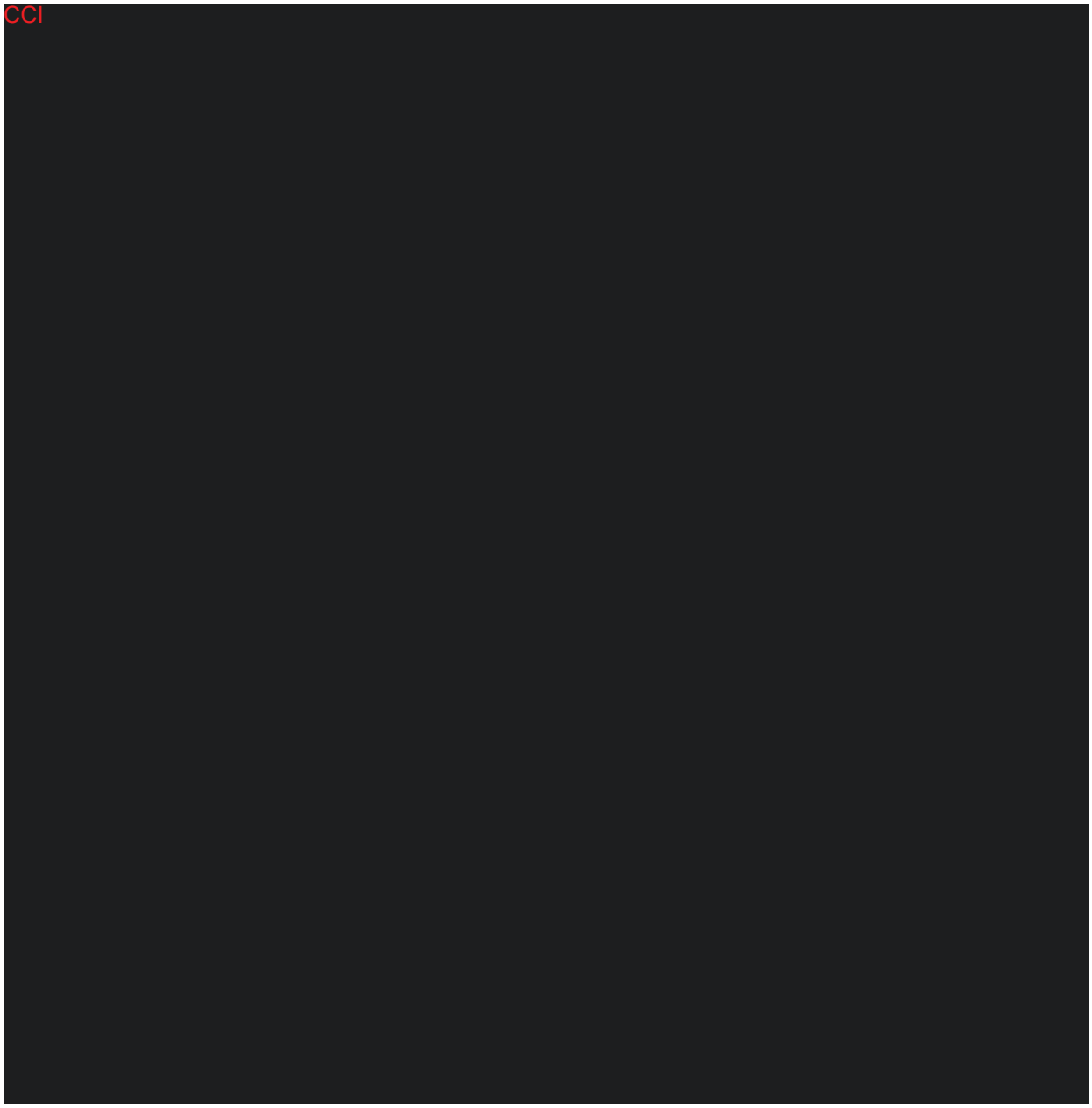
WHO/ECOG PS = World Health Organization/Eastern Cooperative Oncology Group performance status; iv = intravenous; HPV = human papillomavirus; LA = locally advanced; PD-(L)1 = programmed cell death-1 or programmed cell death ligand-1; CCI [redacted]; R/M = recurrent/metastatic; SCCHN = squamous cell carcinoma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

1.3 Number of subjects

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.

CCI [redacted]



2 ANALYSIS SETS

2.1 Definition of analysis sets

There are four analysis sets defined for this study. Definitions of the analysis sets for each outcome variable are provided in Table 2.

Table 2: Summary of outcome variables and analysis populations

Outcome variable	Analysis set
Efficacy Data	
OS	HPV-unrelated Analysis Set and Full analysis set
PFS	HPV-unrelated Analysis Set and Full analysis set
ORR[a], DoR[a] endpoints	HPV-unrelated Analysis Set and Full analysis set
CCI	HPV-unrelated Analysis Set and Full analysis set
PRO Data	
PRO data[b]	HPV-unrelated Analysis Set and Full analysis set
Study Population /Demography Data	
Demography characteristics	HPV-unrelated Analysis Set and Full analysis set
Baseline and disease characteristics	HPV-unrelated Analysis Set and Full analysis set
Important deviations	HPV-unrelated Analysis Set and Full analysis set
Medical/surgical history	HPV-unrelated Analysis Set and Full analysis set
Concomitant medications/procedures	HPV-unrelated Analysis Set and Full analysis set
Biomarker Data	
Biomarker data	HPV-unrelated Analysis Set and Full analysis set
PK Data	
PK data	PK analysis set
Safety Data	
Exposure	Safety analysis set
AEs and SAEs	Safety analysis set
Deaths	Full analysis set
Laboratory measurements	Safety analysis set
Physical examinations and vital signs	Safety analysis set
ECGs	Safety analysis set
WHO/ECOG PS	Safety analysis set
ADA data	ADA analysis set

[a]Subjects who are evaluable for the analysis of ORR are those with measurable disease at baseline. Subjects who are evaluable for the analysis of DoR are those who has a confirmed response in the ORR analysis.
[b] For EORTC QLQ-C30, the population for the analysis of time to global health status/QoL or function deterioration will include a subset of the FAS who have baseline scores of ≥10; The population for the analysis of time to symptom deterioration will include a subset of the FAS who have baseline scores of ≤90. For QLQ-H&N35, the population for the analysis of time to symptom deterioration will include a subset of who have baseline scores ≤90.
AE Adverse event; DoR Duration of response; ECOG Eastern Cooperative Oncology Group; ORR Objective response rate; OS Overall survival; PS Performance status; PFS Progression free survival; PK Pharmacokinetics; PRO Patient reported outcome.

2.1.1 HPV-unrelated analysis set

The primary population is the HPV-unrelated Analysis Set, which will include all randomized subjects 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 and all efficacy analysis including patient reported outcomes (PROs). Treatment arms will be

compared on the basis of randomized study treatment, regardless of the treatment actually received. Subjects who were randomized but did not subsequently go on to receive study treatment are included in the analysis in the treatment arm to which they were randomized.

Analysis of ORR will be based on patients in the HPV-unrelated Analysis Set who have measurable disease at baseline (refer to Section 3.2.3). Analysis of DoR will be based on subjects in the HPV-unrelated Analysis Set who achieve objective response (refer to Section 3.2.4).

2.1.2 Full Analysis Set (Intention to treat (ITT))

The FAS will include all randomized participants. The FAS will be used for all efficacy endpoints 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. The analysis of data using the FAS therefore follows the principles of ITT.

2.1.3 Safety analysis set

The safety analysis set (SAF) will consist of all subjects who received any amount of study treatment. Safety data will be summarized descriptively using the SAF, according to the treatment received. Erroneously treated subjects (e.g., those randomized to Arm A but actually given Arm B intervention) will be summarized according to the treatment they actually received.

2.1.4 Pharmacokinetics analysis set

The pharmacokinetics (PK) analysis set includes all subjects who receive at least one dose of monalizumab 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 analysis. The population will be defined by the study clinical lead, Pharmacokineticist, and Statistician prior to any PK analysis being performed. The PK analysis set will be summarized according to the treatment actually received.

2.1.5 ADA analysis set

The ADA analysis set will include all subjects who have non-missing baseline ADA of monalizumab and at least 1 non-missing post-baseline monalizumab ADA results. All major ADA analysis will be based on the ADA analysis set.

2.2 Protocol deviations

For this study, the following general categories will be considered important protocol deviations (IPDs) and most of them (programmable IPDs) will be programmatically derived from the electronic case report form (eCRF) data. Few observable IPDs may only be identified by site monitoring activities as the data is not captured in any clinical data base. These will be listed and summarized by randomized treatment group and discussed in the clinical study report (CSR) as appropriate:

- Subjects who deviate from key inclusion criteria per the Clinical Study Protocol (CSP) (Deviation 1).

  - **Inclusion 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

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

  - **Inclusion 4**: Prior platinum failure as defined by either:

    a) Disease progression during or after treatment with a platinum-containing regimen for R/M disease or

    b) Recurrence/progression within 6 months of the last dose of platinum as part of multimodal therapy for locally advanced (LA) disease

  - **Inclusion 5**: Received 1 or 2 prior systemic regimens for R/M SCCHN

  - **Inclusion 6**: At least one lesion that qualifies as a RECIST 1.1 TL at baseline. Tumor assessment by CT scan or MRI must be performed within 28 days prior to randomization.

  - **Inclusion 8**: For participants with OPC only: known HPV status prior to randomization

  - **Inclusion 9**: WHO/ECOG PS of 0 or 1 at enrollment

  - **Inclusion 14**: Negative pregnancy test (“highly effective” urine or serum test) for female participants of childbearing potential.

- **Inclusion 19**: Provision of signed and dated, written ICF prior to any mandatory study specific procedures, sampling, and analysis

- Subjects who deviate from key exclusion criteria per the Clinical Study Protocol (CSP) (Deviation 2).

  - **Exclusion 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)

  - **Exclusion 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)

  - **Exclusion 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

  - **Exclusion 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

  - **Exclusion 8**: History of active primary immunodeficiency

  - **Exclusion 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:

    a) Participants with vitiligo or alopecia

    b) Participants with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement

    c) Any chronic skin condition that does not require systemic therapy

    d) Participants without active disease in the last 5 years may be included but only after consultation with the Medical Monitor

e) Participants with celiac disease controlled by diet alone

- **Exclusion 13**: Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥ 500 ms calculated from 3 ECGs (within 15 minutes at 5 minutes apart)

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

- **Exclusion 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.

- **Exclusion 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:

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

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

  c) Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)

- **Exclusion 17**: Receipt of live attenuated vaccine within 30 days prior to the first dose of study intervention.

- **Exclusion 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

- **Exclusion 19**: Prior treatment with monalizumab

- **Exclusion 22**: Previous study intervention assignment in the present study

  - **Exclusion 23**: For women only - currently pregnant (confirmed with positive pregnancy test) or breastfeeding

- Discontinuation Criteria for study product met but patient not withdrawn from study treatment (Deviation 3).
  - RECIST 1.1-defined radiological disease progression
  - Any AE that meets criteria for discontinuation defined in the guidelines for management of IMP-related toxicities for monalizumab/ placebo or as defined in the local label (where available) for cetuximab
  - Investigator determination that the participant is no longer benefiting from study intervention
  - For females of childbearing potential, pregnancy or intent to become pregnant
  - Initiation of subsequent anticancer therapy, including another investigational agent
- Investigational Product (IP) Deviation (Deviation 5).
  - Subject received incorrect IP to that to which they were randomised (including incorrect kit ID# dispensed/administered)
  - Subjects who were randomised but did not receive IP
  - Subject received overdose of IP
  - IP non-compliance (as per study specific definition, i.e. underdose, missed dose)
  - Use of expired IP
- Excluded Medications taken (Deviation 6).
  - Received concomitant medication defined as prohibited as in the CSP
- Deviations related to study procedure (Deviation 7).
  - Pregnancy tests not conducted for WoCBP
  - RECIST 1.1 assessment not performed at baseline (within 28 days before start of study intervention)

- Other important deviations (Deviation 8):
  - Unblinding of treatment (IP and dose preparation/ dispensation by blinded team member)
  - Patients who were incorrectly stratified at randomization.

Subjects who receive the wrong treatment at any time will be included in the SAF as described in Section 2.1.3. During the study, decisions on how to handle errors in treatment dispensing (with regard to continuation/discontinuation of study treatment or, if applicable, analytically) will be made on an individual basis with written instruction from the study physician and/or statistician.

The important protocol deviations will be listed and summarized by randomized treatment group. Only deviation "Subjects who were randomized but did not receive IP" (subcategory of Deviation 5) will lead to exclusion from the safety analysis set. None of the other deviations will lead to subjects being excluded from the analysis sets described in Section 2.1 (with the exception of the PK analysis set, if the deviation is considered to impact upon PK).

A per-protocol analysis excluding patients with specific important protocol deviations is not planned; however, a 'deviation bias' sensitivity analysis may be performed on the progression free survival endpoint excluding patients with important protocol deviations that may affect the efficacy of the trial therapy if >10% of patients in either treatment group:

- Did not have the intended disease or indication or
- Did not receive any randomized therapy.

The need for such a sensitivity analysis will be determined following review of the protocol deviations ahead of database lock and will be documented prior to the primary analysis being conducted.

In addition to the programmatic determination of the deviations above, other study deviations captured from the case report form (CRF) module for inclusion/exclusion criteria will be tabulated and listed. Any other deviations from monitoring notes or reports will be reported in an appendix to the CSR.

3 PRIMARY AND SECONDARY VARIABLES

3.1 Derivation of RECIST visit responses

The analysis of the RECIST 1.1 based secondary endpoints, PFS, ORR, DoR, BoR, will be based on site investigator assessments using RECIST 1.1. CCI [redacted]

For all subjects, the investigator-assessed RECIST tumor response data will be used to determine each subject's visit response according to RECIST version 1.1 (Appendix G of CSP). It will also be used to determine if and when a subject has progressed in accordance with RECIST and their best objective response (BoR) to study treatment.

Baseline radiological tumor assessments are to be performed no more than 28 days before the start of randomized treatment and ideally as close as possible to the start of study treatment. Tumor assessments are then performed every 8 weeks (± 1 week) for first 48 weeks after the randomization then every 12 weeks (± 1 week) thereafter (relative to date of randomization) until RECIST 1.1 defined radiological disease progression plus at least 1 additional follow-up scan.

If an unscheduled assessment is performed, and the subject has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some subjects being assessed at a different frequency than other subjects.

From the investigator's review of the imaging scans, the RECIST tumor response data will be used to determine each subject's visit response according to RECIST version 1.1. At each visit, subjects will be assigned a RECIST 1.1 visit response of complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD), using the information from target lesions (TLs), non-target lesions (NTLs) and new lesions and depending on the status of their disease compared with baseline and previous assessments. If a subject has had a tumor assessment that cannot be evaluated then the subject will be assigned a visit response of not evaluable (NE), (unless there is evidence of progression in which case the response will be assigned as PD).

Refer to Section 3.1.1 for the definitions of CR, PR, SD and PD.

3.1.1 Target lesions (TLs)

Measurable disease is defined as having at least one measurable lesion, not previously irradiated, which is ≥ 10 mm in the longest diameter (LD), (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging

(MRI) and which is suitable for accurate repeated measurements. A subject can have a maximum of five measurable lesions recorded at baseline with a maximum of two lesions per organ (representative of all lesions involved and suitable for accurate repeated measurement) and these are referred to as target lesions (TLs). If more than one baseline scan is recorded, then measurements from the one that is closest and prior to randomization will be used to define the baseline sum of TLs. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement. In which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

All other lesions (or sites of disease) not recorded as TL should be identified as non-target lesions (NTLs) at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits.

TL visit responses are described in Table 3 below.

Table 3: TL visit responses (RECIST 1.1)

Visit Responses	Description
Complete response (CR)	Disappearance of all TLs. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10mm.
Partial response (PR)	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters as long as criteria for PD are not met.
Progressive disease (PD)	A ≥20% increase in the sum of diameters of TLs and an absolute increase of ≥ 5mm, taking as reference the smallest sum of diameters since treatment started including the baseline sum of diameters.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Not evaluable (NE)	Only relevant in certain situations (i.e. if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit; and scaling up could not be performed for lesions with interventions). Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response.
Not applicable (NA)	No TLs are recorded at baseline.

Rounding of TL data

For calculation of PD and PR for TLs percentage changes from baseline and previous minimum should be rounded to one decimal place (d.p.) before assigning a TL response. For example, 19.95% should be rounded to 20.0% but 19.94% should be rounded to 19.9%.

Missing TL data

For a visit to be evaluable, all TL measurements should be recorded. However, a visit response of PD should still be assigned if any of the following occurred:

- A new lesion is recorded.
- A NTL visit overall response of PD is recorded.
- The sum of TLs is sufficiently increased to result in a 20% increase, and an absolute increase of ≥ 5mm, from nadir even assuming the non-recorded TLs have disappeared.

Note: the nadir can only be taken from assessments where all the TLs had a LD recorded.

If there is at least one TL measurement missing and a visit response of PD cannot be assigned, the visit response is NE.

If all TL measurements are missing, then the TL visit response is NE. Overall visit response will also be NE, unless there is a progression of non-TLs or new lesions, in which case the response will be PD.

Lymph nodes

For lymph nodes, if the size reduces to <10mm then these are considered non-pathological. However, a size will still be given, and this size should still be used to determine the TL visit response as normal. In the special case where all lymph nodes are <10mm and all other TLs are 0mm then although the sum may be >0mm the calculation of TL response should be over-written as a CR.

TL visit responses subsequent to CR

Only CR, PD or NE can follow a CR. If a CR has occurred, then the following rules at the subsequent visits must be applied:

- Step 1: If all lesions meet the CR criteria (i.e. 0mm or <10mm for lymph nodes) then response will be set to CR irrespective of whether the criteria for PD of TL is also met i.e. if a lymph node LD increases by 20% but remains <10mm.

- Step 2: If some lesion measurements are missing but all other lesions meet the CR criteria (i.e. 0mm or <10mm for lymph nodes) then response will be set to NE irrespective of whether, when referencing the sum of TL diameters, the criteria for PD are also met.

- Step 3: If not all lesions meet the CR criteria (i.e. a pathological lymph node selected as TL has short axis >10mm and an absolute increase of ≥5mm, taking as reference the smallest short axis for the same TL since treatment started including the baseline or the reappearance of previously disappeared lesion) or a new lesion appears, then response will be set to PD.

- Step 4: If after steps 1 – 3 a response can still not be determined the response will be set to remain as CR.

TL too big to measure

If a TL becomes too big to measure this should be indicated in the database and a size ('*x*') above which it cannot be accurately measured should be recorded. If using a value of *x* in the calculation of TL response would not give an overall visit response of PD, then this will be flagged and reviewed by the study team blinded to treatment assignment. It is expected that a visit response of PD will remain in the vast majority of cases.

TL too small to measure

If a TL becomes too small to measure, then this will be indicated as such on the case report form and a value of 5mm will be entered into the database and used in TL calculations. However, a smaller value may be used if the radiologist has not indicated 'too small to measure' on the case report form and has entered a smaller value that can be reliably measured. If a TL response of PD results (at a subsequent visit) then this will be reviewed by the study team blinded to treatment assignment.

Irradiated lesions/lesion intervention

Previously irradiated lesions (i.e. lesion irradiated prior to entry into the study) should be recorded as NTLs and should not form part of the TL assessment.

Any TL (including lymph nodes), which has had intervention during the study (for example, irradiation / palliative surgery / embolization), should be handled in the following way. Once a lesion has had intervention then it should be treated as having intervention for the remainder of the study noting that an intervention will most likely shrink the size of tumors:

- Step 1: the diameters of the TLs (including the lesions that have had intervention) will be summed and the calculation will be performed in the usual manner. If the visit response is PD, this will remain as a valid response category.

- Step 2: If there was no evidence of progression after step 1, treat the lesion diameter (for those lesions with intervention) as missing and if ≤1/3 of the TLs have missing measurements then scale up as described in the 'Scaling' section below. If the scaling results in a visit response of PD then the subject would be assigned a TL response of PD.

- Step 3: If, after both steps, PD has not been assigned, then, if appropriate (i.e. if ≤ 1/3 of the TLs have missing measurements), the scaled sum of diameters calculated in step 2 should be used, and PR or SD then assigned as the visit response. Subjects with intervention are evaluable for CR as long as all non-intervened lesions are 0 (or <10mm for lymph nodes) and the lesions that have been subject to intervention have a value of 0 (or <10mm for lymph nodes) recorded. If scaling up is not appropriate due to too few non-missing measurements, then the visit response will be set as NE.

At subsequent visits, the above steps will be repeated to determine the TL and overall visit response. When calculating the previous minimum, lesions with intervention should be treated as missing and scaled up (as per step 2 above).

Scaling (applicable only for irradiated lesions/lesion intervention)

If >1/3 of TL measurements are missing (because of intervention) then the TL response will be NE, unless the sum of diameters of non-missing TL would result in PD (i.e. if using a value of 0 for missing lesions, the sum of diameters has still increased by 20% or more compared to nadir and the sum of TLs has increased by ≥5mm from nadir).

If ≤1/3 of the TL measurements are missing (because of intervention) then the results will be scaled up (based on the sizes at the nadir visit to give an estimated sum of diameters) and this will be used in calculations; this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the nadir sum of diameters excluding the lesions with missing measurements.

Example of scaling

Lesion 5 is missing at the follow-up visit; the nadir TL sum including lesions 1-5 was 74mm.

The sum of lesions 1-4 at the follow-up is 68mm. The sum of the corresponding lesions at the nadir visit is 62mm.

Scale up as follows to give an estimated TL sum of 81mm:

68 x 74 / 62 = 81mm

CR will not be allowed as a TL response for visits where there is missing data. Only PR, SD or PD (or NE) could be assigned as the TL visit response in these cases. However, for visits

with ≤1/3 lesion assessments not recorded, the scaled-up sum of TLs diameters will be included when defining the nadir value for the assessment of progression.

Lesions that split in two

If a TL splits in two, then the LDs of the split lesions should be summed and reported as the LD for the lesion that split.

Lesions that merge

If two TLs merge, then the LD of the merged lesion should be recorded for one of the TL sizes and the other TL size should be recorded as 0cm.

Change in method of assessment of TLs

CT and MRI are the only methods of assessment that can be used within this trial. If a change in method of assessment occurs, between CT and MRI this will be considered acceptable and no adjustment within the programming is needed.

3.1.2 Non-target lesions (NTLs) and new lesions

At each visit, the investigator should record an overall assessment of the NTL response. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

NTL response will be derived based on the investigator's overall assessment of NTLs as shown in Table 4:

Table 4: NTL visit responses

Visit Responses	Description
Complete response (CR)	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10 mm short axis).
Progressive disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases, the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Non-CR/Non-PD	Persistence of one or more NTLs with no evidence of progression.

Visit Responses	Description
Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For subjects without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
Not applicable (NA)	Only relevant if there are no NTLs at baseline.

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

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

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

The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor.

New lesions will be identified via a Yes/No tick box. The absence and presence of new lesions at each visit should be listed alongside the TL and NTL visit responses.

A new lesion indicates progression so the overall visit response will be PD irrespective of the TL and NTL response.

Symptomatic progression is not a descriptor for progression of NTLs: it is a reason for stopping study therapy and will not be included in any assessment of NTLs.

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

3.1.3 Overall RECIST 1.1 visit response

Table 5 defines how the previously defined TL and NTL visit responses will be combined with new lesion information to give an overall visit response.

Table 5: Overall visit responses

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

CR Complete response; NA Not Applicable; NE Not evaluable; PD Progressive disease; PR Partial response; SD Stable disease; NED No evidence of disease

3.2 Primary and secondary efficacy variables

3.2.1 Overall survival (OS)

The primary endpoint of the trial is overall survival defined as time from the date of randomization until death due to any cause regardless of whether the subject withdraws from randomized therapy or receives another anti-cancer therapy (i.e. date of death or censoring – date of randomization + 1). Any subject not known to have died at the time of analysis will be censored based on the last recorded date on which the subject was known to be alive (SUR_DAT, recorded within the SURVIVE module of the eCRF).

Note: Survival calls will be made following the date of DCO for the IA or FA (these contacts should generally occur within 7 days of the DCO). If subjects are confirmed to be alive or if the death date is post the DCO date, these subjects will be censored at the date of DCO. The status of ongoing, withdrawn (from the study) and "lost to follow-up" subjects at the time of the final OS analysis should be obtained by the site personnel by checking the subject's notes, hospital records, contacting the subject's general practitioner and checking publicly-available death registries. In the event that the subject has actively withdrawn consent to the processing of their personal data, the vital status of the subject can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

If a subject is known to have died where only a partial death date is available, then the date of death will be imputed as the latest of the last date known to be alive + 1 from the database and the death date using the available information provided:

a. For Missing day only – using the 1st of the month

b. For Missing day and Month – using the 1st of January

If there is evidence of death but the date is entirely missing, it will be treated as missing, i.e. censored at the last known alive date.

3.2.2 Progression free survival (PFS)

The secondary endpoint PFS (per RECIST 1.1 as assessed by the site Investigator) will be defined as the time from the date of randomization until the date of RECIST 1.1-defined radiological PD or death (by any cause in the absence of progression) regardless of whether the subject withdraws from therapy or receives another anticancer therapy prior to progression (i.e., date of PFS event or censoring – date of randomization + 1). Subjects 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 subject progresses or dies after 2 or more missed visits, the subject will be censored at the time of the

latest evaluable RECIST 1.1 assessment prior to the 2 missed visits (Note: NE visit is not considered as missed visit).

Given the scheduled visit assessment scheme (i.e. eight-weekly for the first 48 weeks then twelve-weekly thereafter) the definition of 2 missed visits will change. If the previous RECIST assessment is less than study day 274 (i.e. week 39) then two missing visits will equate to 18 weeks since the previous RECIST assessment, allowing for early and late visits (i.e. 2 x 8 weeks + 1 week for an early assessment + 1 week for a late assessment = 18 weeks). If the two missed visits occur over the period when the scheduled frequency of RECIST assessments changes from eight-weekly to twelve-weekly this will equate to 22 weeks (i.e. take the average of 8 and 12 weeks which gives 10 weeks and then apply same rationale, hence 2 x 10 weeks + 1 week for an early assessment + 1 week for a late assessment = 22 weeks). The time period for the previous RECIST assessment will be from study days 274 to 329 (i.e. week 39 to week 47). From week 47 onwards (when the scheduling changes to twelve-weekly assessments), two missing visits will equate to 26 weeks (i.e. 2 x 12 weeks + 1 week for an early assessment + 1 week for a late assessment = 26 weeks). The following is also summarized in the table:

Scheduled Assessment	**Previous RECIST assessment**	**Two missed RECIST visits window**
Q8W	No evaluable RECIST visits or no baseline RECIST scan	2 x 8 weeks + 1 week = 17 weeks (119 days)
Q8W	Day 1	2 x 8 weeks + 1 week = 17 weeks (119 days)
Q8W up to Week 48	>Day 1 – Day 273 (up to Week 39)	2 x 8 weeks + 2 weeks = 18 weeks (126 days)
	>Day 273 – Day 329 (Week 39 – Week 47) (change period from Q8W to Q12W)	2 x [(8 weeks+12 weeks)/2] + 2 weeks = 22 weeks (154 days)
Q12W thereafter	>Day 329 onwards	2 x 12 weeks + 2 weeks

If the patient has no evaluable visits or does not have baseline data they will be censored at Day 1 unless they die within two visits of baseline (16 weeks plus 1 week allowing for a late assessment within the visit window).
The PFS time will always be derived based on scan/assessment dates not visit dates.

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

- When a subject experienced a disease progression , 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 subject for PFS, the subject will be censored at the latest of the scan dates contributing to a particular overall visit assessment.

Note: for TLs only the latest scan date is recorded out of all scans performed at that assessment for the TLs and similarly for NTLs only the latest scan date is recorded out of all scans performed at that assessment for the NTLs.

3.2.3 Objective response rate (ORR)

The secondary endpoint ORR is defined as the percentage of subjects with a confirmed investigator-assessed response of CR or PR and will be based on a subset of all randomized subjects with measurable disease at baseline per the site investigator.

A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who discontinue treatment without progression, receive a subsequent anti-cancer therapy (note that for this analysis palliative radiotherapy is not considered a subsequent anti-cancer therapy) and then respond will not be included as responders in the ORR (i.e. both visits contributing to a response must be prior to subsequent therapy for the patient to be considered as a responder).

In the case where a patient has two non-consecutive visit responses of PR, then, as long as the time between the 2 visits of PR is greater than 4 weeks and there is no PD between the PR visits, the patient will be defined as a responder. Similarly, if a patient has visit responses of CR, NE, CR, then, as long as the time between the 2 visits of CR is greater than 4 weeks, then a best response of CR will be assigned.

A subject will be classified as a responder if the RECIST criteria for a confirmed CR or PR, are satisfied at any time following randomization prior to RECIST progression, and prior to starting any subsequent cancer therapy. Subjects who discontinue randomized treatment

without progression, receive a subsequent anti-cancer therapy, and then respond will not be included as responders in the ORR.

3.2.4 Duration of response (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 (which is subsequently confirmed) until date of documented progression or death in the absence of disease progression (i.e. date of PFS event or censoring – date of first response + 1). The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR that was subsequently confirmed.

If a subject does not progress following a response, then their DoR will use the PFS censoring time.

Time to response will be also calculated. Time to response is defined as the time from the date of randomization until the date of first documented response. The date of first documented response should coincide with that used for the DoR endpoint.

3.2.5 Best objective response (BoR)

Best objective response (BoR) is calculated based on the overall visit responses from each tumor assessment, described in Section 3.1.3. It is the best response a subject has had following randomization, but prior to starting any subsequent cancer therapy and up to and including RECIST progression or the last evaluable assessment in the absence of RECIST progression. Categorization of BoR will be based on RECIST using the following response categories: CR, PR, SD, PD and NE.

CR or PR must be confirmed. For determination of a best response of SD, the earliest of the dates contributing towards a particular overall visit assessment will be used. SD should be recorded at least 8 weeks minus 1 week, i.e. at least 49 days (to allow for an early assessment within the assessment window), after randomization. For CR/PR, the initial overall visit assessment that showed a response will use the latest of the dates contributing towards a particular overall visit assessment.

BoR will be determined programmatically based on RECIST from the overall visit response using all site investigator data up until the first progression event. The denominators for each case will be consistent with those used in the ORR analysis.

For subjects whose progression event is death, BoR will be calculated based upon all evaluable RECIST assessments prior to death.

For subjects who die with no evaluable RECIST assessments, if the death occurs ≤ 17 weeks (i.e. 16 weeks + 1 week to allow for a late assessment within the assessment window) after randomization, then BoR will be assigned to the progression (PD) category. For subjects who die with no evaluable RECIST assessments, if the death occurs >17 weeks after randomization then BoR will be assigned to the NE category.

3.3 CCI

3.3.1 CCI

CCI

3.3.2 CCI

CCI

3.3.1 CCI

CCI

3.4 Patient reported outcome (PRO) variables

The following PRO questionnaires will be used to assess the patient experience, including global health status/health-related quality of life (HRQoL), functioning and symptoms: EORTC QLQ-C30 with the EORTC QLQ-H&N35 disease specific module, CCI [redacted]. Among them, EORTC QLQ-C30 with the EORTC QLQ-H&N35 disease specific variables are the secondary endpoints and CCI [redacted]. All items/questionnaires will be scored according to published guidelines or the developer's guidelines, if published guidelines are not available as described in the sections below. All PRO analysis will be based on the FAS, unless stated otherwise.

3.4.1 EORTC QLQ-C30

The EORTC QLQ-C30 consists of 30 questions that can be combined to produce 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), and global health status/QoL scale. 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.

Definition of clinically meaningful changes

A clinically meaningful change is defined as an absolute change in the score from baseline of ≥10 for scales from the EORTC QLQ-C30 (Osoba et al. 1998). For example, a clinically meaningful improvement in physical function (as assessed by EORTC QLQ-C30) is defined as an increase in the score from baseline of ≥10, whereas a clinically meaningful deterioration is defined as a decrease in the score from baseline of ≥10. At each post-baseline assessment, the change in global health status/QoL, symptoms, and functioning score from baseline will be categorized as improvement, no change, or deterioration as shown in Table 6.

Table 6: Mean change and clinically meaningful change - EORTC QLQ-C30

Score	Change from baseline	Visit response
EORTC QLQ-C30 global health status/QoL & functional scale scores	Increase of at least 10	Improvement
	Decrease of at least 10	Deterioration
	Otherwise	No change
EORTC QLQ-C30 symptom score	Increase of at least 10	Deterioration
	Decrease of at least 10	Improvement
	Otherwise	No change

EORTC European Organisation for Research and Treatment of Cancer; QLQ-C30 30-Item Core Quality of Life Questionnaire.

Time to HRQoL or function deterioration

Time to QoL or function deterioration will be defined as the time from the date of randomization until the date of the first clinically meaningful deterioration (as defined in Table 6) that is confirmed at a subsequent visit (except if it was the subject's last available assessment) or death (by any cause) in the absence of a clinically meaningful deterioration, regardless of whether the subject discontinues the study treatment(s) or receives another anticancer therapy prior to global health status/QoL or function deterioration. Death will be included as an event only if it occurs within 2 PRO assessment visits from the last available PRO assessment.

Subjects whose global health status/QoL or function (as measured by EORTC QLQ-C30) have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment, where the global health status/QoL or function could be evaluated. Also, if global health status/QoL or function deteriorates or the subject dies after 2 or more missed PRO assessment visits, the subject will be censored at the time of the last PRO assessment, where global health status/QoL or function could be evaluated prior to the 2 missed visits.

The population for the analysis of time to global health status/QoL or function deterioration will include a subset of the FAS who have baseline scores of ≥10.

Time to symptom deterioration

For each of the symptom scales in the EORTC QLQ-C30, time to symptom deterioration will be defined as the time from randomization until the date of the first clinically meaningful symptom deterioration (an increase in the score from baseline of ≥10) or death (by any cause) in the absence of a clinically meaningful symptom deterioration, regardless of whether the patient withdraws from study treatment or receives another anticancer therapy prior to symptom deterioration.

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

The population for the analysis of time to symptom deterioration will include a subset of the FAS who have baseline scores of ≤90.

3.4.2 EORTC QLQ-H&N35

The QLQ-H&N35 is a H&N-specific module from the EORTC comprising 35 questions to assess H&N symptoms. QLQ-H&N35 will be scored as described in Section 8 Appendix 1 EORTC QLQ – H&N 35 Scoring Procedure. The module includes 7 multi-item domain scales and 11 single-item scales. For all items and scales, high scores indicate increased symptomatology/more problems.

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

Definition of clinically meaningful change

A clinically meaningful change is defined as an absolute change in the score from baseline of ≥10 for scales/items from QLQ-H&N35. For example, a clinically meaningful deterioration or worsening in dry mouth (as assessed by QLQ-H&N35) is defined as an increase in the score from baseline of ≥10. At each post-baseline assessment, the change in symptom score from baseline will be categorized as improved, no change, or deterioration, as shown in Table 7.

Table 7: Mean change and clinically meaningful change - EORTC QLQ-H&N35

Score	Change from baseline	Visit response
QLQ-H&N35 symptom scales and items	Increase of at least 10	Deterioration
	Decrease of at least 10	Improved
	Otherwise	No change

EORTC European Organisation for Research and Treatment of Cancer; QLQ-H&N35 35-Item Head&Neck Cancer Quality of Life Questionnaire.

Time to symptom deterioration

For each of the symptom scales/items in the QLQ-H&N35, time to symptom deterioration will be defined as the time from randomization until the date of the first clinically meaningful symptom deterioration that is confirmed at a subsequent visit (except if it was the subject's last available assessment) or death (by any cause) in the absence of a clinically meaningful symptom deterioration, regardless of whether the subject discontinues the study treatment(s) or receives another anticancer therapy prior to symptom deterioration. Only deaths occurring within 2 PRO assessment visits from the last available PRO assessment will be included as events.

Subjects whose symptoms (as measured by the QLQ-H&N35) have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment, where the symptom could be evaluated. Also, if symptoms progress or the subject dies after 2 or more missed PRO assessment visits, the subject will be censored at the time of the last PRO assessment, where the symptom could be evaluated prior to the 2 missed visits.

The population for the analysis of time to symptom deterioration will include a subset of the FAS who have baseline scores ≤90.

3.4.3

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3.4.4

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3.4.5 CCI

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3.4.6 Compliance

Summary measures of compliance over time will be derived for all PRO questionnaires. These will be based upon:

- Received questionnaire: A questionnaire that has been received and has a completion date and at least one individual item completed.

- Expected questionnaire: A questionnaire that is expected to be completed at a scheduled assessment time e.g., a questionnaire from a subject who has not withdrawn from the study at the scheduled assessment time but excluding subjects in countries with no available translation. For subjects that have progressed, the latest of progression and

safety follow-up will be used to assess whether the subject is still under PRO follow-up at the specified assessment time. Date of study discontinuation will be mapped to the nearest visit date to define the number of expected forms.

- Evaluable questionnaire: A questionnaire with a completion date and at least one subscale that is non-missing.

Compliance over time will be calculated separately for each visit, including baseline, as the number of subjects with an evaluable questionnaire at the time point (as defined above), divided by number of subjects still expected to complete questionnaires. Similarly, the evaluability rate over time will be calculated separately for each visit, including baseline, as the number of evaluable questionnaires (per definition above), divided by the number of received questionnaires.

3.5 CCI

3.6 Safety variables

Safety and tolerability will be assessed in terms of adverse events (AEs) [including serious adverse events (SAEs)], deaths, physical examinations, laboratory findings, WHO/ECOG PS, vital signs, electrocardiograms (ECGs) and exposure, which will be collected for all subjects.

Data from all cycles of treatment will be combined in the presentation of safety. The SAF will be used for reporting of safety data, apart from deaths which should be reported for FAS.

3.6.1 Exposure and dose delay/interruptions

Participants in Arm A will receive monalizumab [redacted] and cetuximab [redacted] initial dose followed by [redacted]. Participants in Arm B will receive placebo Q2W and cetuximab [redacted] initial dose followed by [redacted].

Participants in Arm A or Arm B will remain on study intervention until RECIST 1.1-defined radiological disease progression unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

Calculation of exposure (i.e. duration of treatment) for monalizumab or placebo will be defined as follows:

- Total (or intended) exposure (months) of monalizumab or placebo: = (min(last monalizumab/placebo dose date where dose > 0 + 13, date of death, date of DCO) – first monalizumab/placebo dose date +1) /(365.25/12)

Actual exposure of monalizumab or placebo:

- Actual exposure = intended exposure – total duration of dose delay/interruption, where intended exposure will be calculated as above, and a dose delay/interruption is defined as any length of time where the subject has not taken any of the planned dose.

As monalizumab or placebo are dosed Q2W (+/- 2 days), duration of dose delay/interruption will be defined as follows:

- Duration of monalizumab/placebo dose delay/interruption = Sum of (Date of the monalizumab /placebo dose - Date of previous monalizumab/placebo dose –16 days) / (365.25/12)
  If the calculation of the duration of dose delay/interruption results in a negative value because of out of scheduled subsequent doses, the duration of dose delay/interruption will be set to ‘0’.

Dose reductions are not permitted per CSP for monalizumab (or placebo). The actual exposure calculation makes no adjustment for any dose reductions that may have occurred.

Exposure to cetuximab will be defined as follows:

Calculation of exposure for cetuximab will be defined as follows:

- Total (or intended) exposure (months) of cetuximab: = (min(last cetuximab dose date where dose > 0 + 6, date of death, date of DCO) – first cetuximab dose date +1) /(365.25/12).
- Actual exposure of cetuximab= intended cetuximab exposure – total duration of cetuximab dose delay/interruption, where intended exposure will be calculated as above, and a dose delay/interruption is defined as any length of time where the subject has not taken any of the planned dose.
- Duration of cetuximab dose delay/interruption = Sum of (Date of the cetuximab dose - Date of previous cetuximab dose – X days). X=8 if previous dose was on Day 1 of a cycle, X=9 if previous dose was on Day 8 of a cycle.
  If the calculation of the duration of dose delay/interruption results in a negative value because of out of scheduled subsequent doses, the duration of dose delay/interruption will be set to '0'.

Dose modifications for cetuximab should be followed local standard clinical practice. The number of cetuximab dose reductions/delays/interruptions will be tabulated.

Duration of dose delay/interruption will only be calculated where the investigator has recorded 'Treatment cycle delayed' in the EX form of the eCRF.

Number of treatment cycles received

Exposure will also be measured by the number of cycles received. A cycle corresponds to a period of 14 days. If a cycle is prolonged, this should still be counted as one cycle. A cycle will be counted if treatment is started even if the full dose is not delivered.

Subjects who permanently discontinue during a dose interruption

If a subject permanently discontinues study treatment during a dose interruption, then the date of last administration of study medication recorded on DOSDISC will be used in the programming.

Safety Follow-up

Total Safety Follow-up = min ((last dose date +90), date of withdrawal of consent, date of death, date of DCO) – first dose date +1.

3.6.2 Dose intensity

Relative dose intensity (RDI) is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation. Relative dose intensity (RDI) for monalizumab/placebo will be defined as follows:

RDI = 100% * d/D

where d is the actual monalizumab/placebo dose delivered up to the actual last day of dosing and D is the intended cumulative monalizumab/placebo dose up to the or the actual last day of dosing. D is the total monalizumab/placebo dose in mg that would be delivered, if there were no modification to dose or schedule. When accounting for the calculation of intended cumulative dose 2 days should be added to the date of last dose to reflect the protocol allowed window for dosing.

RDI for cetuximab will be defined similarly. When accounting for the calculation of intended cumulative dose, to reflect the protocol allowed window for dosing, 2 days should be added to the date of last dose if last dose was on Day 1 of a cycle; 1 day should be added to the date of last dose if dose was on Day 8 of a cycle.

Actual cumulative dose (d) will be derived based on the volume before and after infusion as recorded by the investigator in the exposure page of the eCRF, up to the actual last day of dosing.

Planned cumulative dose (D) will be based on the expected number of treatment cycles multiplied by the planned dose. The expected number of treatment cycles will be calculated from first dose date to last dose date (plus 2 days for monalizumab/placebo to account for the Protocol visit window and for cetuximab plus 2 days if last dose was on Day 1 of a cycle, plus 1 day if last dose was on Day 8 of a cycle) divided by the number of days in the cycle, i.e. 14 days.

3.6.3 Adverse events (AEs)

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

The term AE is used to include both serious and 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.

AEs and SAEs will be collected throughout this study. For this study, on treatment will be defined between date of start dose and 90 days following the last dose of study treatment or until the initiation of the first subsequent anti-cancer therapy (including radiotherapy, except for palliative radiotherapy) following discontinuation of study treatment (whichever occurs

first). If an event starts outside of this period and it is considered possible that it is due to late onset toxicity to study drug, then it should be reported as an AE or SAE.

On treatment AEs (or treatment emergent AEs [TEAEs]) will be defined as any AEs that started after dosing or that started prior to dosing and worsened (by investigator report of a change in intensity) following exposure to treatment. If an AE is not worse than the baseline (pre-dose) severity, then it will not be classified at a TEAE.

The medical dictionary for regulatory activities (MedDRA) [using the latest or current MedDRA version] will be used to code AEs. AEs will be graded according to the National Cancer Institute (NCI) common terminology criteria for adverse event (CTCAE) version 5.0. The CTCAE grade will be assigned by the investigator as follows:

- Grade 1: Mild AE
- Grade 2: Moderate AE
- Grade 3: Severe AE
- Grade 4: Life-threatening or disabling AE
- Grade 5: Death related to AE

Missing start and stop dates for AEs will be handled using the rules described in Section 3.6.10.3. AEs that have missing causality (after data querying) will be assumed to be related to study.

3.6.4 AEs of special interest (AESI)

Adverse events of special interest (AESIs) are events of scientific and medical interest specific to understanding of the monalizumab safety profile and require close monitoring and rapid communication by the Investigator to the Sponsor. An AESI may be serious or non-serious. All AESIs will be identified by the Investigator and recorded in the eCRF. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this IP.

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.

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

3.6.5 Laboratory measurements

Laboratory data will be collected throughout the study as described in the schedule of activities of the CSP. Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be collected as described in Section 8.2.4 of the CSP.

For the derivation of baseline and post baseline visit values, the rules described in Section 3.6.10 of this document considering definition of baseline, visit windows and how to handle multiple records will be used.

Change from baseline in hematology and clinical chemistry variables will be calculated for each post-dose visit on treatment. CTCAE (version 5.0) grades will be defined at each visit according to the CTCAE grade criteria, using local or project ranges as required after conversion of lab results to corresponding AZ preferred units. In the case that laboratory parameters have CTCAE grades defined for both high and low ranges, the parameter will be derived separately for high and low values, identified by including a description of the clinical term . For example, CTCAE grades for Hemoglobin are assessed for high and low values, which would be displayed under the clinical terms of ‘Hemoglobin: Hemoglobin increased’ or ‘Hemoglobin: Anemia’ respectively.

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)] x 0.02)

If creatinine clearance (CrCL) is not calculated/reported by the laboratory, it will be derived during creation of the reporting database using the following formula:

- Males:
  CrCL(mL/min) = Weight (kg) × (140 - age) / 72 × serum creatinine (mg/dL)

- Females:
  CrCL(mL/min) = Weight (kg) × (140 - age) × 0.85 / 72 × serum creatinine (mg/dL)

Absolute values will be compared to the project reference range and classified as low (below range), normal (within range or limits of range) and high (above range).

The maximum or minimum on treatment value (depending on the direction of an adverse effect) will be defined for each laboratory parameter as the maximum (or minimum) post-dose value at any time.

3.6.6 Vital signs

The following vital signs will be measured as described in Section 8.2.2 of the CSP: Systolic and diastolic blood pressure (BP), pulse rate, temperature, respiratory rate and temperature. Body weight will also be recorded at screening visit, day 1 of each cycle and end of treatment visit.

For the derivation of baseline and post-baseline visit values, the definitions and rules described in Section 3.6.10 for visit windows, and how to handle multiple records will be used.

Situations in which vital signs results should be reported as AEs are described in Section 8.3.5 of the CSP.

3.6.7 Physical examinations

Physical examinations will be performed as described in Section 8.2.1 of the CSP. Abnormalities recorded prior to the first dose of study treatment will be recorded as part of the subject's baseline signs and symptoms. Abnormalities first recorded after first dose of study treatment will be recorded as AEs unless unequivocally related to the disease under study. Situations in which physical examination results should be reported as AEs are described in Section 8.3.5 of the CSP.

3.6.8 Electrocardiograms (ECGs)

Triplicate 12-lead ECGs will be recorded at scheduled visits and as clinically indicated throughout the study as described in Section 8.2.3 of the CSP. 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.

For the derivation of baseline and post-baseline visit values, the average of the triplicates will be used. In addition, the definitions and rules described in Section 3.6.10 for visit windows will be used.

The following ECG variables will be collected: ECG machine that automatically calculates the heart rate and measures PR duration, QRS duration, QT duration and overall ECG evaluation.

The overall evaluation of an ECG will either be "normal" or "abnormal" with abnormalities categorized as either "clinically significant" or "not clinically significant".

The QT interval corrected for heart rate using Fridericia's correction (QTcF) will be calculated in the eCRF as follows (where QT and RR are in seconds):

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

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

3.6.9 World Health Organisation (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status (PS)

The WHO/ECOG PS will be assessed as described in Section 8.1.4.8 of the CSP as 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 (e.g., light house work or office work)

2. Ambulatory and capable of self-care, but unable to carry out any 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 changes from baseline or screening will be reported as AE.

3.6.10 General considerations for safety assessments

3.6.10.1 Definition of baseline

Baseline will be defined as the last non-missing measurement of the variable under consideration prior to the intake of the first dose of study treatment. That is, the latest result prior to the start of study treatment. If two visits are equally eligible to assess subject status at baseline (e.g., screening and baseline assessments both on the same date prior to the first dose with no washout or other intervention in the screening period), the average will be used as the baseline value. For non-numeric laboratory tests (i.e., some of the urinalysis parameters) where taking the average is not possible, the best value would be taken as baseline as this is

most conservative. In the scenario where there are two assessment recorded on the day, one with time recorded and the other without time recorded, the one with the time recorded would be selected as baseline. Where safety data are summarized over time, time on study will be calculated in relation to date of first study treatment.

3.6.10.2 Time windows for safety assessments

Time windows will be defined for all presentations of safety data that summarize values by visit (Note: this also applies to the PRO data) according to the following conventions:

- The time windows should be exhaustive so that data recorded at any time point (scheduled or unscheduled) has the potential to be summarized. Inclusion within the time window should be based on the actual data and not the intended date of the visit.

- The window for visits following baseline will be constructed in such a way that the upper limit of the interval falls half way between the two visits (the lower limit of the first post baseline visit will be Day 2). If an even number of days exist between two consecutive visits, then the upper limit will be taken as the midpoint value minus 1 day. For example, the visit windows for laboratory data (every 2 weeks between scheduled assessments up to Cycle 6 Day 1 then every 4 weeks thereafter) are:

    - Day 15, visit window 2 – 22
    - Day 29, visit window 23 – 36
    - Day 43, visit window 37 – 50
    - Day 57, visit window 51 – 64
    - Day 71, visit window 65 – 85
    - Day 99, visit window 86 – 113

- For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment (as defined in Section 4.2.7.4) will be used (regardless of where it falls in an interval).

- Listings will display all values contributing to a time point for a subject.

- For visit-based summaries, if there is more than one value per subject within a time window then the closest value to the scheduled visit date will be summarized. If the values are equidistant from the nominal visit date, then the earlier value will be used. Data listings will highlight the values used in the summary table, wherever feasible. Note: In summaries of extreme values, all post-baseline values collected are used including those collected at unscheduled visits regardless of which value is closest to the scheduled visit date.

- For summaries at subject level, all values will be included when deriving a subject level statistic such as a maximum regardless of whether they appear in the corresponding visit-based summary.

3.6.10.3 Handling of missing data

Missing safety data will generally not be imputed. However, safety assessments of the form of "<x" (i.e., below the lower limit of quantification) or ">x" (i.e., above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but will be displayed as "<x" or ">x" in the listings.

For missing start dates for AEs and concomitant medications/procedures, the following will be applied:

- Missing day: Impute the 1st of the month unless month and year are the same as month and year of the first dose of study drug then impute first dose date.

- Missing day and month: Impute 1st January unless year is the same as first dose date then impute first dose date.

- Completely missing date: Impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date.

When imputing a start date, ensure that the new imputed date is sensible e.g., prior to the end date of the AE.

For missing stop dates of AEs or concomitant medications/procedures, the following will be applied:

- Missing day: Impute the last day of the month unless month is the same as month of last dose of study drug then impute last dose date.

- Missing day and month: Impute 31st December unless year is the same as last dose date then impute last dose date.

- Completely missing: Look at whether the AE/medication is still ongoing before imputing a date and also when it started in relation to study drug. If the ongoing flag is missing, then assume that AE is still present / medication is still being taken (i.e. do not impute a date). If the AE/medication has stopped and start date is prior to first dose date then impute the 1st dose date, if it started on or after first dose date then impute a date that is after the last dose date.

Flags will be retained in the database indicating where any programmatic imputation has been applied, and in such cases, any durations would not be calculated.

If a subject is known to have died where only a partial death date is available, then the date of death will be imputed as the latest of the last date known to be alive +1 from the database and the death date using the available information provided:

- Missing day only: Using the 1st of the month.
- Missing day and month: Using the 1st January.

Patients with a partial date of birth (i.e. for those countries where year of birth only is given) will have an assumed date of birth of 1st January of the year.

3.7 Pharmacokinetic (PK) variables

PK concentration data will be collected as described in Section 8.5.1 of the CSP.

The actual sampling times will be used in the PK calculations. PK parameters will be determined using standard non-compartmental methods. Peak and trough concentration PK parameters will be obtained from raw PK data measurements (as data allow). Samples below the lower limit of quantification will be treated as missing in the analysis.

Plasma concentrations that are not quantifiable (NQ) or if there are missing values (e.g. no result [NR]) will be handled as follows:

- Where there is NR, these will be set to missing.
- At a time point where there is less than or equal to 50% of the values are NQ, all NQ values will be set to the lower limit of quantification (LLOQ), and all descriptive statistics will be calculated.
- At a time point where more than half of the values are NQ, the mean, standard deviation (SD), geometric mean and coefficient of variation (CV)% will be set to Not Calculated (NC). The maximum value will be reported from the individual data, and the minimum and median will be set to NQ.
- If all values are NQ at a time point, no descriptive statistics will be calculated for that time point. Not calculated (NC) will be written in the field for standard deviation and CV% and NQ will be written in fields for mean, geometric mean, minimum, median and maximum.
- The number of NQ values (n below LLOQ) will be reported for each time point.

Data from patients excluded from the PK analysis set will be included in the data listings, but not in the descriptive statistics.

3.8 Immunogenicity variables

Samples will be measured for the presence of ADAs (Anti-drug antibody) for monalizumab using validated assays. ADA sample analysis will be performed for Arm A only (for monalizumab only). Tiered analysis will be performed to include screening, confirmatory, titer and nAb assay components, and positive / negative cut points previously statistically determined from drug-naïve validation samples will be used. ADA data will be collected at scheduled visits as shown in the CSP (Section 8.5.2). ADA result from each sample will be reported as either positive or negative. If the sample is positive, the ADA titer will be reported as well. In addition, the presence of neutralizing ADA may be tested for all ADA-positive samples using a ligand-binding assay. The nAb results will be reported as positive or negative.

The number of subjects in the ADA analysis set who fulfill the following criteria will be determined. The percentage of subjects in each of the categories listed below will be calculated, using the number of subjects in the ADA analysis set of the treatment group as the denominator.

- ADA positive at any visit; the percentage of ADA-positive subjects in the ADA analysis set is known as ADA prevalence. A subject is defined as being ADA positive if a positive ADA result is available at any time, including baseline and all post-baseline measurements; otherwise ADA negative.

- The sum of both treatment-induced and treatment-boosted ADA; the percentage of subjects fulfilling this criterion in the ADA analysis set is known as ADA incidence.

- ADA positive post-baseline and positive at baseline.

- ADA positive post-baseline and not detected at baseline (treatment-induced ADA).

- ADA not detected post-baseline and positive at baseline.

- Treatment-boosted ADA, defined as a baseline positive ADA titer that was boosted to a 4-fold or higher level (greater than the analytical variance of the assay) following drug administration.

- Treatment-emergent ADA persistently positive, defined as treatment-emergent ADA+ subjects having at least 2 post-baseline ADA positive measurements with at least 16

weeks (112 days) between the first and last positive measurement, or an ADA positive result at the last available assessment.

- Treatment-emergent ADA transiently positive, defined as treatment-emergent ADA+ subjects having at least one post-baseline ADA positive measurement and not fulfilling the conditions for TE-ADA persistently positive.

- nAb positive at any visit.

3.9 CCI

CCI

4 ANALYSIS METHODS

The primary objective of the study is to confirm the superiority of monalizumab plus cetuximab combination therapy (Arm A) compared to placebo plus cetuximab therapy (Arm B) in terms of OS in the HPV-unrelated participants with R/M SCCHN after receiving an ICI and platinum-based chemotherapy.

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

The formal statistical analysis will be performed to test the following main hypotheses in HPV-unrelated Analysis Set:

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

There will be 3 data cut-offs (DCO) for this study consisting of 2 interim analysis and 1 final analysis:

Interim Analysis 1 (IA1): The first interim analysis will be performed when approximately 99 OS events have been observed in the HPV-unrelated participants (25% information fraction) who had been 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.

Interim Analysis 2 (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.

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 Analysis Set (approximately 80% maturity). Based on enrolment assumptions, it is expected that this will occur approximately 42 months after randomization of the first subject.

Refer to Section 5 for further details of planned interim analysis.

4.1 General principles

Efficacy and PRO data will be summarized and analyzed based on HPV-unrelated Analysis Set and FAS. Safety and treatment exposure data will be summarized based upon the SAF. Study population and demography data will be summarized based upon the FAS. PK data will be analyzed using the PK analysis set.

The below mentioned general principles will be followed throughout the study:

- Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, upper and lower quartiles (where applicable), 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 group. Overall totals will be calculated for baseline summaries only.

- For continuous data, the mean and median will be rounded to 1 additional decimal place compared to the original data. The standard deviation will be rounded to 2 additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data. For categorical data, percentages will be rounded to 1 decimal place.

- SAS® version 9.4 (or higher) will be used for all analysis.

In general, for efficacy and PRO endpoints the last observed measurement prior to randomization will be considered the baseline measurement. However, if an evaluable assessment is only available after randomization but before the first dose of randomized treatment then this assessment will be used as baseline. For safety endpoints the last observation before the first dose of study treatment will be considered the baseline measurement unless otherwise specified. For assessments on the day of first dose where time is not captured, a nominal pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to first dose.

Assessments on the day of the first dose where neither time nor a nominal pre-dose indicator are captured will be considered prior to the first dose if such procedures are required by the protocol to be conducted before the first dose.

In all summaries change from baseline variables will be calculated as the post-treatment value minus the value at baseline. The percentage change from baseline will be calculated as (post-baseline value - baseline value) / baseline value x 100.

For time variables provided in months, the time in days will be divided by 30.4375 days to obtain the time in months.

4.2 Analysis methods

Table 8 details which endpoints are to be subjected to formal analysis, together with pre-planned sensitivity analysis, making it clear which analysis is regarded as primary for that endpoint.

Table 8: Formal statistical analysis to be conducted and pre-planned sensitivity analysis

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

Endpoints analyzed	Notes
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 <u>Secondary confirmatory analysis</u> For HPV-unrelated Analysis Set, stratified log-rank tests (adjusting for WHO/ECOG PS and number of lines of prior therapy in the R/M setting) and stratified Cox proportional hazards model with the same stratification factors, using PFS according to RECIST 1.1 using Investigator assessments For FAS, stratified log-rank tests (adjusting for HPV status, WHO/ECOG PS, and number of lines of prior therapy in the R/M setting) and stratified Cox proportional hazards model with the same stratification factors, using PFS according to RECIST 1.1 using Investigator assessments <u>Sensitivity and supplemental analysis</u> Analysis using alternative censoring rules – attrition bias Subgroup analysis using Cox proportional hazard model
Objective response rate (Secondary) in HPV-unrelated Analysis Set and FAS	For HPV-unrelated Analysis Set, logistic regression adjusted for WHO/ECOG PS and number of lines of prior therapy in the R/M setting, using tumor data according to RECIST 1.1 by Investigator assessment For FAS, logistic regression adjusted for HPV status, WHO/ECOG PS, and number of lines of prior therapy in the R/M setting, using tumor data according to RECIST 1.1 by Investigator assessment
Duration of response (Secondary) in HPV-unrelated Analysis Set and FAS	KM plot of DoR based on tumor data according to RECIST 1.1 using Investigator assessments. Median DoR calculated from the KM curve.

Endpoints analyzed	Notes
CCI	CCI
CCI	CCI
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	Adjusted mean change from baseline using MMRM analysis (overall and by each visit)

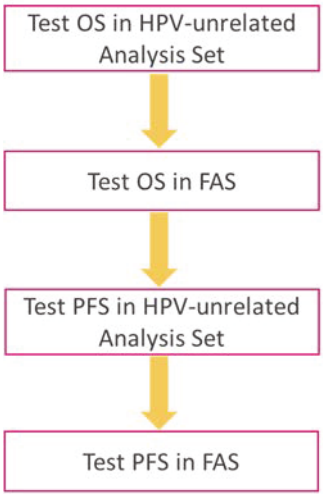
Endpoints analyzed	Notes
Time to symptom, function, or HRQoL deterioration of key PRO endpoints using EORTC QLQ-C30 and QLQ- H&N35 (Secondary) in HPV-unrelated Analysis Set and FAS	Stratified log-rank test (for p-value), HR from Cox model (with 95% CI), KM plot
CCI	Summary descriptive statistics, stacked bar chart
CCI	Summary statistics for health state utilities and visual analogue scale, including change from baseline.
CCI	Descriptive statistics (as appropriate, including means, median, ranges or frequencies and percentages)

CR Complete response; CCI
CCI 24w Percentage of subjects who have a best objective response of CR or PR or who have SD for at least 24 weeks (±7 days), following the start of study treatment; DoR Duration of response; EORTC European Organisation for Research and Treatment of Cancer; FAS Full analysis set; HR Hazard ratio; HRQoL Health related quality of life; KM Kaplan Meier; MMRM Mixed-effect model repeated measure; OS Overall survival; CCI ; CCI ; CCI ; PR Partial response; CCI ; CCI ; QLQ-H&N35 35-Item Quality of Life Questionnaire Head and Neck Questionnaire; QLQ-C30 30-Item Core Quality of Life Questionnaire; QoL Quality of life; RECIST Response Evaluation Criteria in Solid Tumors; SD Stable disease .

4.2.1 Multiplicity

CCI

Figure 2 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.

Progression-free survival will be formally tested at 2-sided significance levels of 0.05 only if OS is statistically positive (IA or FA). At time of OS IA, the PFS data will be mature given its expected short median of 2.3 months in this population (Cohen EEW et al, 2019b; Ferris et al, 2016; Rischin et al, 2019) and it will be tested at 5% significance level.

4.2.2 Primary efficacy endpoint overall survival (OS)

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) for generation of the p-value and using a method that corresponds to the Breslow approach for handling ties (Breslow, 1974). The HR and its CI will be estimated from a stratified Cox proportional hazards model (Cox, 1972) (with ties = Efron and the stratification variables included in the strata statement) and the CI calculated using the profile likelihood approach.

The effect of treatment (Arm A versus Arm B) will be estimated by the hazard ratio (HR) together with its corresponding 95% CI and p-value for the HPV-unrelated Analysis Set.

The stratification variables in the statistical modelling will be based on the values entered into IVRS at randomization, even if it is subsequently discovered that these values were incorrect.

Kaplan-Meier (KM) plots of OS will be presented by treatment arm. Summaries of the number and percentage of subjects 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 and 25^{th} and 75^{th} percentiles for OS for each treatment.

Assumptions of proportionality

The assumption of proportionality will be assessed by examining plots of complementary log-log (event times) versus log (time). The Grambsch-Therneau non-proportionality test may also be used to check proportional hazards (PH) violation (Grambsch and Therneau 1994).

As a lack of proportionality is expected (due to delayed effect in IO agents), a three-component stratified MaxCombo test will be used as a sensitivity analysis with the same stratification factors as the primary analysis. The MaxCombo test is an adaptive procedure, optimizing test statistics as the maximum of the log rank test ($FH^{0,0}$) and selected Fleming-Harrington (FH) weighted log-rank tests (Fleming and Harrington 1991) ($FH^{0,1}$ and $FH^{1,1}$) , i.e. Zmax = max{ $FH^{0,0}$, $FH^{0,1}$ and $FH^{1,1}$}, with multiplicity adjustment based on the asymptotic multivariate distribution (Karrison et al, 2016). The Fleming-Harrington tests of $FH^{0,1}$ and $FH^{1,1}$ assign less weight to early events and are more powerful in the scenario of delayed effect, while the log-rank test is optimal in the scenario of proportional hazards (Schoenfeld 1981). Under PH, the power loss from Zmax is minimal (Lin et al. 2020). As a result, the Zmax statistic is a robust test with consideration of possible delayed effect scenarios (NPH) and proportional hazards scenario and is recommended by the Cross-Pharma Non-proportional Hazard Working Group when NPH are expected (Lin et al. 2020).

Under non-proportional hazards, the HR from the primary analysis can still be meaningfully interpreted as an average HR over time unless there is extensive crossing of the survival

curves. However, the variation in treatment effect will be described by presenting piecewise HR calculated over distinct time-periods: 0-6 months, 6-12 months, 1-2 years, 2-3 years, etc. In addition, the summary of estimated OS rates at each year [or other specified clinically relevant timepoints] after randomisation will be used to characterize the patterns observed in any treatment effects.

The Restricted Mean Survival Time (RMST) will also be analysed up to the minimum of the largest observed event time in each of the two arms [or suitable clinically relevant timepoint], using an area-under-the-curve approach (Kaplan-Meier method), to estimate RMST with standard error, for each treatment group, along with the estimate of difference in means between treatment groups, confidence interval and p-value. In addition, the pseudovalues approach (Andersen et al. 2004) and Royston-Parmar model (Royston and Parmar 2011, 2013) may also be used; all RMST analyses will control for WHO/ECOG PS (0 or 1), and number of lines of prior therapy in the R/M setting (1 or 2).

Sensitivity and supplemental analysis

The following sensitivity and supplemental analysis will be performed.

A summary of the duration of follow-up will be summarized using median time from randomization to date of censoring (date last known to be alive) and its 25^{th} and 75^{th} percentiles in censored (not recurred) patients only, presented by treatment group, using the reverse Kaplan-Meier method.

A sensitivity analysis will be conducted to assess for the potential impact of COVID deaths on OS. This will be assessed by repeating the OS analysis except that any patient who had a death with primary/secondary cause as COVID-19 Infection will be censored at their COVID infection death date.

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

- Sex (male vs female)
- Age at randomization (< 65 vs ≥ 65 years of age)

- Human papillomavirus status (OPC HPV positive vs OPC HPV negative and non-OPC)
- WHO/ECOG PS (0 vs 1)
- Number of prior lines of therapy in the R/M setting (1 vs 2)
- Race (Asian vs non-Asian)
- Region (European vs Asian Pacific vs North/Latin America vs Australia)
- CCI [redacted]
- CCI [redacted]
- PD-L1 expression level (high versus low)

For these subgroup analysis any subject with missing values will be excluded from that particular subgroup.

For subgroup analyses listed above, the human papillomavirus status, WHO/ECOG PS and number of prior lines of therapy in the R/M setting subgroups will be determined based on the data recorded in the CRF and not the stratification factor entered into the IxRS.

The cut-off for CCI [redacted] will be defined prior to DBL using data outside of the INTERLINK-1 study.

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 analysis is to assess the consistency of treatment effect across expected prognostic and/or predictive factors. Forest plots will be presented.

No adjustment to the significance level for testing of the subgroup and sensitivity analysis will be made, since all these analysis will be considered supportive of the analysis of OS and PFS. For each subgroup level of a factor, the HR (for the treatment comparisons of interest) and 95% CI will be calculated from a Cox proportional hazards model that only contains a term for treatment. The Cox models will be fit using a SAS PROC PHREG with the Efron method to control for ties, using the by statement to obtain HR and 95% CI for each subgroup level separately. These will be presented on a forest plot including the HR and 95% profile likelihood CI, along with the results of the overall primary analysis.

If there are too few events available for a meaningful analysis of a particular subgroup comparison (it is not considered appropriate to present analysis where there are less than 20 events within a subgroup category (i.e., when the events in the treatment comparison does not

add up to 20) in a subgroup), the relationship between that subgroup and the primary endpoint (OS) will not be formally analyzed. In this case, only descriptive summaries will be provided.

4.2.3 Secondary efficacy endpoints

4.2.3.1 Progression free survival (PFS)

The confirmatory secondary PFS analysis will also be based on the programmatically derived RECIST 1.1 using the Investigator tumor assessments. The analysis will be performed in the HPV-unrelated Analysis Set and the FAS using a stratified log-rank test, adjusting for the same stratification factors used for primary analysis in section 4.2.2 (HPV status [for FAS only], WHO/ECOG PS, and number of lines of prior therapy in the R/M setting). Similar to the primary analysis, the HR and its CI in PFS will also be estimated from a stratified Cox proportional hazards model (Cox, 1972) and the CI calculated using the profile likelihood approach. The effect of Arm A versus Arm B in PFS 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 subjects experiencing a PFS event and the type of event (RECIST 1.1 or death) will be provided along with median PFS and 25th and 75th percentiles for PFS for each treatment. Assumption of proportionality will also be assessed for PFS.

Sensitivity and supplemental analysis

The following sensitivity and supplemental analysis will be performed:

Attrition bias will be assessed by repeating the PFS analysis except that the actual PFS event times, rather than the censored times, of subjects who progressed or died in the absence of progression immediately following 2 or more non-evaluable tumor assessments will be included. In addition, subjects 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 Kaplan-Meier plot of the time to censoring where the censoring indicator of the PFS analysis is reversed.

A sensitivity analysis will also be conducted to assess for the potential impact of COVID deaths on PFS. This will be assessed by repeating the PFS analysis except that any patient who had a PFS event due to death where primary/secondary cause of death was due to COVID-19 Infection will be censored at their last evaluable assessment prior to their COVID infection death date.

Subgroup analysis

Subgroup analysis will be conducted comparing PFS (per RECIST 1.1 using Investigator assessments) between Arm A and Arm B in the subgroups of the HPV-unrelated Analysis Set and the FAS, as specified in Section 4.2.2.

4.2.3.2 Objective rate (ORR)

The ORR will be based on the site investigator RECIST 1.1 data and using all scans regardless of whether they were scheduled or not. The ORR will be compared between treatment A versus treatment B using logistic regression models adjusting for the same stratification factors as the primary endpoint as covariates in the model. The results of the analysis will be presented in terms of an odds ratio (an odds ratio greater than 1 will favour treatment A) together with its associated profile likelihood 95% CI (e.g. using the option 'LRCI' in SAS procedure GENMOD) 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 subjects in the HPV-unrelated Analysis Set and the FAS who had measurable disease at baseline.

In addition to logistic regression, a Crochran-Mantel Haenszel (CMH) test will also be presented. The CMH test will be stratified using the same stratification factors as the primary endpoint. The results of the analysis will be presented in terms of an odds ratio together with the 95% CI and p-value. The odds ratio, 95% CI and p-value will be obtained using SAS PROC FREQ and the CMH test option. The STRATUM variable used in the TABLE statement will be based on primary tumor location and disease status.

Summaries will be produced that present the number and percentage of subjects with a tumor response (CR/PR). Overall visit response data will be listed for all subjects (i.e, the FAS). For each treatment arm, best objective response (BoR) will be summarized by n (%) for each category (CR, PR, SD, PD and NE). No formal statistical analysis are planned for BoR.

4.2.3.3 Duration of response (DoR)

KM plots of DoR based on the Investigator assessment of RECIST 1.1 will be presented. Median DoR and 25th and 75% percentiles for DoR will also be summarized and calculated from the KM curve. Only subjects who have a confirmed response will be included in this summary table. Median time to response and 25th and 75% percentiles for time to response will be also presented in the summary table.

4.2.4 CCI

4.2.4.1 CCI

CCI

4.2.4.2 CCI

CCI

4.2.4.3 CCI

CCI

CCI

4.2.5 Patient reported outcomes (PROs)

All patient reported outcomes will be summarized for the HPV-unrelated Analysis Set and the FAS.

Compliance rates summarizing questionnaire completion at each visit will be tabulated.

4.2.5.1 EORTC QLQ-C30

Time to deterioration

The primary assessment of symptoms, impacts, and HRQoL will focus on time to deterioration (TTD), which will be analyzed using a stratified log-rank test as described for the PFS endpoint. Separate analysis will be conducted for time to deterioration of global health status/QoL, function (including physical, role, cognitive, emotional and social), multi-term symptoms (including fatigue and pain), and single items (nausea/vomiting, dyspnoea, insomnia, appetite loss, constipation and diarrhoea). The effect of Arm A versus Arm B will be estimated by the HR together with its corresponding CI and p-value. Kaplan-Meier plots will be presented by treatment group. Summaries of the number and percentage of patients who have an event as well as who were censored will be provided along with the medians, 25^{th} and 75^{th} percentiles for each treatment.

Adjusted mean change from baseline

Additional analysis of HRQoL, impacts, and symptoms will focus on comparing mean change from baseline in the global health status/QoL, functions (physical, role, cognitive, social, and emotional), multi-term symptoms (fatigue and pain), and single items (nausea/vomiting, dyspnoea, insomnia, appetite loss, constipation and diarrhoea) score between treatment groups. The analysis population for mean change in HRQoL, impacts, or symptoms data will be the FAS and will include all randomized patients with an evaluable baseline assessment and at least 1 evaluable post-baseline assessment.

Change from baseline will be derived using a mixed model repeat measures (MMRM) analysis of all the post-baseline scores for each visit. The model will include treatment, visit, and treatment-by-visit interaction as explanatory variables and the baseline score as a covariate. Adjusted mean change from baseline estimates per treatment group and corresponding 95% CIs will be presented along with an overall estimate of the treatment difference, 95% CI, and p-value.

Change from baseline

Finally, summaries of absolute and unadjusted change from baseline values of each EORTC QLQ-C30 scale/item will be reported by visit for each treatment group. Graphical presentations may also be produced as appropriate.

4.2.5.2 EORTC QLQ-H&N35

Time to deterioration

The primary assessment of TTD, as described for the EORTC QLQ-C30, will be evaluated for single items (teeth [item 39], opening mouth [item 40], dry mouth [item 41], sticky saliva [item 42], coughing [item 45], felt ill [item 47], pain killers [item 61], nutritional supplements [item 62], feeding tube [item 63], weight loss [item 64] and weight gain [item 65]) and symptom scales (pain, swallowing, senses problems, speech problems, trouble with social eating, trouble with social contact and less sexuality) of the EORTC QLQ-H&N35. TTD will be presented using a Kaplan-Meier plot as well as the HR together with the corresponding 95% CI and p-values. Summaries of the number and percentage of patients experiencing a clinically meaningful deterioration or death and the median TTD and 25th and 75th percentiles for TTD will also be provided for each treatment group.

Adjusted mean change from baseline

Additionally, comparing mean change from baseline using the MMRM as described for the EORTC QLQ-C30 will be repeated for single items (teeth [item 39], opening mouth [item 40], dry mouth [item 41], sticky saliva [item 42], coughing [item 45], felt ill [item 47], pain killers [item 61], nutritional supplements [item 62], feeding tube [item 63], weight loss [item 64] and weight gain [item 65]) and symptom scales (pain, swallowing, senses problems, speech problems, trouble with social eating, trouble with social contact and less sexuality) of the EORTC QLQ-H&N35. All assumptions and outputs as described for the EORTC QLQ-C30 are applicable.

Change from baseline

As described for the EORTC QLQ-C30, summaries of absolute and unadjusted change from baseline values of each EORTC QLQ-H&N35 single item/symptom scale will be reported by visit for each treatment group. Graphical presentations may also be produced as appropriate.

4.2.5.3 CCI

CCI

4.2.5.4 CCI

CCI

4.2.5.5 CCI

CCI

4.2.6 CCI

CCI

CCI

[redacted]

4.2.7 Safety data

Safety and tolerability data from all cycles of treatment will be combined and will be presented by treatment arm using the SAF. Safety summaries will be descriptive only. No formal statistical analysis will be performed on the safety variables.

The following sections describe the planned safety summaries for AEs, vital signs, laboratory parameters, ECG and WHO performance status. However, additional safety summaries (not specified in this SAP) may need to be produced to aid interpretation of the safety data.

4.2.7.1 Adverse events

All AEs, both in terms of current MedDRA preferred term and CTCAE grade, will be summarized descriptively by count (n) and percentage (%) for each treatment group. Any AE occurring before randomized treatment (i.e. before the administration of the first infusion on Study Day 1) will be included in the AE listings, but will not be included in the summary tables (unless otherwise stated). These will be referred to as 'pre-treatment'. However, any AE occurring before the administration of the first dose on Study Day 1 that increases in severity after the first dose will be regarded as treatment emergent and thus will be included in the summary tables. Note: If an AE is not worse than baseline (pre-dose) severity then it will not be classified as TEAE.

AEs observed up until 90 days following last dose of the study treatment or until the initiation of the first subsequent anti-cancer therapy (including radiotherapy, except for palliative radiotherapy) following discontinuation of study treatment (whichever occurs first) will be used for reporting of all the AE summary tables. This will more accurately depict AEs attributable to study treatment only as some of AEs up to 90 days following discontinuation of the study treatment are likely to be attributable to subsequent therapy.

However, to assess the longer-term toxicity profile, limited AE summaries may also be produced containing AEs observed up until 90 days following discontinuation of the monalizumab plus cetuximab combination therapy or placebo plus cetuximab therapy (i.e. without taking subsequent therapy into account). Any events in this period that occur after a

subject has received further therapy for cancer (following discontinuation of study treatment) will be flagged in the data listings.
A separate listing of AEs occurring more than 90 days after discontinuation of study treatment will be produced. These events will not be included in AE summaries.

All reported AEs will be listed along with the date of onset, date of resolution (if AE is resolved) and investigator's assessment of severity and relationship to study drug. Frequencies and percentages of subjects reporting each preferred term (PT) will be presented (i.e. multiple events per subject will not be accounted for apart from on the episode level summaries which may be produced).

Summary information (the number and percent of subjects by system organ class and PT separated by treatment group) will be tabulated for the following category:

- All AEs
- All AEs possibly related to monalizumab/placebo or cetuximab
- All AEs possibly related to monalizumab/placebo
- All AEs possibly related to cetuximab
- All AEs possibly related to monalizumab/placebo and cetuximab
- AEs with CTCAE grade 3 or 4
- AEs with CTCAE grade 3 or 4, possibly related to monalizumab/placebo or cetuximab
- AEs with CTCAE grade 3 or 4, possibly related to monalizumab/placebo
- AEs with CTCAE grade 3 or 4, possibly related to cetuximab
- AEs with CTCAE grade 3 or 4, possibly related to monalizumab/placebo and cetuximab
- Most common AEs
- Most common AEs with CTCAE grade 3 or 4
- AEs with outcome of death

- AEs with outcome of death possibly related to monalizumab/placebo or cetuximab
- AEs with outcome of death possibly related to monalizumab/placebo
- AEs with outcome of death possibly related to cetuximab
- AEs with outcome of death possibly related to monalizumab/placebo and cetuximab
- All SAEs
- All SAEs possible related to monalizumab/placebo or cetuximab
- All SAEs possible related to monalizumab/placebo
- All SAEs possible related to cetuximab
- All SAEs possible related to monalizumab/placebo and cetuximab
- AEs leading to discontinuation of monalizumab/placebo
- AEs leading to discontinuation of cetuximab
- AEs leading to discontinuation of monalizumab/placebo and cetuximab
- AEs leading to discontinuation of monalizumab/placebo, possibly related to monalizumab/placebo
- AEs leading to discontinuation of cetuximab, possibly related to cetuximab
- AEs leading to discontinuation of monalizumab/placebo and cetuximab, possibly related to monalizumab/placebo and cetuximab
- SAEs leading to discontinuation of monalizumab/placebo
- SAEs leading to discontinuation of cetuximab
- SAEs leading to discontinuation of monalizumab/placebo and cetuximab
- SAEs leading to discontinuation of monalizumab/placebo, possibly related to monalizumab/placebo
- SAEs leading to discontinuation of cetuximab, possibly related to cetuximab

- SAEs leading to discontinuation of monalizumab/placebo and cetuximab, possibly related to monalizumab/placebo and cetuximab
- AEs leading to dose reduction of cetuximab
- AEs leading to dose interruption of monalizumab/placebo
- AEs leading to dose interruption of cetuximab
- AEs leading to cycle delay of monalizumab/placebo
- AEs leading to cycle delay of cetuximab
- AEs leading to cycle delay or interruption of monalizumab/placebo
- AEs leading to cycle delay or interruption of cetuximab
- AEs of special interest (AESI)
- AESI possibly related to monalizumab/placebo or cetuximab
- AESI possibly related to monalizumab/placebo
- AESI possibly related to cetuximab
- AESI possibly related to monalizumab/placebo and cetuximab
- Immune-mediated AEs
- Immune-mediated AEs possibly related to monalizumab/placebo or cetuximab
- Immune-mediated AEs possibly related to monalizumab/placebo
- Immune-mediated AEs possibly related to cetuximab
- Immune-mediated AEs possibly related to monalizumab/placebo and cetuximab
- Infusion reaction AEs
- Infusion reaction AEs possibly related to monalizumab/placebo or cetuximab
- Infusion reaction AEs possibly related to monalizumab/placebo

- Infusion reaction AEs possibly related to cetuximab
- Infusion reaction AEs possibly related to monalizumab/placebo and cetuximab
- Anaphylactic reaction AEs
- Anaphylactic reaction AEs possibly related to monalizumab/placebo or cetuximab
- Anaphylactic reaction AEs possibly related to monalizumab/placebo
- Anaphylactic reaction AEs possibly related to cetuximab
- Anaphylactic reaction AEs possibly related to monalizumab/placebo and cetuximab

The following AE categories will be summarized for the number and percent of subjects by Standardized MedDRA Query (SMQ) grouped term and PT separated by treatment group:

- Hemorrhages adverse events
- Hemorrhages adverse events possibly related to monalizumab/placebo
- Hemorrhages adverse events possibly related to cetuximab

Relatedness will be assessed in relation to either study treatment, monalizumab/placebo or cetuximab, as determined by the Investigator.

An overall summary of the number and percentage of subjects in each category will be presented (subject level). The same summary will be displayed at the episode level presenting the number of events in each category. For the truncated AE tables of most common AEs, all events that occur in at least 5% of subjects overall will be summarized by preferred term, by decreasing frequency. This cut-off may be modified after review of the data. When applying a cut-off (e.g., 5%), the raw percentage should be compared to the cut-off, no rounding should be applied first (i.e., an AE with frequency 4.9% will not appear if the cut-off is 5%).

Each AE event rate (per 100 subject years) will also be summarized by preferred term within each system order class for the output summarizing all AEs. For each preferred term, the event rate is defined as the number of subjects with that AE divided by the total treatment duration (days) of randomized treatment summed over subjects and then multiplied by 365.25 x 100 to present in terms of per 100 subject years.

AEs will be assigned CTCAE grades and summaries of the number and percentage of subjects will be provided by maximum reported CTCAE grade, system organ class and preferred term. For each AE, time to first onset of the AE from date of first dose may be presented in the listing.

Deaths

A summary of deaths will be provided with number and percentage of patients, categorized as:

- Total number of deaths (regardless of date of death)
- Related to disease under investigation
- AE outcome of death only and onset date prior to initiation of subsequent anti-cancer therapy
- AE outcome of death only and onset date falling after 90 days following last dose of study medication or initiation of subsequent anti-cancer therapy (whichever is earlier)
- Both related to disease under investigation and with AE outcome of death and onset date prior to initiation of subsequent anti-cancer therapy
- Death related to disease under investigation and AE with outcome of death > 90 days after last dose of study medication or ≥ date of subsequent therapy, whichever occurs first
- Deaths > 90 days after last dose of study medication or ≥ date of subsequent therapy (whichever occurs first), unrelated to AE or disease under investigation
- Patients with unknown reason for death
- Other deaths

A summary of deaths will be also provided by HPV status recorded in CRF.
A corresponding listing will also be produced.

4.2.7.2 Adverse events of special interest (AESI)

AESI and imAE will be summarized using the same methods as described for AE's above.

Frequencies, percentages and rates of AESI and imAE will be tabulated by MedDRA preferred term and AESI/imAE group term and treatment group. AE's by maximum CTCAE grade, SAEs, AEs leading to dose delay, discontinuation and death will be summarized for each treatment group.
A listing of AESIs and imAEs including time to onset, time to resolution, and whether treated with systemic steroids, high dose steroids, other immunosuppressants, or endocrine therapy, will be presented.

4.2.7.3 Exposure

Exposure will be summarized for the SAF. The following summaries will be produced:

- Total (intended) exposure.
- Actual exposure (monalizumab or matching placebo, cetuximab).
- RDI (monalizumab or matching placebo, cetuximab).
- Number of cycles received (monalizumab or matching placebo, cetuximab).
- Summary of interruptions for monalizumab or matching placebo, cetuximab.

4.2.7.4 Laboratory measurements

Laboratory data obtained until 90 days after the last dose of study treatment or until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment (whichever occurs first) will be used for reporting. This will more accurately depict laboratory toxicities attributable to study treatment only as a number of toxicities up to 90 days following discontinuation of study treatment are likely to be attributable to subsequent anti-cancer therapy.

Data summaries and listings will be provided by AZ preferred units.

All laboratory data will be listed. Flags will be applied to values falling outside – reference ranges (which will be explicitly noted on these listings where applicable), and to values for which CTCAE grading applies.

Scatter plots (shift plots) of baseline to maximum/minimum values (as appropriate) on treatment (i.e., on treatment is defined as data collected between the start of treatment and the relevant follow-up period following the last dose of study treatment) may be produced for certain parameters if warranted after data review.

Box-plots of absolute values by week, and box-plots of change from baseline by week, may be presented for certain parameters if warranted after data review.

Shift tables of laboratory values by worst common toxicity criteria (CTCAE) grade will be produced, and for specific parameters separate shift tables indicating hyper- and hypo-

directionality of change will be produced. The laboratory parameters for which CTCAE grade shift outputs will be produced are:

- Hematology: Hemoglobin (Anemia and Hemoglobin increased), Leukocytes, Lymphocytes (absolute count) (Lymphocyte count decreased or increased), Neutrophils (absolute count), Platelets

- Clinical Chemistry: ALT, AST, Albumin, Alkaline Phosphatase (ALP), Total bilirubin, Magnesium (Hypomagnesemia and Hypermagnesemia Sodium (Hyponatremia, and Hypernatremia), Potassium (Hypokalemia, and Hyperkalemia), Corrected Calcium (Hypocalcemia, and Hypercalcemia), Glucose (hypo- and hyper-), Gamma-glutamyl transferase, Creatinine, Creatinine clearance

For parameters with no CTCAE grading that are listed in the CSP, shift tables from baseline to worst value on treatment will be provided. Additional summaries will include a shift table of urinalysis (Bilirubin, Blood, Glucose, Ketones, Protein) comparing baseline value to maximum on treatment value.

The denominator used in laboratory summaries of CTCAE grades will only include evaluable subjects. If a CTCAE criterion involved a change from baseline, evaluable subjects are those who have both a pre-dose and at least 1 post-dose value recorded. If a CTCAE criterion does not consider changes from baseline. Evaluable subjects are those who have at least 1 post-dose value recorded.

Hy's law (HL)

For patients with potential Hy's Law where ALT or AST (i.e. ≥ 3x ULN) plus Total Bilirubin (i.e. ≥ 2x ULN) are elevated at any time during the study, liver biochemistry test results over time will be plotted (described below), and individual patient data will be listed.

The following summaries will include the number (%) of patients who have:

- Elevated ALT, AST, and Total bilirubin during the study

- ALT ≥3x – ≤5x, >5x – ≤8x, >8x – ≤10x, >10x – ≤20x, and >20x ULN during the study.

- AST ≥3x – ≤5x, >5x – ≤8x, >8x – ≤10x, >10x – ≤20x, and >20x ULN during the study.

- Total bilirubin ≥2x – ≤3x, >3x – ≤5x, >5x ULN during the study.

- ALT or AST ≥3x – ≤5x, >5x – ≤8x, >8x – ≤10x, >10x – ≤20x, >20x ULN during the study.
- ALT or AST ≥3x ULN and total bilirubin ≥2x ULN during the study (potential Hy's law): the onset date of ALT or AST elevation should be prior to or on the date of total bilirubin elevation.

Plots of maximum post-baseline ALT and AST vs. maximum post-baseline total bilirubin, expressed as multiples of ULN, will also be produced with reference lines at 3×ULN for ALT and AST, and 2×ULN for Total bilirubin. In each plot, total bilirubin will be in the vertical axis.

Liver biochemistry test results over time for patients with elevated ALT (i.e. ≥3x ULN) or AST (i.e. ≥3x ULN), and elevated total bilirubin (i.e. ≥2x ULN) (at any time) will be plotted.

Individual patient data where ALT or AST plus total bilirubin are elevated at any time will be listed also.

Abnormal Thyroid function

Elevated thyroid stimulating hormone (TSH) will be summarized per treatment group in terms of number (%) of subjects with elevated TSH (higher than the upper normal range), low TSH (lower than lower normal range), elevated TSH post-dose and within normal range at baseline, low TSH post-dose and within normal range at baseline. Shift tables showing baseline to maximum and baseline to minimum will be produced.

4.2.7.5 Electrocardiograms

ECG data obtained up until the safety follow-up will be included in the summary tables. Absolute values and change from baseline for ECG heart rate, PR duration, QRS duration, QT duration, and RR duration may be presented.

Overall evaluation of ECG is collected in terms of normal or abnormal, and the relevance of the abnormality is termed as "clinically significant" or "not clinically significant". ECG evaluations will be summarized using a shift table of baseline to worst evaluation on-treatment during the study if a sufficient number of ECG assessments are recorded.

4.2.7.6 Physical examination

Individual physical examination data will not be summarized.

4.2.7.7 Vital signs

Summaries for vital signs data will include all data obtained until 90 days after the last dose of study treatment. Absolute values and change from baseline for diastolic and systolic BP, pulse, respiratory rate, temperature and weight will be summarized at each visit. The denominator in vital sign data should include only those subjects with recorded data.

Box plots for absolute values and change from baseline by week may be presented for certain vital signs parameters if warranted after data review.

4.2.7.8 WHO/ECOG performance status

All WHO/ECOG performance status data will be summarized over time. Absolute values and change from baseline for WHO/ECOG PS will be summarized at each visit.

4.2.8 Pharmacokinetic data

PK concentration data for monalizumab will be summarized for all subjects in the PK analysis set.

Serum concentrations of monalizumab will be summarized by nominal sample time using standard summary statistics for PK concentrations (geometric mean, geometric coefficient of variation, arithmetic mean, standard deviation, minimum, maximum and n). All serum concentrations will be listed.

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

4.2.9 Immunogenicity analysis

Immunogenicity results of all subjects will be listed regardless of ADA positive/negative status. The number and percentage of subjects who develop detectable ADA to monalizumab within each ADA response category listed in Section 3.8 will be summarized based on the ADA analysis set. ADA titer and nAb data will be listed for samples confirmed positive for the presence of anti-monalizumab antibodies. Details for the presentation and derivation of ADA data is provided in Section 3.8. AEs in ADA positive subjects by ADA positive category will be listed.

The effect of immunogenicity on PK, efficacy and safety will be evaluated if data allow.

4.2.10 CCI

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4.2.11 Demographic, initial diagnosis and baseline characteristics data

The following will be summarized for all subjects in the HPV-unrelated Analysis Set and FAS (unless otherwise specified) by treatment group:

- Subject disposition (including screening failures and reason for screening failure)
- Important protocol deviations
- Inclusion in analysis sets
- Demographics (age, age group [<50, ≥ 50 - <65, ≥65 - <75 and ≥75 years], sex, race and ethnicity, region)
- Subject characteristics at baseline (height [cm], weight [kg], weight group [<70, ≥70 – <90, and ≥ 90 kg], Body Mass Index [BMI] and BMI group [<18.5, ≥18.5 – 25.0, ≥25.0 – <30.0, ≥30.0 kg/m^2])
- Subject recruitment by region, country and center
- Previous disease-related treatment modalities
- Prior cancer therapies
- Disease characteristics at baseline (PD-L1 status, HPV status, ECOG performance status, primary tumor location, histology type, tumor grade, AJCC stage, platinum sensitivity, best response to first and last previous PD-1 or PD-L1 therapy, best response to immediate last line of therapy, and overall disease classification)
- Extent of disease at baseline

- TNM classification at diagnosis
- Medical history (past and current)
- Disease related relevant surgical history
- Relevant surgical history
- Disallowed concomitant medications
- Allowed concomitant medications
- Post-discontinuation cancer therapy
- Nicotine use, categorized (never, current, former)
- Stratification factors recorded at randomization by IVRS and on eCRF

The medications will be coded following AZ standard drug dictionary/WHO Drug dictionary as applicable.

4.2.12 Concomitant and other treatments

All concomitant and other treatment data will be listed for all subjects in the FAS.

Concomitant medications and procedures will be summarized by treatment arm, ATC classification and preferred WHO name for HPV-unrelated Analysis Set and FAS. Subjects with the same concomitant medication/procedure multiple times will be counted once per medication/procedure. A medication/procedure that can be classified into more than once chemical and/or therapeutic subgroup will be presented in each subgroup.

Concomitant medications are those which are taken at any time between first dose of monalizumab, cetuximab, or placebo and on or before 90 days after the last monalizumab, cetuximab, or placebo dose date of the study or before the initiation of the first subsequent anti-cancer therapy (including radiotherapy, except for palliative radiotherapy) following discontinuation of monalizumab, cetuximab, or placebo, whichever occurs first. This includes medications which were started before first dose of monalizumab, cetuximab, or placebo in the study, but stopped during the study or were ongoing at completion of or withdrawal from the study.

Some previous and concomitant medications summary tables could present only the preferred WHO name.

4.2.13 COVID-19

Depending on the extent of any impact, summaries of data relating to patient's diagnosed with COVID-19 and the impact of COVID-19 on study conduct may be generated including:

- Summary of COVID-19 disruption
- Listing for patients affected by the COVID-19 pandemic
- Listing for patients with reported issues in the Clinical Trial Management System due to the COVID-19 pandemic

5 INTERIM ANALYSIS

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5.1 Independent data monitoring committee

This study will use an external independent data monitoring committee (IDMC) to assess ongoing safety analysis as well as the interim efficacy analysis.
The first IDMC meeting will occur after the first DCO, which will be triggered once one of the following events occurs:

- Approximately 6 months after first patient randomized or 60 participants are randomized (trigger for IDMC general data review);
- First 8 evaluable Japanese patients complete the safety and tolerability assessment period or meeting criteria for convening a Japan specific ad-hoc IDMC meeting [details in Appendix of IDMC charter] (trigger for IDMC Japan-specific data review).

After the first IDMC meeting, the IDMC will meet at least every 6 months thereafter. For IA1 and IA2, the IDMC will review unblinded interim efficacy data as outlined above. Following each meeting, the IDMC will report to the sponsor and may recommend changes in the conduct of the study.

This committee will be composed of therapeutic area experts and biostatisticians, who are not employed by AstraZeneca and are free from conflict of interest.

Following the reviews, the IDMC will recommend whether the study should continue unchanged, be stopped, or be modified in any way. Once the IDMC has reached a recommendation, a report will be provided to AstraZeneca. The report will include the

recommendation and any potential protocol amendments and will not contain any unblinding information.

The final decision to modify or stop the study will sit with the sponsor. The sponsor or IDMC may call additional meetings if at any time there is concern about the safety of the study.

Full details of the IDMC procedures and processes can be found in the IDMC Charter. The safety of all AstraZeneca/MedImmune clinical studies is closely monitored on an ongoing basis by AstraZeneca/MedImmune representatives in consultation with the Subject Safety Department. Issues identified will be addressed; this could involve, for instance, amendments to the Clinical Study Protocol and letters to investigators.

6 CHANGES OF ANALYSIS FROM PROTOCOL (NOT APPLICABLE)

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8 APPENDIX 1 EORTC QLQ – H&N 35 SCORING PROCEDURE

Head & Neck cancer module: QLQ-H&N35

The head & neck cancer module is meant for use among a wide range of patients with head & neck cancer, varying in disease stage and treatment modality (i.e. surgery, radiotherapy and chemotherapy) (Bjordal and Kaasa, 1992; Bjordal et al., 1994, 1999, 2000). The module comprises 35 questions assessing symptoms and side effects of treatment, social function and body image/sexuality (Appendix 2b). The module has been developed according to the guidelines, and pretested on patients from Norway, Sweden, Denmark, the UK and French-speaking Belgium. It has been field tested in Norway, Sweden and The Netherlands, and in a large cross-cultural study involving more than ten countries (EORTC Protocol 15941).

Scoring of the head & neck cancer module

The head & neck cancer module incorporates seven multi-item scales that assess pain, swallowing, senses (taste and smell), speech, social eating, social contact and sexuality. There are also eleven single items. For all items and scales, high scores indicate more problems (i.e. there are no function scales in which high scores would mean better functioning).

The scoring approach for the QLQ-H&N35 is identical in principle to that for the symptom scales / single items of the QLQ-C30.

Scale name	Scale	Number of items	Item range*	QLQ-H&N35 Item numbers
Symptom scales / items				
Pain	HNPA	4	3	1 – 4
Swallowing	HNSW	4	3	5 – 8
Senses problems	HNSE	2	3	13,14
Speech problems	HNSP	3	3	16,23,24
Trouble with social eating	HNSO	4	3	19 – 22
Trouble with social contact	HNSC	5	3	18,25 – 28
Less sexuality	HNSX	2	3	29,30
Teeth	HNTE	1	3	9
Opening mouth	HNOM	1	3	10
Dry mouth	HNDR	1	3	11
Sticky saliva	HNSS	1	3	12
Coughing	HNCO	1	3	15
Felt ill	HNFI	1	3	17
Pain killers	HNPK	1	1	31
Nutritional supplements	HNNU	1	1	32
Feeding tube	HNFE	1	1	33
Weight loss	HNWL	1	1	34
Weight gain	HNWG	1	1	35

* "Item range" is the difference between the possible maximum and the minimum response to individual items.

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Document ID:	Doc ID-004931579	
Version Label:	1.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
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19-Jul-2022 18:51 UTC	PPD	Author Approval

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