STATISTICAL ANALYSIS PLAN (SAP)

Title:	A Phase 2, Randomised, Double-Blind, Placebo-Controlled, Proof-of-Concept Study to Evaluate the Efficacy, Safety, and Tolerability, and Effects on Tumour Biomarkers of the NOX1/4 Inhibitor Setanaxib, when Administered with the PD-1 Inhibitor Pembrolizumab, in Patients with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)
NCT number:	NCT05323656
Unique Protocol ID:	GSN000400
Document Date:	08 April 2024

Statistical Analysis Plan (SAP)

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Protocol Version No./Date:	v5.0 / 12 December 2023 * v4.2 / 25 April 2023 (United Kingdom) * harmonized protocol for the EU countries in preparation for CTR transition incorporating Global Amendments 1 and 2, and the country specific changes previously implemented in Local Amendment 1 for France (Version 2.1 protocol).
CRF Version No./Date:	v5.0 / 19 September 2023
SAP Version No./Date:	v2.0 / 08 April 2024

1.0 Approvals

Sponsor	
Sponsor Name:	Calliditas Therapeutics Suisse SA
Representative/ Title:	/ Senior Statistician
Signature /Date:	
ICON	
Biostatistician / Title:	/ Principal Biostatistician
Signature /Date:	

(NOTE: Electronic Signatures should only be used if all parties have the ability to eSign.)

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2.0 Change History

Version/Date	Change Log
v0.1 / 7th March 2022	Created as new
v0.2 / 30th March 2023	Updates based on Sponsor Feedback to SAP v0.1. Updates based on moving from Protocol v2.0 to v3.0 (and local v3.1 / v3.2). Updates to conform to the ICON SAP Template.
v0.3 / 12th June 2023	Updates based on Sponsor Feedback to SAP v0.2.
v1.0 / 20th June 2023	Updates based on Sponsor Feedback to SAP v0.3. Rounded version for approval of scope (ToC).
v1.1 / 7th November 2023	Minor updates in parallel to TFL Shell creation.
v1.2 / 21st November 2023	Updates based on Sponsor Feedback to both SAP and TFL Shells v1.1.
v1.3 / 28th November 2023	Minor Updates based on Sponsor Feedback to v1.2.
v1.4 / 1st December 2023	Incorporated Sponsor request to re-derive Overall Visit Responses.
v1.5 / 15th January 2024	Minor updates in line with Dry Run 1 production.
v1.6 / 6th April 2024	Minor updates based on moving to Protocol v5.0. Incorporated Sponsor feedback from Dry Run 1.
v2.0 / 8th April 2024	Minor change to the Database Lock description. Up versioned for Final Signatures.

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3.0 Table of Contents

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4.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under the Calliditas Therapeutics Suisse SA Protocol GSN000400.

5.0 Scope

The SAP outlines the following:

- Study Objectives
- Study Design
- Study Estimands
- Applicable Study Definitions
- Statistical Methods

6.0 Introduction

This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). This version of the SAP has been developed by ICON using protocol version v5.0 dated 12 December 2023 along with the local amendment for the United Kingdom (v4.2 dated 25 April 2023) and CRF v5.0 dated 19 September 2023. Any further changes to the protocol or eCRF that have an impact on the design or the planned statistical analysis will require updates to the SAP.

The initial version of the SAP will be signed prior to the biomarker interim analysis (see Section 11.0 for details). The final version of the SAP, will be issued for sponsor approval prior to the data cut off for the updated analysis (see Section 8.4 for details on the timing of database lock).

A separate Independent Data Monitoring Committee (IDMC) SAP (v1.0 dated 16 December 2022) documents the details of the regular safety and tolerability reviews performed by an unblinded IDMC.

The full set of tables, listings and figures (TLFs) described in this SAP will be produced for the primary analysis and the updated analysis. If there are patients continuing in the study after the updated analysis, a small set of adverse events (AEs), serious adverse events (SAEs) and other selected safety data listings will be updated and included in an addendum to the CSR. The full set of outputs will not be reproduced.

6.1 Changes from Protocol

6.1.1 Major Changes

- **Initial Data Cut-Off for Primary Analysis**

  Section 8.1 of the protocol states the *"initial data cut-off will occur approximately 9 weeks after completion of enrolment, when all patients are expected to have had at least 3 cycles of pembrolizumab, at least one post-treatment scan, and the opportunity for a post-treatment tumour biopsy."*. During the preparation of this SAP a decision was made to extend this to approximately 15 weeks after completion of enrolment, with the aim for patients to have at least two post-treatment scans. This is clarified in Section 12.5 of this SAP.

- **Inclusion of the HPV Stratification Factor in Modelling**

  Section 8.4.2 of the protocol states the fitted analysis of covariance (ANCOVA) model as the only method to analyse the primary efficacy endpoint and without reference to human papillomavirus (HPV) status as a possible covariate. HPV status has been used as the stratification factor in the design of the study and not accounting for this factor in the analysis model may enhance the unexplained variability in the fitted linear model. Therefore, the HPV status will be included as a covariate in the ANCOVA model, if there are at least 10 patients at each level within each treatment group.

  The same approach has been taken for the analysis of the cancer-associated fibroblasts (CAFs), cluster of differentiation 8 ($CD8^+$), tumour-infiltrating lymphocytes (TILs) and the programmed cell death ligand 1 (PD-L1) expressions.

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The HPV stratification factor, as well as the possible treatment-covariate interaction, have also been added as predictors for the Cox proportional hazards model described in Section 10.8.1 of this SAP.

- **Duration of Response (DoR)**

  As DoR is a time-to-event endpoint, it was decided that an analysis using the Kaplan Meier method would be more appropriate than the Confidence Interval (CI) approach for a binomial proportion. This is described in Section 12.5.4.2 of this SAP.

- **Supportive Analyses**

  Section 8.4.5 of the protocol describes a competing risk approach, using Fine & Gray (1999) methods to further analyse PFS. It was decided during the preparation of this SAP to remove this analysis from the scope of this SAP.

- **Primary Estimand**

  Section 8.4.2 of the protocol describes the use of a treatment policy strategy to handle intercurrent events. The treatment policy strategy allows for data to be used regardless of the presence of any intercurrent events. However as one of the listed intercurrent events is the use of alternative or additional therapy, any percentage change from baseline after this intercurrent event cannot be considered for the analysis due to an improvement being possibly related to the new therapy rather than IMP. Hence the SAP has implemented a hybrid of strategies for handling intercurrent events. This is clarified in Section 9.1.1 of this SAP.

6.1.2 Minor Changes

- Section 8 of the protocol only discusses an estimand and intercurrent events related to the primary objective. The estimand framework has been built in Section 9.0 of this SAP for all the secondary objectives related to estimation of the treatment effect.
- Section 8.4.6 of the protocol describes a summary of abnormal physical examination findings should be presented. During the review of the initial SAP draft, the study team decided that a listing of all findings would be sufficient.
- Section 8.4.6 of the protocol also describes discrepancies between randomisation stratification information (obtained from IRT) and strata formed based on Screening factor collected on eCRFs (HPV status) will be explored. The HPV status on the CRF Randomisation page is integrated from the IRT data and so this presentation isn't necessary.
- Section 8.4.6 of the protocol also describes a presentation of modified World Health Organisation (WHO) ratings. These ratings are not collected for this study, hence no presentations will be provided.
- Section 8.2 of the protocol define the PK analysis set as *"…all patients who receive at least 1 dose of setanaxib and have at least 1 measured concentration at a scheduled PK time point post-dose."* A clarification was added to note that any concentration below the quantification limit (BQL) is considered to be a measured concentration and therefore included.

6.1.3 Clarifications

- The protocol uses "Major" as well "Important" to describe significant protocol violations. The SAP will use "Important" to align with ICON standard terminology.
- The protocol describes that the Per-Protocol Analysis Set (PPS) will include all patients in the FAS who complied sufficiently with the protocol with respect to exposure to IMP, availability of tumour assessments, and absence of important protocol deviations likely to impact efficacy outcome. These components are assed manually in the review of the deviation log, and the flag labelled "Impact to Primary Endpoint (Y/ N)" will be solely used for excluding subjects from the PPS. See Section 9.2.4 for details.
- The protocol uses terms for both "patient" and "subject", this SAP will use "patient" throughout.

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- The protocol uses “IMP or placebo” whilst the eCRF uses “IMP” to refer to setanaxib/placebo. This SAP will use IMP in the same way as the eCRF, to mean setanaxib/placebo.

7.0 Study Objectives and Endpoints

7.1 Primary Objective and Endpoint

Primary Objective	Primary Endpoint
• To compare the change in tumour size per Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST v1.1) in recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• Best percentage change in tumour size, defined as the best percentage change from Baseline in the sum of diameters of target lesions (TLs), as assessed by RECIST v1.1

7.2 Secondary Objectives and Endpoints

Key Secondary Objectives	Key Secondary Endpoints
• To compare the progression-free survival (PFS) per RECIST v1.1 in recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• PFS, defined as time from randomisation to the first documented disease progression per RECIST v1.1 or death due to any cause, whichever occurs first. PFS at 3, 6, and 12 months and median PFS will be summarised
• To compare the change from Baseline in CAFs level in tumour tissue from recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• Change from Baseline in CAFs level in tumour tissue
• To compare the change from Baseline in the number of $CD8^+$ TILs and regulatory T-cells in tumour tissue from recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• Change from Baseline in the number of $CD8^+$ TILs and regulatory T-cells in tumour tissue
Other Secondary Objectives	**Other Secondary Endpoints**
• To assess the overall response rate (ORR), the DoR and disease control rate (DCR) per RECIST v1.1 in recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• Proportion of the patients who have a complete response (CR) or partial response (PR) per RECIST v1.1 will be used to assess ORR • The minimum time when CR or PR is first observed to the time of progression of disease (PD) or death will be used to assess DoR • Proportion of the patients in whom the best overall response is determined as CR, PR, or stable disease (SD) per RECIST v1.1 will be used to assess DCR
• To assess the overall survival (OS) in recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• OS, defined as the time from Randomisation to death due to any cause. Patients without documented death at the time of the final analysis will be censored at the date of the last follow-up.
• To evaluate the safety and tolerability profile of setanaxib and pembrolizumab, versus placebo and pembrolizumab, in recurrent or metastatic SCCHN patients	• AEs: monitoring for AEs at all visits • Adverse events of special interest (AESIs):

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	○ Anaemia ○ Hypothyroidism • Vital signs: ○ Pulse rate ○ Systolic blood pressure (SBP) ○ Diastolic blood pressure (DBP) • 12-lead electrocardiogram (ECG): clinically significant abnormalities • Physical examination: abnormal findings • Laboratory tests: ○ Haematology ○ Biochemistry ○ Urinalysis ○ Thyroid function test
• To compare the change from Baseline in PD-L1 expression in tumour tissue from recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• Levels of PD-L1 expression in tumour tissue
• To compare the change from Baseline in patterns of gene expression and differential gene expression in tumour tissue from recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab, using Ribonucleic acid (RNA) sequencing	• Gene expression quantification and analysis of patterns of gene activation for CAFs and $CD8^+$ TILs, and regulatory T-cells
• To assess the plasma exposure of setanaxib and its metabolite GKT138184	• Pre-dose and post-dose plasma concentrations of setanaxib and GKT138184: ○ Area under the concentration-time curve over the last 24-h dosing interval at steady state (AUC[0-24]-ss) ○ Minimum plasma concentration at steady state (Cmin-ss) ○ Maximum plasma concentration at steady state (Cmax-ss)

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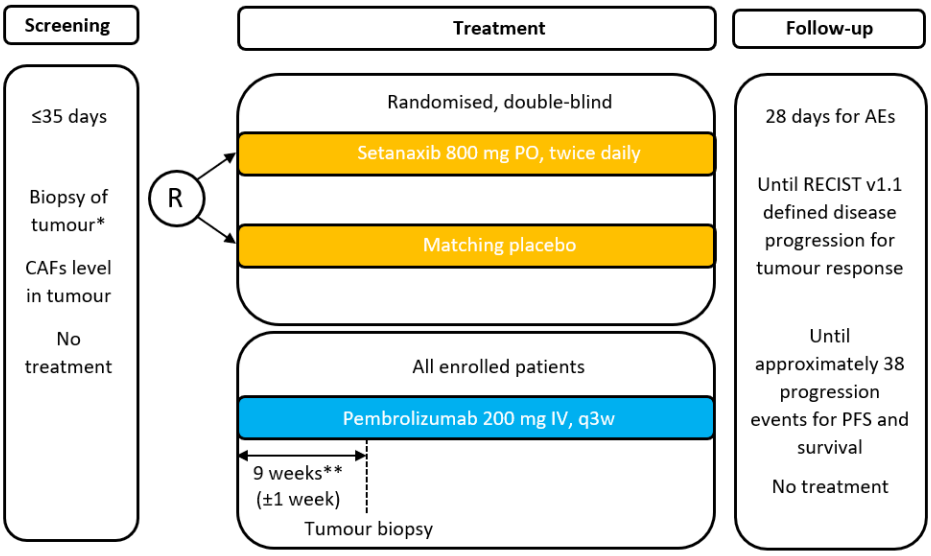
7.3 Exploratory Objectives and Endpoints

Exploratory Objectives	Exploratory Endpoints
• To assess the relationship between setanaxib and GKT138184 plasma exposure and response, if data permits	• Where data permit, the pharmacokinetics (PK) (setanaxib and GKT138184 plasma exposure)/pharmacodynamics (e.g., changes in biomarkers, efficacy, and safety parameters) relationship may be explored graphically and/or using appropriate PK/pharmacodynamic modelling techniques
• To compare the change from Baseline in patterns of gene expression and differential gene expression in tumour tissue from recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab, using RNA sequencing	• Gene expression quantification and analysis of patterns of gene activation for relevant immuno-oncology, inflammatory, and other relevant gene signatures
• To compare changes in circulating biomarkers detectable in peripheral blood in recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• Evaluations of pre-, on-treatment, and progression peripheral blood samples for circulating biomarkers which may include but will not be limited to panels of cytokines, chemokines and other soluble biomarkers; T-cell receptor repertoire analysis; and analysis of gene expression biomarkers associated with immunomodulatory effects

8.0 Study Design

This is a randomised, double-blind, placebo-controlled, proof-of-concept, Phase 2 study assessing setanaxib co-administered with pembrolizumab in patients with recurrent or metastatic SCCHN. The safety and efficacy of setanaxib 800 mg BID will be assessed against matching placebo over up to 105 weeks of treatment. The design is depicted in Figure 1.

Figure 1 Study Schematic



AE=adverse event; CAFs=cancer-associated fibroblasts; IV=intravenously; PFS=progression-free survival; PO=per os (orally, or via either a feeding tube or a percutaneous endoscopic gastrostomy device in case patients are unable to swallow tablets); q3w=every 3 weeks; R=randomisation; RECIST v1.1=response evaluation criteria in solid tumours version 1.1
* For patients with a suitable archival tumour biopsy sample available, the archival sample may be used to assess CAFs level and determine eligibility (Note: this can only be performed after the patient has provided signed informed consent). This will not dispense from the need for a recent pre-study tumour biopsy.

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The study plans to randomise approximately 50 patients at up to approximately 35 investigational centres in North America and Europe, to the IMP, according to a 1:1 randomisation ratio, stratified by HPV status. Depending on the number of patients providing evaluable Week 9 biopsy and imaging data, up to an additional 20 patients (making a maximum of 70 patients) may be randomised to ensure an adequate amount of data is available for the efficacy and biomarker analyses.

The study will consist of an up to 35-day Screening Period, an up to 24-month Treatment Period (Day 1 to Week 105), and a 28-day Safety Follow-up Period. The total duration of the study for patients remaining in the study until their final follow-up assessment will be up to approximately 114 weeks (approximately 2 years and 2 months).

All patients included in this study will receive pembrolizumab, with setanaxib or placebo given as add-on therapy to a recognised and approved standard-of-care agent.

Treatment with pembrolizumab will continue until: RECIST v1.1-defined disease progression is determined by the investigator (Eisenhauer et al 2009), unacceptable toxicity, or a maximum of 24 months. If progression is suspected, but not confirmed, study treatment may continue until confirmation of radiological progression. Treatment with setanaxib or placebo will continue throughout the period of pembrolizumab therapy. When pembrolizumab is discontinued, blinded study treatment will also be discontinued.

Baseline assessments will be performed on Day 1 (Visit 2). Post-Baseline assessments will be performed every 3 weeks up to pembrolizumab discontinuation. Following permanent IMP discontinuation at any time during the study, patients will undergo an End-of-Treatment (EoT) Visit as soon as possible and a Safety Follow-up Visit at 28 days after the last dose.

Initial tumour imaging is performed within 35 days prior to the date of treatment and will be used as the Baseline scan for the tumour assessments. Tumour assessments will then be conducted from the date of randomisation and continue until RECIST v1.1-defined disease progression, irrespective of treatment discontinuation. Efficacy Follow-up for PFS and survival will continue until approximately 38 progression events have occurred. AEs will be recorded up to 28 days after study treatment discontinuation, while any further anti-cancer medication will be recorded until disease progression.

The primary endpoint is best percentage change in tumour size. A population with measurable disease will be selected to generate the maximum tumour response data. The secondary endpoints related to numbers of CAFs, $CD8^+$ TILs, and regulatory T-cells in tumour tissue, and gene expression analysis in tumour tissue will be used to demonstrate the underlying mechanisms of action of setanaxib and support the primary objective.

Safety and tolerability data will be regularly reviewed by an unblinded IDMC, with the first assessment after approximately 12 patients (6 per treatment group) have had the opportunity to complete at least one cycle of pembrolizumab +/- setanaxib, followed by periodic assessments at a frequency defined in the IDMC Charter. The IDMC may recommend changes to the setanaxib dose regimen or study conduct based on the safety data reviews.

After approximately 12 patients (6 per treatment group) have completed their Baseline and post-treatment biopsy, initial gene expression and biomarker data in tumour tissue may be reviewed by the sponsor, who will be unblinded to randomised treatment assignment, although subject IDs will remain masked. A second review may be performed, if required.

8.1 Sample Size Considerations

An overall sample size of approximately 50 patients (25 per treatment group) is considered sufficient to assess the primary endpoint of the best percentage change in tumour size following treatment with setanaxib when administered with pembrolizumab, versus placebo when administered with pembrolizumab, in patients with recurrent or metastatic SCCHN. With 25 patients per treatment group, using a 2-sided t-test, there will be 85% power to detect a 20% mean difference between the treatment groups in best percentage change in tumour size, with an estimated SD of 30% and a 2-sided alpha of 20%. To mitigate risks from a higher than expected number of patients discontinuing the study early or declining to have imaging or biopsies at Week 9, up to an additional 20 patients (making a maximum of 70 patients) may be randomised.

The key secondary endpoints of numbers of CAFs, $CD8^+$ TILs, and regulatory T-cells in tumour tissue and gene expression analysis in tumour tissue will be used to determine proof of concept. With 25 patients per treatment group, there will be 90% power to detect a limit fold change (LFC) of more than 1.5 in gene sequencing endpoints measured in tumour tissue, assuming at least 20 patients have an evaluable Baseline and post-Baseline tissue sample.

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For the key secondary endpoint of PFS, if the true hazard ratio for PFS is 0.5, approximately 38 progression events as defined by RECIST v1.1 will be required to have > 80% power to demonstrate a statistically significant difference in PFS with 2-sided p<0.2.

8.2 Randomisation

Randomisation will be performed via centralised interactive response technology (IRT). On Day 1, eligible patients will be assigned to setanaxib or placebo in a 1:1 ratio, stratified by HPV status. Each patient will receive a unique randomisation number when he/she is assigned treatment. Patients will be allocated to treatment according to the randomisation code.

8.3 Blinding

The investigator, the site personnel, the sponsor and their representatives involved in monitoring and conducting the study, and the patients will be blinded to treatment assignments.

The randomisation lists containing the true treatment assignment and kit lists containing the IMP kit assignments of patients will be maintained by ICON IRT system and ALMAC Clinical Services respectively. This information will not be accessible to any blinded project team members prior to the primary analysis, nor to the investigators or patients prior to updated analysis.

Additional details regarding the unblinding process can be found in the Data Blinding and Documentation Plan for further details.

8.4 Database Lock

The data cut off for the updated analysis (or primary analysis if the updated analysis is not performed due to close proximity to the primary), will also be the final database lock, as long as there are no patients remaining on treatment at the time of the data cut off. If patients remain on treatment after this data cut off, then an interim lock will be used for the primary analysis and the final database lock will occur once all patients have completed study treatment or withdrawn from the study. An updated safety analysis will be performed if the final database lock occurs after the interim lock. Full details of the primary and updated analyses are given in Section 12.5.

9.0 Study Estimands

An estimand is a precise description of the treatment effect reflecting the clinical question posed by a given clinical trial objective. The estimand consists of five attributes: the treatment, the population, the variable, the specification of intercurrent events and how to account for these, and the population level summary.

9.1 Estimand Attributes

9.1.1 Primary Estimands

Primary Objective	Primary Estimand Attributes
• To compare the change in tumour size per RECIST v1.1 in recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• **Treatment:** setanaxib + pembrolizumab versus placebo + pembrolizumab. • **Population:** Patients in the FAS who also have measurable disease at baseline. • **Variable:** Best percentage change in tumour size defined as the percentage change from Baseline in the sum of diameters of target lesions, as assessed by RECIST v1.1.

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	• **Intercurrent Events:** 1. Premature study discontinuation 2. Use of certain alternative or additional therapy including a new anti-cancer therapy 3. Premature study drug discontinuation/interruption 4. PD or Death • **Strategy:** Hybrid (While on Treatment / Treatment Policy / Hypothetical) A While on Treatment approach will address the first 2 intercurrent events listed above. Any values for the variable of interest after the occurrence of either of the first 2 intercurrent events listed are considered irrelevant in defining the treatment effect of interest, i.e. only values prior to the occurrence of the intercurrent event are considered. A Treatment Policy approach will be taken where a patient prematurely discontinues treatment, i.e. all data will be used up to the point of PD. A hypothetical approach will be taken where a patient has no evaluable post-baseline assessments, as a result of PD or death, by performing imputation (See Section 10.7.6). • **Population Level Summary Measure:** The LS Mean difference (or geometric mean ratio if a log transformation has been applied), 80% CI and associated p-value for the treatment comparison will be obtained from the ANCOVA model.

9.1.2 Secondary Estimands

The attributes of the secondary estimands are the same as described for the primary estimand in Section 9.1.1 unless otherwise specified in the secondary attributes list below;

Key Secondary Objectives	Secondary Estimand Attributes
• To compare the PFS per RECIST v1.1 in recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• **Variable:** Time from randomisation to the first documented disease progression per RECIST v1.1 or death due to any cause, whichever occurs first. • **Intercurrent Events:** 1. Lacking disease evaluation. 2. Premature study discontinuation 3. Use of certain alternative or additional therapy including a new anti-cancer therapy • **Strategy:** Hypothetical A hypothetical strategy will be applied using censoring rules (see Section 10.8.1). • **Population Level Summary Measure:** The HR of PFS between the competing treatment groups.
• To compare the change from Baseline in CAFs level in tumour tissue from recurrent or	• **Variable:**

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metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	Change from Baseline in CAFs level in tumour tissue. • **Strategy:** Treatment Policy A Treatment Policy strategy will address the intercurrent events listed, by considering the intercurrent events irrelevant in defining the treatment effect of interest. The value for the variable of interest is used regardless of whether or not the intercurrent events occur.
• To compare the change from Baseline in the number of $CD8^+$ TILs and regulatory T-cells in tumour tissue from recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• **Variables:** $CD8^+$: Change from Baseline in $CD8^+$ TILs numbers in tumour tissue. T-Cells: Change from Baseline in FOXP3 values. • **Strategy:** Treatment Policy As described for CAFs level above.

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Other Secondary Objectives	Other Secondary Estimands
• To assess the ORR, the DoR and DCR per RECIST v1.1 in recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• **Variables:** ORR: Proportion of the patients who have a CR or PR per RECIST v1.1. DCR: Proportion of the patients in whom the best overall response is determined as CR, PR, or SD per RECIST v1.1. • **Intercurrent Events:** 1. Premature study discontinuation 2. Use of certain alternative or additional therapy including a new anti-cancer therapy 3. PD or Death 4. Premature study drug discontinuation/interruption • **Strategy:** Hybrid **(**While on Treatment / Treatment Policy) A While on Treatment approach will be taken to address the first 3 intercurrent events. Any values for the variable of interest after the occurrence of the intercurrent events listed are considered irrelevant in defining the treatment effect of interest, i.e. only values prior to the occurrence of the intercurrent event are considered. A Treatment Policy approach will be taken where patients prematurely discontinue/interrupt study treatment. The value for the variable of interest is used regardless of whether or not the intercurrent event occurs. • **Population Level Summary Measure:** ORR and DCR: The summary measure of associated 90% Agresti-Coull confidence interval of ORR and DCR at each treatment group.
	• **Variable:** DoR: The minimum time when CR or PR is first observed to the time of PD or death. • **Intercurrent Events:** 1. Premature study discontinuation 2. Use of certain alternative or additional therapy including a new anti-cancer therapy 3. Premature study drug discontinuation/interruption • **Strategy:** Hypothetical A hypothetical strategy will be applied using censoring rules (see Section 10.9.4). • **Population Level Summary Measure:** DoR: Kaplan Meier estimates of the median and quartiles along with their 90% CIs using the Brookmeyer-Crowley method.

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• To assess the OS in recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	Note: The secondary endpoint of OS will not be formally compared between the treatment groups. • **Variable:** Time from randomisation to death due to any cause. • **Intercurrent Events:** 1. Study completion / Data cut off • **Strategy:** Hybrid of Treatment Policy **and** Hypothetical A Treatment Policy approach will be taken where patients experience any intercurrent event other than study completion / data cut off. The value for the variable of interest is used regardless of whether or not the intercurrent event occurs. A hypothetical strategy will be applied using censoring rules (see Section 10.8.2). • **Population Level Summary Measure:** Kaplan Meier estimates of the median and quartiles along with their 90% CIs using the Brookmeyer-Crowley method.
• To evaluate the safety and tolerability profile of setanaxib and pembrolizumab, versus placebo and pembrolizumab, in recurrent or metastatic SCCHN patients	This safety objective is not related to estimating or defining the magnitude of the treatment effect, hence the construction of an estimand is not applicable.
• To compare the change from Baseline in PD-L1 expression in tumour tissue from recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• **Variable:** Change from Baseline levels of PD-L1 expression in tumour tissue. • **Strategy:** Treatment Policy As described for CAFs level above.
• To compare the change from Baseline in patterns of gene expression and differential gene expression in tumour tissue from recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab, using RNA sequencing	The biomarker objective does not relate to estimating or defining the magnitude of the treatment effect, hence the construction of an estimand is not applicable.
• To assess the plasma exposure of setanaxib and its metabolite GKT138184	The PK objective does not relate to estimating or defining the magnitude of the treatment effect, hence the construction of an estimand is not applicable.

9.1.3 Exploratory Estimands

The exploratory objectives described in Section 0 do not relate to estimating or defining the magnitude of the treatment effect, hence the construction of exploratory estimands is not applicable.

9.2 Population Sets

9.2.1 All Enrolled Analysis Set

The all enrolled analysis set (ENRL) consists of all patients who signed informed consent for this study.

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9.2.2 All Randomised Analysis Set

The all randomised analysis set consists of all patients who were randomised into the study. Patients will be summarised by the treatment group they were randomised to.

9.2.3 Full Analysis Set

The Full Analysis Set (FAS) will include all randomised patients who receive at least one full dose of IMP (i.e. 800mg or two tablets). Patients will be analysed according to randomised treatment regardless of the treatment they actually received. This analysis set will be the primary set used for all efficacy analyses.

9.2.4 Per-Protocol Analysis Set

The PPS will include all patients in the FAS who complied sufficiently with the protocol with respect to exposure to IMP, availability of tumour assessments, and absence of important protocol deviations likely to impact efficacy outcomes. This will be identified via the Protocol Deviation Log, where a patient with any deviation categorised as "Y" for the flag "Impact to Primary Endpoint (Y/ N)" will be excluded.

Patients will be analysed based on the treatment group they were randomised to regardless of the actual treatment received.

9.2.5 Safety Analysis Set

The Safety Analysis Set will include all randomised patients who receive at least one tablet of IMP. Patients will be analysed according to treatment they actually received. This analysis set will be used for summaries of safety data.

9.2.6 Pharmacokinetics Analysis Set

The PK Analysis Set will include all patients who receive at least one dose of setanaxib and have at least one measured concentration, including any BQL, at a scheduled PK time point post-dose. Patients will be analysed according to treatment they actually received.

10.0 Conventions and Derivations

10.1 Baseline, Change and Percent Change from Baseline

Baseline is defined as the last non-missing value before the first dose of IMP. Baseline values will generally be assessed at the Day 1 visit, the exception to this is the Initial tumour imaging scan which will be performed within 35 days prior to the date of treatment and will be used as the Baseline scan for the tumour assessments. For re-screened patients, the value associated with their screen failure record will not be considered for baseline.

If time of assessment is not collected and the assessment is collected on the same date as the first dose, the assessment will be assumed to be per protocol, i.e. prior to first dose. If multiple continuous assessments occur on the same day as first dose and no time is recorded, the average value will be used as baseline.

Change from baseline at any post-baseline time point will be defined as:

- $Absolute\ Change\ from\ Baseline = (Value\ at\ Post\ Baseline\ Time\ Point - Value\ at\ Baseline)$
- $Ratio\ of\ Postbaseline\ to\ Baseline = \left(\frac{Value\ at\ Post\ Baseline\ Time\ Point}{Value\ at\ Baseline}\right)$

Percentage change from baseline at any post-baseline time point will be defined as:

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- $Percentage\ Change\ from\ Baseline = 100 * \left(\frac{Value\ at\ Post\ Baseline\ Time\ Point - Value\ at\ Baseline}{Value\ at\ Baseline}\right)$

10.2 Study Day and Durations

The reference start date for safety and PK assessments will be the start date of IMP, whilst for all efficacy assessments it will be the date of randomisation.

Study Day is calculated as follows. Where (Prior) indicates the date of assessment if before the reference start date, and (Post) indicates it is on or after:

- $Study\ Day\ (Prior) = (Date\ of\ Assessment - Reference\ Start\ Date)$
- $Study\ Day\ (Post) = (Date\ of\ Assessment - Reference\ Start\ Date) + 1$

Whilst Section 10.13 details the imputation of partial dates, the duration of any event involving partial or missing dates will not be calculated. Otherwise where the duration of an event or the time since an event, is to be presented in days, the calculation is given as;

- $Duration\ (days) = (End\ Date - Start\ Date) + 1$

If a duration is required to be presented in a different time unit, the appropriate conversions are given below;

- $Duration\ (Years) = \left(\frac{Duration\ (days)}{365.25}\right)$
- $Duration\ (Months) = \left(\frac{Duration\ (days)}{30.4375}\right)$
- $Duration\ (Weeks) = \left(\frac{Duration\ (days}{7}\right)$

10.3 Screening Failures

Screening failures are patients who have signed informed consent and failed screening criteria in the study. These patients will not be enrolled into the treatment phase.

10.4 Visit Windowing

For the purposes of the analysis, observations will be assigned to analysis visits using the windows detailed in Table 1. All visits (including unscheduled, EoT and safety follow-up visits) will be windowed to the appropriate analysis visit regardless of the visit label entered in the eCRF. Safety follow-up visits will only contribute to the Safety follow-up analysis visit. Tabulations will only summarise scheduled time points for the assessments.

If more than one quantitative measurement falls within a post baseline visit window, then the following rules will apply;

- For PK assessments, the latest value on or prior to the day of IMP administration within a given window will be selected. If there is more than one record on the selected day, then;
    - For Analysis Visit Week 9, the arithmetic mean of the assessments will be calculated.
    - For all other Analysis Visits, the latest pre-dose assessment will be used.
- For all other assessments, the value closest to the target day will be selected. If more than one assessment is equidistant from the target day, the assessment later in time will be selected. If more than one record remains, then the arithmetic mean of the assessments will be calculated.
    - ECG assessments are scheduled to be collected at pre-dose and post-dose timepoints on Study Day 1 and 22. Where multiple assessments occur on the same day in these instances, the timepoint will be preserved.
- If the EoT assessment and a scheduled assessment reside within the same visit window, the scheduled assessment will be selected.

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If more than one quantitative measurement meets the Baseline definition (Section 10.1), then then the arithmetic mean of the assessments will be calculated.

If more than one qualitative measurement falls within a baseline or post-baseline visit window, then a conservative approach will be taken by selecting the worst result.

Table 1. Analysis Visit Windows

Analysis Visit	Target Study Day	Window for Safety	Window for Efficacy (Tumour Biopsies / Assessments)
Baseline	1		
Day 1	1		
Week 3	22	(±5)	
Week 6	43	(±5)	
Week 9	64	(±5)	(±7)
Week 12	85	(±5)	
Week 15	106	(±5)	(±7)
Week 18	127	(±5)	
Week 21	148	(±5)	(±7)
Week 24	169	(±5)	
Week 27	190	(±5)	(±7)
Week 30	211	(±5)	
Week 33	232	(±5)	(±7)
Week 36	253	(±5)	
Week 39	272	(±5)	(±7)
Week 42	295	(±5)	
Week 45	316	(±5)	(±7)
Week 48	337	(±5)	
Week 51	358	(±5)	(±7)
Week 54	379	(±5)	
Week 57	400	(±5)	(±7)
Week 60	421	(±5)	
Week 63	442	(±5)	(±7)
Week 66	463	(±5)	
Week 69	484	(±5)	(±7)
Week 72	505	(±5)	
Week 75	526	(±5)	(±7)
Week 78	547	(±5)	
Week 81	568	(±5)	(±7)

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Week 84	589	(±5)	
Week 87	610	(±5)	(±7)
Week 90	631	(±5)	
Week 93	652	(±5)	(±7)
Week 96	673	(±5)	
Week 99	694	(±5)	(±7)
Week 102	715	(±5)	
Week 105	736	(±3)	(±7)
Safety Follow-Up	EoT+28 days	(±7)	

10.5 Study Drug Exposure

10.5.1 Actual Treatment Assignment

The actual treatment assigned to a patient will be the treatment that the patient first received regardless of any dispensing issues at a later visit. For example, if a patient was randomised to the placebo+pembrolizumab group but the patient's first dose in the study was setanaxib+pembrolizumab, they will be assigned as having an actual treatment as the setanaxib+pembrolizumab group they first received, even if they were later dispensed placebo+pembrolizumab at all remaining visits.

10.5.2 Administration Dates

The date of first dose of IMP will be the date recorded on the "Study Drug Administration (IMP)" page of the eCRF for the first non-zero dose. The date of first dose of pembrolizumab will be the date recorded on the "IV/Infusion Administration" page of the eCRF.

Date of last dose of IMP will be the "Completion/Discontinuation Date" on the "End of Treatment (IMP)" page of the eCRF. If date of last dose of IMP is not available because the patient is ongoing at the time of a data cut, then the date of the data cut will be used. If the patient is lost to follow-up (identified via the EoT eCRF page), then the date of the last scheduled visit or the date of last telephone contact where a non-zero dose is recorded, will be used.

10.5.3 Duration of Exposure

The total duration of exposure to treatment will be calculated for each treatment component (IMP and pembrolizumab) regardless of temporary interruptions in administration, and will be expressed in weeks (to 1 decimal place [dp]). Exposure to pembrolizumab will include the 3 weeks after the last infusion date, hence the duration of exposure is defined as;

- $Duration\ of\ IMP\ Exposure\ (Weeks) = \frac{((Last\ Dose\ Date - First\ Dose\ Date)+1)}{7}$
- $Duration\ of\ Pembrolizumab\ Exposure\ (Weeks) = \frac{((Last\ Dose\ Date - First\ Dose\ Date)+22)}{7}$

10.5.4 Number of Doses/Infusions

The total number of administered doses/infusions is defined for each treatment component as the total number of doses/infusions of that component administered to the patient during the treatment period.

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10.5.5 Cumulative Dose and Planned Cumulative Dose

Cumulative dose is defined for each treatment component as the sum of all doses of that component administered to the patient during the treatment period.

Planned cumulative dose for a study treatment component is defined as the total dose planned per protocol, up to a patients last dose. The planned cumulative dose will be only used for relative dose intensity and compliance calculations. Planned cumulative dose will not be summarised.

- $Planned\ Cumulative\ Dose\ (mg) = Planned\ Daily\ Dose(mg) * Duration\ of\ Exposure\ (Days)$

10.5.6 Actual and Relative Dose Intensity

Actual dose intensity (ADI) and relative dose intensity (RDI) will be derived for IMP only, for patients with a non-zero duration of exposure. These are defined as;

- $ADI\ (mg/day) = \left(\frac{Cumulative\ Dose\ (mg)}{Duration\ of\ IMP\ Exposure\ (days)}\right)$
- $RDI\ (\%) = \left(\frac{ADI}{\left(\frac{Planned\ Cumulative\ Dose\ (mg)}{Duration\ of\ IMP\ Exposure\ (days)}\right)}\right) * 100$

10.5.7 Treatment Compliance

Compliance will be assessed for the study overall for IMP only, and is calculated as;

- $Compliance\ (\%) = \left(\frac{Cumulative\ Dose\ (mg)}{Planned\ Cumulative\ Dose\ (mg)}\right) * 100$

Noncompliance is defined as receiving less than 80% or more than 120% of assigned study drug at any visit.

10.6 Prior, Concomitant and Prohibited Medications

Prior medications are defined as those medications which started prior to the first dose date of IMP. See Section 6.6 of the Protocol for a list of prohibited prior medications.

Concomitant medications will be defined as medications starting prior to but ongoing after the first dose date of IMP, or with a start date on or after the first dose date of the IMP, up to and including 28 days after the last dose date of IMP.

Medications which start prior to the first dose date of IMP and are ongoing at the time of first dose will be summarised as both prior and concomitant medications.

Post Treatment medications are medications that started more than 28 days after the last dose of study medication.

The Sponsor will perform ongoing manual review of all medications, flagging any medication deemed to be prohibited in line with Section 6.8 of the protocol.

10.7 Primary Endpoint

10.7.1 Sum of Diameters (SOD)

Tumour size is defined as the sum of the longest diameters (SOD) of the TLs based upon RECIST assessments. This is based on RECIST TL measurements taken at baseline and at the time point of interest. Whilst the SOD is collected on the Disease Response eCRF page, this will be programmatically derived following RECIST 1.1, as the SOD (longest for non-nodal lesions, short axis for nodal lesions) for all TLs.

10.7.2 Target Lesions Too Small to Measure

If a TL is recorded on the eCRF as “Diameter too small to measure” then a value of 5 mm will be imputed to prevent false responses or progressions.

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10.7.3 Scaling of Missing Target Lesions

If a TL is missing, then a scaling rule will be applied to account for this missing data. A worked example is provided in Table 2.

If > 1/3 of TL measurements are missing, then TL response will be NE, unless the SOD 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, then the results will be scaled up based on the sizes at the nadir visit to give an estimated SOD and this will be used in calculations. This is equivalent to comparing the visit SOD of the non-missing lesions to the nadir SOD excluding the lesions with missing measurements.

The nadir SOD can be any visit that predates the missing measurement, including a "too small to measure" assessment previously imputed using the rule in Section 10.7.2. A newly imputed SOD can also become the new nadir.

Table 2. Example of Scaling

Lesion ID	TL Longest Diameter at Nadir Visit	TL Longest Diameter at Analysis Visit
1	7.2	7.1
2	6.7	6.4
3	4.3	4.0
4	8.6	8.5
5	2.5	Missing (because of Intervention)
SOD	29.3	26

Lesion 5 has a missing diameter at the follow-up assessment. The sum of lesions 1-4 at the follow-up assessment is 26 mm. The sum of the corresponding lesions at nadir time point is 26.8 mm. Scale up as follows to give an estimated TL SOD;

- $TL\ SOD\ (mm) = SOD\ at\ Nadir * \left(\frac{Sum\ of\ Non-Missing\ Diameters\ at\ Follow\ Up}{Sum\ of\ Corresponding\ Diameters\ at\ Nadir}\right) = 29.3 * \left(\frac{26}{26.8}\right)$

10.7.4 Split and Merged Target Lesions

The following RECIST v1.1 rules for handling split and merged target lesions are incorporated as part of the data collected on the eCRF;

- If a TL splits in two, then the longest diameters of the split lesions should be summed and reported as the longest diameter for the lesion that split.
- If two TLs merge, then the longest diameter of the merged lesion should be recorded for one of the TL sizes and the other TL size should be recorded as 0 mm.

10.7.5 Change in Method of Target Lesion Assessment

The same imaging technique regarding modality (CT or MRI scan), ideally the same scanner, and the use of contrast should be used in a patient throughout the study to optimise the reproducibility of the assessment of existing and new tumour burden and improve the accuracy of the assessment of response or progression based on imaging.

If a change in method of assessment occurs between CT and MRI, any affected lesions should be treated as missing. When calculating the SOD that includes missing values as a result of a change in assessment method, the scaling rules in Section 10.7.3 will be followed.

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10.7.6 Best Percentage Change for Primary Endpoint

Best percentage change from baseline in tumour size will be derived as the largest percentage decrease or the smallest percentage increase in tumour size from baseline.

In order to account for intercurrent events;

- Only values prior to the occurrence of premature study discontinuation or the use of alternative or additional therapy including a new anti-cancer therapy will be considered.
- Where a patient prematurely discontinues treatment, all values will be considered up to the point of PD.
- Where a patient has no evaluable post-baseline assessments, but presents evidence of either death or PD, a value of 20% will be imputed as the best percentage change from baseline. If a log transformation is required for analysis, a value of 0.182321557 will be imputed as the ratio of log(best postbaseline) to log(baseline), which represents a 20% increase when back transformed to the original scale (exp[0.182321557]=1.2).

  Note that the BOR in these instances should also be imputed as PD (see Section 10.9.2).

  Patients whose data have been imputed will be flagged in listings and waterfall plots where appropriate.

10.8 Survival

10.8.1 Progression Free Survival

The definition of PFS is the time from randomisation to the first documented disease progression per RECIST v1.1 or death due to any cause, whichever occurs first. This is calculated as:

$$PFS\ (days) = (Date\ of\ (PD\ or\ Censoring)\ -\ Date\ of\ Randomization) + 1$$

The event time for PFS will be censored on the date of randomisation with duration of 1 day for;

- Patients lacking any evaluation of disease after first study treatment (unless, they die within 2 scheduled tumour assessments of baseline, this will be treated as an event with the date of death as the event date).

The event time for PFS will be censored at the date of the last available assessment documenting absence of PD for the following scenarios;

- Patients who prematurely discontinue from the study.
- Any PD that occurs immediately after two consecutive missed visits.
- Patients who receive subsequent systemic anti-cancer therapy.
- Patients who are alive and progression-free at the time of a data cut off or End of Study.

10.8.2 Overall Survival

The definition of OS is the time from randomisation to death due to any cause. This is calculated as:

$$OS\ (days) = (Date\ of\ (Death\ or\ Censoring) - Date\ of\ Randomization) + 1$$

The OS for patients without a reported date of death at the time of data cut off or end of study, will be censored at the date last known to be alive.

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10.9 Disease Response

10.9.1 Overall Visit Response

The first on study imaging assessment should be performed at Visit 5 (Week 9 ±1 week), and then every 6 weeks (±1 week) through the first year, and every 9 weeks (±1 week) thereafter for up to 24 months. Tumour assessments will be conducted from the date of randomisation and continue until PD, irrespective of treatment discontinuation.

RECIST v1.1 will be used to determine each patient's overall visit response according to target lesions, non-target lesions (NTLs) and new lesions (Table 3). The overall visit responses are recorded on the Disease Response page of the eCRF, however these will be programmatically re-derived based on the target response, non-target response, and new lesion indicator, also collected on the Disease Response page of the eCRF for each visit. The derived overall visit response will be used in the analysis of secondary endpoints.

Table 3. Overall Visit Response

TLs	NTLs	New Lesions	Overall Visit Response
CR	CR	No	CR
CR	Non-CR / Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD / NE	No	PR
SD	Non-PD / NE	No	SD
NE	Non-PD	No	NE
PD	Any	Yes / No	PD
Any	PD	Yes / No	PD
Any	Any	Yes	PD

10.9.2 Best Objective Response

The BOR is selected as the best response of the individual programmatically derived overall visit responses, in sequential order from are CR, PR, SD*, PD and not evaluable (NE),

* Note that for SD, the patient must be stable at or after the first scheduled scan at 9 weeks (+/- 1 week). If an unscheduled scan is conducted prior to the week 9 assessment and shows SD, it will be listed but not included in the summary of BOR.

In cases where an overall visit spans multiple days, determination of the date on which the BOR occurred will follow these rules;

- For SD, the earliest of the dates contributing towards the overall visit assessment will be used.
- For CR or PR, the latest of the dates contributing towards the overall visit assessment will be used.

In order to account for intercurrent events;

- Only values prior to the occurrence of premature study discontinuation or the use of alternative or additional therapy including a new anti-cancer therapy will be considered.
- Where a patient prematurely discontinues treatment, all values will be considered up to the point of PD.

In cases where a patient has no evaluable post-baseline assessments, but presents evidence of either death or PD, the BOR will be imputed as PD.

10.9.3 Objective Response Rate

The ORR (as per RECIST v1.1) is defined as the number (%) of patients with a BOR of CR or PR. The denominator will be based on the FAS, limited to those who have measurable disease at baseline. Patients who discontinue

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treatment without PD and go on to have a CR or PR after receiving subsequent systemic anti-cancer therapy will not be considered a responder.

10.9.4 Duration of Response

The DoR is defined as the number of days from the date of first documented CR or PR until the date of first documented PD or death in the absence of PD, whichever is earlier. The number of patients in the FAS with measurable disease at baseline and had a best overall response of CR or PR, will be used.

$$DoR\ (days) = (Earliest\ Date\ of\ PD\ or\ Death - Earliest\ Date\ of\ CR\ or\ PR) + 1$$

If a patient does not experience PD following an initial CR or PR, then the corresponding DoR will be censored using the same rules defined for PFS (See Section 10.8.1).

10.9.5 Disease Control Rate

The DCR is the number (%) of patients achieving a BOR of CR, PR or SD. The denominator for DCR related analyses will be the same as described for ORR (See Section 10.9.3).

10.10 Adverse Events

10.10.1 Treatment-Emergent Adverse Events

A treatment-emergent adverse event (TEAE) is an AE that occurs, having been absent before the first dose of IMP, or having worsened in severity or seriousness after the first dose of IMP, up to and including 28 days after the date and time of last dose of IMP.

Any AEs that occur 28 days after the date of the last dose of IMP will be considered a post-treatment AE and will be listed only.

10.10.2 AEs Leading to Discontinuation of Study

AEs leading to discontinuation of the study will be identified from the *question "Did the adverse event cause the patient to be discontinued from the study?"* on the Adverse Events eCRF page.

10.10.3 TEAEs Leading to IMP Withdrawal

A TEAE will be classified as an TEAE leading to study drug withdrawal if the answer to the question *"Action Taken with IMP (Setanaxib/Placebo)"* on the Adverse Events eCRF page is "Drug Withdrawn" or "Unknown".

Instances of "Adverse Event" recorded as a reason for discontinuation of IMP on the End of Treatment (IMP) eCRF page will also be considered TEAEs leading to study drug withdrawal. Taking a conservative approach, patients from both sources will contribute to summaries of TEAEs leading to IMP withdrawal, although only counted once if they appear in both.

10.10.4 IMP-Related TEAEs

A TEAE will be classified as related to study drug if the *"Relationship to IMP (Setanaxib/Placebo)"* is assessed as "Related". Any AEs with a missing relationship, will be conservatively categorised as "Related".

10.10.5 AESIs

AESIs will be programmatically identified using the MedDRA codes provided in Section 15.2.

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10.11 Electrocardiogram Parameters

All 12-lead ECG results will be recorded within the eCRF, the exception being the RR interval which will be derived using the formula given;

$$RR\ (msec)\ = (\frac{60{,}000}{Heart\ Rate\ (bpm)})$$

QTcF values will be categorised using the following intervals as specified in the International Council for Harmonisation (ICH) Topic E14;

Absolute Values
- ≤ 450 msec
- > 450 msec to ≤ 480 msec
- > 480 msec to ≤ 500 mssec
- > 500 msec

Change from Baseline
- ≤ 30 msec
- > 30 msec to ≤ 60 msec
- > 60 msec

10.12 Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restrictions
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of walking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of walking hour
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

10.13 Handling of Missing Dates

Imputation for partial dates prior to enrolment (e.g. date of initial diagnosis) will be performed only if the month and year are known, using the earliest possible date (e.g. 1st of the month). For the purposes of assigning AEs as TEAEs or medications as prior/concomitant, imputation of partial dates will be performed. The imputation rules for AEs and medications are outlined in Appendix 15.1.

Listings will display the collected date and not the imputed date.

11.0 Interim Analyses

11.1 IDMC Reviews of Safety and Tolerability

Safety and tolerability data will be regularly reviewed by an unblinded IDMC, with the first assessment after approximately 12 patients (6 per treatment group) have had the opportunity to complete at least one cycle of pembrolizumab +/- setanaxib, followed by periodic assessments at a frequency defined in the IDMC Charter. The role and responsibilities of the IDMC will be outlined in the IDMC Charter, whilst the TLFs for the IDMC meetings are documented in the IDMC SAP.

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11.2 Sponsor Review of Gene Expression and Biomarker Data

The Sponsor will conduct an interim review of initial gene expression and biomarker data in tumour tissue. This will occur after approximately 12 patients (6 per treatment group) have completed their Baseline and post-treatment biopsy. The review will be performed by personnel who are not part of the main study team. For further details, please refer to the standalone Biomarker Analysis Plan.

12.0 Statistical Methods

With the exception of the unblinded statistician and programmers supporting the IDMC, all personnel involved with the analysis of the study will remain blinded until the initial database soft lock at the time of the primary analysis. Further details on the blinding and unblinding are given in the study Blinding Plan.

In this study, it is planned to recruit approximately 35 investigational centres in USA and Europe. Unless specified otherwise, data from all participating sites will be combined for the analysis, so that an adequate number of patients will be available for analysis. In the event that a single site enrols a large proportion of patients, a site effect may be explored as described in Section 12.5.5, otherwise no site effect will be assessed.

All table summaries will be presented by treatment group (including an overall group for safety tables) and by analysis visit where appropriate. Unscheduled visits will be windowed as described in Section 10.4. Unscheduled visit values will contribute to any assessment of worst/most severe results, but otherwise will only be displayed in listings. Additional details related to specific presentations are given in programming notes of the supporting TFL shells.

Categorical variables will be summarised descriptively using counts and percentages. Percentages will be rounded to one decimal place, except 100%, which will be displayed without any decimal places and percentages will not be displayed for zero counts.

Continuous variables will be summarised using univariate statistics, including the number of observations (n), mean, standard deviation, median, minimum and maximum. The minimum and maximum values will be displayed to the same level of precision as the raw data, the mean and median to a further decimal place and the standard deviation to two additional decimal places. In addition, for tumour and biomarker summaries, the geometric mean and the interval of (geometric mean +/- geometric standard deviation) may also be presented.

Analyses will be performed using SAS® (SAS Institute, Cary, NC, US) version 9.4 or higher.

12.1 Patient Disposition

The disposition of patients in the All Enrolled Analysis Set will be summarised descriptively for;

- Non-Randomised Patients, along with the reasons for non-randomisation.
- Patients within each analysis set.

Additionally, patients in the All Randomised Analysis Set who are still on-treatment, who completed/discontinued treatment and who completed/discontinued study, along with the reasons for completion/discontinuation will also be summarised.

Patients in the Full Analysis Set will also be summarised descriptively by geographical region (North America, Europe) and country.

All enrolled patients will be presented in a listing along with indication of study completion, date of completion/discontinuation, primary reason for discontinuation and date of first study dose and last study dose. An additional listing will be provided for patients who are not randomised and the associated reasons.

12.2 Demographic and Baseline Characteristics

The demographics, baseline characteristics and medical history (including SCCHN cancer history) will be presented for patients in the Full Analysis Set.

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The demographic and baseline variables, including age (years), height (cm), weight (kg), body mass index (BMI) (kg/m^2), ECOG performance and HPV status will be summarised descriptively. The categorical variables for sex (including childbearing potential for females), ethnicity and race will be presented by frequency and percentage.

The disease characteristics of patients' SCCHN cancer history will be summarised descriptively for lymph nodes, lymph node location, laterality and directionality and the tumour, node, metastasis (TNM) stage of disease at diagnosis. The time since diagnosis will also be presented.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 25.0 or higher, and summarised by system organ class (SOC) and preferred term (PT).

Listings will be presented for demographic and baseline characteristics, medical history and SCCHN cancer history separately.

12.3 Treatments

12.3.1 Extent of Study Drug Exposure

Exposure will be summarised for patients in the Safety Analysis Set. Descriptive statistics will be provided for both treatment components for the duration of exposure (weeks), the number of doses/infusions administered and cumulative dose received (mg).

The following summaries will be provided for IMP only. Actual and relative dose intensities as well as overall treatment compliance. The number and percentage of patients with overall compliance ≥ 80% - ≤ 120% will be presented. Patients with at least one dose reduction, at least one missed dose along with the recorded reasons for reduced or missed doses will also be presented.

Dose administration, drug accountability and overall treatment compliance will also be listed.

12.3.2 Prior and Concomitant Medications

All medications received will be coded using WHO Drug Dictionary (WHODD) (Version March 2022 [Global B3] or higher).

Both prior and concomitant medications will be summarised separately for patients in the Safety Analysis Set and will be presented by preferred drug name.

A listing will be presented for all, including post-treatment, medications along with indication as to whether each record was prior, concomitant or post treatment.

A summary of the number of therapies for prior systemic anti-cancer therapy regimens, prior radiation therapies, prior/on-study cancer surgeries, subsequent systemic anti-cancer therapy regimens and subsequent radiation therapies will be presented. All of these therapies will also be listed.

12.4 Protocol Deviations

Important protocol deviations are defined in the Protocol Deviation Guidance Document for the study and will be entered into the system of record (PSO). The study team and the Sponsor will conduct on-going reviews of the deviation data from PSO to identify the important deviations impacting the primary efficacy endpoints on a case by case basis. Site level deviations will be applied to all patients actively participating in the study at the time of the site level deviation. Final review of protocol deviations will be conducted and finalised prior to the data cut off for the primary analysis and the updated analysis (see Section 8.4 for database lock details).

The number and percentage of patients with at least one important protocol deviation within each deviation category will be presented based on the FAS. In the instances where multiple deviations for a patient, they will contribute to the count of more than one deviation category.

All protocol deviations will be listed.

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12.5 Efficacy Analyses

The data cut-off for the primary analysis will occur approximately 15 weeks after completion of enrolment, when all patients are expected to have had at least 5 cycles of pembrolizumab, at least two post-treatment scans, and the opportunity for a post-treatment tumour biopsy. This analysis will include the primary endpoint of best percentage change in tumour size and all secondary endpoints (excluding Cox proportional hazards for PFS) will be analysed. Investigators and patients will continue to be blinded to randomised study treatment after initial unblinding of data for the primary analysis until the final database lock.

An updated analysis may be performed after approximately 38 progression events have been reported. This updated analysis will include only the secondary endpoints of PFS, and OS in addition to an updated waterfall plot for the primary endpoint of best percentage change in tumour size.

During ongoing review of the overall progression event count, if the predicted timing of the initial and updated analyses are expected to be close in proximity, one analysis may be performed.

Efficacy analyses will be conducted using the FAS. To understand the robustness of the results from important protocol deviations, the primary efficacy analyses will also be performed using the PPS.

12.5.1 Hypothesis Testing Strategy

The statistical hypothesis to be tested for the primary analysis with change in tumour size as the primary endpoint (defined in Section 10.7.6) is as follows:

- H_0: the mean best percentage change in the tumour size between the treatment groups are the same
- H_A: the mean best percentage change in the tumour size between the treatment groups are different

Since only two treatment groups are being tested there is no requirement for controlling the Family Wise Error Rate and the therefore multiplicity adjustments are not considered here.

12.5.2 Primary Estimand

The primary estimand attributes are given in Section 9.1. All analysis visits will be summarised using univariate statistics and a waterfall plot for the best percentage change from baseline will also be presented.

12.5.2.1 Imputation Methods

Imputation of missing target lesions will be performed using the scaling methods described in Section 10.7.3 and missing best percentage change from baseline will be imputed as described in Section 10.7.6.

Where analysis is performed on the ratio of postbaseline to baseline, zero values will be replaced with a constant equal to half of the smallest observed non-zero result across all patients (baseline and postbaseline).

No other imputation methods will be explored.

12.5.2.2 Primary Analysis

The primary efficacy analysis will evaluate the effect of setanaxib on the best percentage change in tumour size using an ANCOVA model, including covariates for treatment, baseline tumour size and the randomisation stratification HPV status (if there are at least 10 subjects at each level within each treatment group).

The number of patients, unadjusted mean, and adjusted least squares (LS) means for each treatment group will be presented, together with the difference in adjusted LS means, 80% and 95% CIs and corresponding p-value from the fitted ANCOVA model.

A plot of the residuals against the fitted values will be produced to check the assumption of constant variance. Any systematic effect in this residual plot along will indicate that a suitable transformation (log transformation) should be applied on the response of the model as appropriate to stabilise the variability of the error.

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A normal probability plot will also be plotted of the residuals of the fitted ANCOVA model in addition to a Shapiro-Wilk test, used to test for the distribution of normality of the residuals. If the normal probability plot shows a concave curve of the residuals against the normal quantiles along with the p-value obtained from the Shapiro-Wilk test being less than 0.05, then this indicates a violation of the ANCOVA model assumption of the errors being normally distributed.

If the ANCOVA model assumptions are not upheld, logarithmic transformations on the response will be applied to normalise the data. The log(post-baseline) to log(baseline) ratio will be analysed using an ANCOVA model, including covariates for treatment, log-transformed baseline tumour size and the randomisation stratification HPV status.

The number of patients, unadjusted geometric mean, and adjusted geometric LS means for each treatment group will be presented, together with the difference in adjusted geometric LS means, 80% and 95% CIs and corresponding p-value from the fitted ANCOVA model.

The validity of the assumptions of the fitted transformed model will be checked similarly.

If the assumptions are not satisfied for the log-transformed model, a non-parametric method will be performed using a Ranked ANCOVA (Quade D. [1967]). A linear regression of the ranks of the best percentage change from baseline based on the ranks of the covariate for baseline tumour size and HPV status fitted as a class variable (ignoring treatment). The residuals from this regression model will then be analysed using an ANOVA model with treatment as the independent variable. The resulting p-value from the F test of this ANOVA will be reported.

12.5.2.3 Sensitivity Analyses

There are no planned sensitivity analyses of the primary endpoint.

12.5.3 Key Secondary Estimands

The secondary estimand attributes are given in Section 9.1.2.

12.5.3.1 Progression Free Survival (PFS)

The key secondary endpoint of PFS will be summarised by Kaplan-Meier plots presented by treatment group. The median, upper quartile, lower quartile PFS and the proportion of patients who are progression-free at 3, 6, and 12 months will be presented along with 80% Wald CIs, obtained using the Brookmeyer-Crowley method (1982). Patients who have not progressed by the time of the data cut-off will be censored following the rules defined in Section 10.8.1.

The comparison between the treatment groups of PFS will be performed by fitting a Cox proportional hazard model (Cox 1975) with treatment group, HPV status (if there are at least 10 patients in each HPV status within each treatment group) and the interaction term between treatment and HPV status (if statistically significant at the 5% level). Efron's method (1977) will be used to handle tied events in any of the independent event intervals. The covariate-adjusted hazard ratio between the treatment groups, based on the profile partial likelihood from the fitted Cox proportional hazards model, will be presented as a measure of the treatment effect along with the respective 80% and 95% Wald CIs and the asymptotic p-value from the Wald test for the difference in the covariate-adjusted log hazards in the fitted model.

If the interaction term between treatment and HPV status is statistically significant, the hazard ratio would be presented separately for HPV+ and HPV- along with the p-value of the interaction term and the 95% Wald CI based on the profile partial likelihood estimate for the interaction effect. Additionally, a Kaplan-Meier plot will be presented by treatment group and HPV status if there are at least 10 patients in each HPV status within each treatment group.

The proportionality of hazards will be examined for the fitted Cox proportional hazards model for PFS using Log-minus-log plots and Schoenfeld residuals. If the proportional hazard assumption is violated between the treatment groups, a modified max combo (Roychoudhury et al 2021) using the Fleming and Harrington 1981 weights (Fleming & Harrington 1981) such as FH(0,0), FH(0.5,0.5), FH(0,0.5), FH(0.5,0) will be implemented for estimating the performance of the competing treatment groups for PFS. The p-value obtained from each of the modified max combo tests will be reported.

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12.5.3.2 Change from Baseline in CAFs Level in Tumour Tissue

For the key secondary endpoint of CAFs level, (also referred to as smooth muscle actin [SMA]), it is hypothesised based on the mode of action of setanaxib that there will be a reduction in CAFs level. Data for patients with both baseline and postbaseline results, will be summarised using univariate statistics and will be graphically presented using both boxplots and spaghetti plots for each treatment group.

This secondary efficacy analysis will evaluate the effect of setanaxib on the ratio of postbaseline to baseline CAFs level using an ANCOVA model, including the same covariates as described for the primary analysis in Section 12.5.2.2. Zero values will be replaced as described in Section 12.5.2.1.

A summary of the qualitative CAFs level (in order of increasing severity: Negative, Low Positive, Moderate Positive, Strong Positive) will also be provided.

12.5.3.3 Change from Baseline in $CD8^+$ TILs and Regulatory T-Cells in Tumour Tissue

For the key secondary endpoints of $CD8^+$ TILs and regulatory T-cells (FOXP3) it is hypothesised based on the mode of action of setanaxib that there will be an increase in $CD8^+$ TILs and a decrease in FOXP3. These secondary efficacy analyses will repeat the analysis described for CAFs level in Section 12.5.3.2.

12.5.3.4 Sensitivity Analyses

In anticipation of small numbers of progression events within the subgroups of HPV status, a sensitivity analysis of the methods described in Section 12.5.3.1, will be repeated without HPV status.

12.5.4 Other Secondary Efficacy Analyses

The secondary estimand attributes are given in Section 9.1.2.

12.5.4.1 Objective Response Rate (ORR) and Disease Control Rate (DCR)

The point estimates of ORR and DCR (see Sections 10.9.3 and 10.9.5 respectively) will be summarised using descriptive statistics along with associated 90% Agresti-Coull CIs for each treatment group.

12.5.4.2 Duration of Response (DoR) and Overall Survival (OS)

The secondary endpoints of DoR and OS will not be formally compared between the treatment groups, but will be summarised using Kaplan-Meier plots presented by treatment group.

Specifically, for OS, the median, upper quartile, lower quartile OS and the proportion of patients who are alive at 3, 6, and 12 months will be presented along with 80% Wald CIs, obtained using the Brookmeyer-Crowley method (1982).

DoR will only be presented if there are at least 5 responders in either treatment group, otherwise this data will be listed only.

Censoring rules for both DoR and OS are described in Sections 10.9.4 and 10.8.2 respectively.

12.5.4.3 Gene Expression

For the secondary endpoint of changes in patterns of gene expression and differential gene expression in tumour tissue, analysis will be described in the standalone biomarker analysis plan.

12.5.4.4 Change from Baseline in PD-L1 Expression in Tumour Tissue

The analysis for the key secondary endpoint of PD-L1 expression will repeat the analysis described for CAFs level in Section 12.5.3.2.

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12.5.4.5 Sensitivity Analyses

There are no planned sensitivity analyses of the other secondary endpoints.

12.5.5 Supportive Analyses

It was noted during enrolment that one site, Fayette, has enrolled a large proportion of patients. To explore a potential site effect, a supportive site subgroup analysis will evaluate the effect of setanaxib on the best percentage change in tumour size using an ANCOVA model, including the same covariates as described for the primary analysis in Section 12.5.2.2, repeated for each site subgroup (Fayette vs Other). The number of patients, unadjusted mean, and adjusted LS means for each treatment group will be presented, together with the difference in adjusted LS means and 80% CI. No p-value will be presented for these analyses.

There are no further efficacy analyses planned, see Section 6.1.1 for additional details.

12.6 Safety Analyses

Safety analyses will be conducted using the Safety Analysis Set and will be summarised descriptively, unless otherwise noted in the sections that follow. All safety related outputs will be produced at the time of both the primary analysis and the updated analysis (see Section 12.5).

12.6.1 Adverse Events

All AEs recorded in the eCRFs will be coded using MedDRA (version 25.0 or higher) and graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Events that are not coded at the time of a data snapshot will be included and presented using the verbatim term (in uppercase letters) as the PT and “UNCODED” for the SOC. Events with missing severity at the time of the data snapshot will be left as missing.

Summary tables will present the number of events reported as well as the number and percentage of patients reporting them, unless otherwise specified.

An overall summary of TEAEs, will be provided, including line items for the following;

- TEAEs
- Severe (CTCAE Grade ≥3) TEAEs
- TEAEs Related to IMP
- TEAEs with a Fatal Outcome
- TEAEs of Special Interest (see Section 10.10.5)
- Serious TEAEs
- Serious TEAEs Related to IMP
- TEAEs Leading to a Reduction of the IMP Dose
- TEAEs Leading to the Discontinuation of IMP (Drug Withdrawal)
- TEAEs Leading to Discontinuation from the Study

A summary of TEAEs by SOC, PT and maximum severity will also be presented by patient (not events). Patients who experience multiple events within the same SOC/PT will be counted only once in the most severe grade.

The following types of TEAEs will also be summarised by SOC and PT:

- TEAEs
- Severe (CTCAE Grade ≥3) TEAEs
- TEAEs Related to IMP
- TEAEs of Special Interest
- TEAEs Leading to the Discontinuation of IMP (Drug Withdrawal)

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- TEAEs Leading to Discontinuation from the Study

TEAEs will also be summarised by PT only.

All AEs (including non-TEAEs) will be listed and any AE occurring after a patient has received another anti-cancer therapy (after discontinuation of study treatment) will be flagged.

12.6.2 Deaths and Serious Adverse Events

A summary of serious TEAEs by SOC, PT, and maximum severity will also be presented by patient (not events). Patients can experience multiple events within the same SOC/PT, they will be counted only once in the most severe grade.

The following types of TEAEs will also be summarised by SOC and PT:

- Serious TEAEs
- Serious TEAEs Related to IMP
- TEAEs with a Fatal Outcome

Separate listings will be provided for all SAEs and all AEs with a fatal outcome.

12.6.3 Laboratory Data

Central laboratory data (haematology, serum chemistry, thyroid function) and local laboratory data (urinalysis) will be converted to Système International (SI) units. Any results containing the character values of "<" or ">" will be converted to the equivalent lower/upper limit of quantification (LLQ/ULQ). For each laboratory category and parameter noted in Table 4, absolute and change from baseline values will be summarised by analysis visit and treatment group using univariate statistics.

Shift tables of CTCAE grades from baseline to worst post-baseline will also be presented for the central laboratory data.

The change from baseline values for haematology, serum chemistry and thyroid function will be further summarised using box and whisker plots.

Standard reference ranges from the central laboratory will be used for the assessment of results being low, normal or high. Parameter results outside of the standard reference ranges will be flagged in the data listings.

Local laboratory urinalysis data will be listed only.

Table 4. Laboratory Parameters

Category	Parameters	
Haematology	• Haematocrit • Haemoglobin • Absolute and Relative Reticulocyte Counts • Red Blood Cell (RBC) Count • White Blood Cell (WBC) Count • Differential WBC Count	• Platelet Count • Absolute Neutrophil Count • Mean Cell Volume • International Normalised Ratio (INR) (Screening only).
Serum Chemistry	• Alkaline Phosphatase (ALP) • Alanine Aminotransferase (ALT) • Aspartate Aminotransferase (AST) • Amylase • Total and Conjugated Bilirubin • Gamma-Glutamyltransferase (GGT) • Glucose • Total Protein	• Albumin • Creatinine • Urea • Total Cholesterol • Triglycerides • Sodium • Potassium • Chloride

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Category	Parameters	
Thyroid Function	TSH and Free T4	
Urinalysis	• pH • Protein • Glucose • Ketones	• Bilirubin • Blood • Microscopic Examination of the Sediment
Pregnancy Test†	• Serum Pregnancy Test • Urine Pregnancy Test	

Note: Categories denoted with † will be listed only.

Note: WBC and Reticulocyte Counts will be expressed as absolute values. Differential counts will be expressed as both absolute counts and percentages of WBCs.

12.6.4 Vital Signs

Absolute and change from baseline values for pulse rate, SBP, DBP weight, oral temperature and body temperature will be summarised by analysis visit and treatment group using univariate statistics. The change from baseline for each parameter at each analysis visit will be further summarised using box and whisker plots by treatment group.

All vital signs data will be provided in a listing.

12.6.5 Physical Examinations, ECGs, and Other Observations Related to Safety

The absolute values and change from baseline values of each ECG parameter (Mean Heart Rate, PR Interval, QRS duration, QT interval, RR interval (see Section 10.11) and QTcF) will be summarised using univariate statistics at each analysis visit by treatment group. The interpretation of the ECG will be presented by result category (Abnormal Clinically Significant, Abnormal Non-Clinically Significant, Normal, Unevaluable and Unknown) at each analysis visit.

The absolute and change from baseline values for QTcF intervals will be further summarised using categorical intervals (see Section 10.11). Shift tables from baseline absolute interval to the maximum post baseline interval and maximum change from baseline interval will be presented.

All 12-lead ECG data will be provided in a listing, with abnormal interpretations flagged.

All physical examination findings will be provided in a listing only.

Baseline ECOG performance status will be summarised as part of the baseline characteristics, all ECOG data will be listed. The grading of ECOG performance status is defined in Section 10.12.

12.7 Pharmacokinetic Analyses

The PK Analysis Set will be used for PK analyses.

The initial PK analysis will be performed during the primary analysis, when all patients are expected to have had at least 3 cycles of pembrolizumab, at least one post-treatment scan, and the opportunity for a post-treatment tumour biopsy. The final pharmacokinetic analysis will be performed at the end of the study after DBL. If the predicted timing of the initial and final analyses are expected to be close in proximity, one analysis may be performed. The analysis will be reported formally and summarised for the CSR.

Observed plasma concentrations of setanaxib and GKT138184, along with blood sampling dates and actual blood sampling time relative to last dose, will be listed by patient, actual treatment (See Section 10.5.1), and nominal time point (Day 1, Week 3, Week 24, Week 51, Week 105, day of the second biopsy and at EoT). The listing would display the concentrations with the nominal time and actual time.

Observed plasma concentrations of setanaxib and GKT138184 will be summarised by actual treatment (See Section 10.5.1), nominal time point (Day 1, Week 3, Week 24, Week 51, Week 105, day of the second biopsy and at EoT) and

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analyte (setanaxib or GKT138184) using univariate statistics (n, mean, geometric mean, median, standard deviation, standard error of the mean, coefficient of variation, minimum and maximum).

Further details regarding the PK analysis and exploratory PK/PD analyses will be provided in a separate PK analysis plan.

13.0 References

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14.0 Glossary of Abbreviations

Glossary of Abbreviations:	
ADI	Actual Dose Intensity
AE	Adverse Event
AESI	Adverse Event of Special Interest

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Glossary of Abbreviations:	
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	Below the Quantification Limit
BOR	Best Objective Response
CAF	Cancer-Associated Fibroblast
$CD8^+$	Cluster of Differentiation 8
CI	Confidence Interval
CR	Complete Response
eCRF	Electronic Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
DCR	Disease Control Rate
DoR	Duration of Response
dp	Decimal Point
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EoT	End of Treatment
FAS	Full Analysis Set
GGT	Gamma-Glutamyltransferase
HPV	Human Papillomavirus
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product, referring to Setanaxib/Placebo
INR	International Normalised Ratio
IRT	Interactive Response Technology
IV	Intravenous
LFC	Limit Fold Change
LLQ	Lower Limit of Quantification
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NTL	Non-Target Lesion
ORR	Overall Response Rate
OS	Overall Survival
PD	Progression of Disease
PD-L1	Programmed Cell Death Ligand 1

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Glossary of Abbreviations:	
PFS	Progression-Free Survival
PHP	Hypertext Preprocessor
PK	Pharmacokinetics
PPS	Per Protocol Analysis Set
PR	Partial Response
PSO	ICON System of Record
PT	Preferred Term
RBC	Red Blood Cell
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic Acid
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SD	Stable Disease
SI	Système International
SMA	Smooth Muscle Actin
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TIL	Tumour-Infiltrating Lymphocytes
TL	Target Lesion
TNM	Tumour, Node, Metastasis
ULQ	Upper Limit of Quantification
WBC	White Blood Cells
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

15.0 Appendix

15.1 Handling of Partial Adverse Event and Medication Dates

If the imputation rules specified here result in illogical dates, adjust accordingly. If any estimated start date is after a complete/imputed end date, set the start date to be the first day in the end date month. If any estimated end date is prior to a complete/imputed start date set to be the last day of the start date month.

Table 5. Handling of Partial AE Dates

Date of Interest	Missing	Condition	Imputation
AE start date	Day	M and Y is the same as M and Y of first dose of IMP	Date of first dose of IMP

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Date of Interest	Missing	Condition	Imputation
		Y is prior to Y of first dose of IMP	Last day of the month
		Y is the same as Y of first dose of IMP, M is prior to M of first dose of IMP	Last day of the month
		M and/or Y is after first dose of IMP	First day of the month
	Day, Month	Y is the same as the Y of first dose of IMP	Date of first dose of IMP
		Y is prior to Y of first dose of IMP	Use 31st of December
		Y is after Y of first dose of IMP	Use 1st of January
	Month	Treat day as missing and use imputation rules for D and M as missing	See Day, Month imputation rules
	Day, Month, Year	None-date is completely missing	Date of first dose of IMP
AE End Date	Day	M and Y same as date of last dose of IMP	Date of last dose of IMP
		M and Y not the same as date of last dose of IMP/date of last dose of IMP is missing	Set to the last day of the month, or the end of study/death date whichever is earliest
	Day, Month	Y is the same as last dose of IMP	Date of last dose of IMP
		Y is not the same as date of last dose of IMP/date of last dose of IMP is missing	Set to 31st of Dec, or the end of study/death date whichever is earliest
	Day, Month	Treat day as missing and use imputation rules for D and M as missing	See D, M imputation rules
	Day, Month, Year	None	No imputation, assume Ongoing

Note: D=Day, M=Month, Y=Year.

Table 6. Handling of Partial Medication Dates

Date of Interest	Missing	Condition	Imputation
Medication start date	Day	M and Y is the same as M and Y of first dose of IMP	Date of first dose of IMP
		M and/or Y is not the same as the first dose of IMP	First day of the month
	Day, Month	Y is the same as the Y of first dose of IMP	Date of first dose of IMP
		Y is not the same as first dose of IMP	Use 1st of January
	Month	Treat day as missing and use imputation rules for D and M as missing	See D, M imputation rules
	Day, Month, Year	None-date is completely missing	Assume prior and concomitant. Impute as the last day prior to the first dose of IMP.
Medication End Date	Day	M and Y same as date of last dose of IMP	Date of last dose of IMP
		M and Y not the same as date of last dose of IMP/date of last dose of IMP is missing	Set to the last day of the month, or the end of study/death date whichever is earliest
	Day, Month	Y is the same as last dose of IMP	Date of last dose of IMP

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Date of Interest	Missing	Condition	Imputation
		Y is not the same as date of last dose of IMP/date of last dose of IMP is missing	Set to the 31st of Dec, or the end of study/death date whichever is earliest
	Month	Treat day as missing and use imputation rules for D and M as missing	See D, M imputation rules
	Day, Month, Year	None	No imputation, assume Ongoing

Note: D=Day, M=Month, Y=Year.

15.2 Coded Terms for Adverse Events of Special Interest

The AESIs of Anaemia and Hypothyroidism will be programmatically identified using the following MedDRA preferred term codes;

Hypothyroidism

- 10010510
- 10018096
- 10021114
- 10028665
- 10036697
- 10043693
- 10059844
- 10060819
- 10065306
- 10076644
- 10078564
- 10083075
- 10086754
- 10087670
- 10087712
- 10087924

Anaemia

- Anaemia macrocytic (10002064)
- Aplasia pure red cell (10002965)
- Aplastic anaemia (10002967)
- Erythroblast count decreased (10058505)
- Erythroid maturation arrest (10015279)
- Erythropenia (10015287)
- Hypoplastic anaemia (10021074)
- Microcytic anaemia (10027538)
- Proerythroblast count decreased (10060229)
- Red blood cell count decreased (10038153)
- Reticulocyte count decreased (10038790)
- Reticulocytopenia (10038795)

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