Reporting and Analysis Plan

Study ID: 207871

Official Title of Study: A Phase I/II, Open-label, Two Part Study of GSK3359609 in Combination with Tremelimumab in Subjects with Selected, Advanced Solid Tumors

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Title	:	Reporting and Analysis Plan for A Phase I/II, Open-label, Two Part Study of GSK3359609 in Combination with Tremelimumab in Subjects with Selected, Advanced Solid Tumors
Compound Number	:	GSK3359609
Effective Date	:	Refer to Document Date

Description:

- The purpose of this RAP is to describe the planned analyses and outputs to be included in the Clinical Study Report for Protocol 2018N362439_01.
- This RAP is intended to describe analyses of the primary, secondary and other endpoints required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable, as well as the interim analysis at the end of Part 1 when selecting the recommended Phase 2 dose.

RAP Author(s):

Approver	Date	Approval Method
PPD Lead Statistician (Oncology, Clinical Statistics)	16-DEC-2020	e-mail
PPD Principal Statistician (Oncology, Clinical Statistics, Complementary Worker)	14-DEC-2020	e-mail

RAP Team Review Confirmation:

Approver	Date	Approval Method
PPD (MM) Medical PPD (Oncology)	16-DEC-2020	e-mail
PPD Safety Lead, Pharmacovigilance Safety and Medical Governance	16-DEC-2020	e-mail
PPD Clinical Development Manager (Oncology)	14-DEC-2020	e-mail
PPD (OSL) Clinical Development Manager (Clinical Operations)	16-DEC-2020	e-mail
PPD (CPMS) PPD Clinical Pharmacology (Clinical Pharmacology Modelling & Simulation)	16-DEC-2020	e-mail
PPD (Study Data Manager) Principal Clinical Data Manager (Oncology Global Clinical and Data Operations)	15-DEC-2020	e-mail
PPD Principal Programmer (Oncology, Clinical Programming)	16-DEC-2020	e-mail

Clinical Statistics and Clinical Programming Line Approvals:

Approver	Approval Method
PPD Senior Statistics PPD (Oncology, Clinical Statistics)	Pharma TMF eSignature
PPD Programming PPD (Oncology, Clinical Programming)	Pharma TMF eSignature

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol:

Revision Chronology:		
2018N362439_00	03-AUG-2018	Original
2018N362439_01	20-SEP-2018	Amendment 1 (Protocol was amended at the request of a regulatory authority to provide additional clarification and guidance on specific aspects of the protocol)

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There are no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 1 (Dated: 20-SEP-2018).

This study is terminating at the end of Part 1 and reporting out an abbreviated Clinical Study Report (CSR). Therefore, all references in this document to the Interim analysis, Dose selection, Part 2 analyses and Part 2 displays are not applicable. Efficacy displays that were exclusively for Part 2 will now be produced for Part 1 using the All Treated Population where appropriate and where data is available. Primary, secondary and a reduced selection of exploratory endpoints will be reported for Part 1 only.

2.2. Study Objective(s) and Endpoint(s)

2.2.1. PART 1: Dose Escalation

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• Determine safety, tolerability and the R2PD of GSK3359609 in combination with tremelimumab	• Frequency and severity of DLTs, AEs, AESI, SAEs and AE/SAE/DLTs leading to dose modifications/delays/withdrawals; changes in laboratory, vital signs, and ECG safety assessment parameters
Secondary Objectives	**Secondary Endpoints**
• Evaluate clinical activity of GSK3359609 in combination with tremelimumab.	• ORR, DCR
• Characterize the PK properties of GSK3359609 and tremelimumab when administered in combination	• Cmax, Cmin, AUC (0-t) of GSK3359609 and tremelimumab as data permit
• Determine immunogenicity of GSK3359609 and tremelimumab when administered in combination	• Detection and characterization of ADA against GSK3359609 and/or tremelimumab

Objectives	Endpoints
Exploratory Objectives	**Exploratory Endpoints**
• Evaluate clinical activity of GSK3359609 in combination with tremelimumab	• PFS, OS, TTR, DoR
• Evaluate pharmacodynamic changes in markers of target engagement, immune cell profiles, immune activation and function or tumor biology post treatment compared to that at screening	• Immunophenotyping and functional analysis • Other biomarkers such as gene expression changes, relevant transcripts, TCR diversity, and/or soluble analytes

AEs = adverse events; SAEs = serious adverse events; DLTs = dose limiting toxicities; AESI = adverse events of special interest; RP2D = recommended phase 2 dose; ORR = overall response rate; DCR = disease control rate; Cmax = maximum observed concentration; Cmin = minimum observed concentration; AUC (0-t) = area under the concentration-time curve over the dosing interval; ADA = anti-drug antibodies; PFS = progression-free survival; OS = overall survival; TTR = time to response; DoR = duration of response; TCR = T cell receptor.

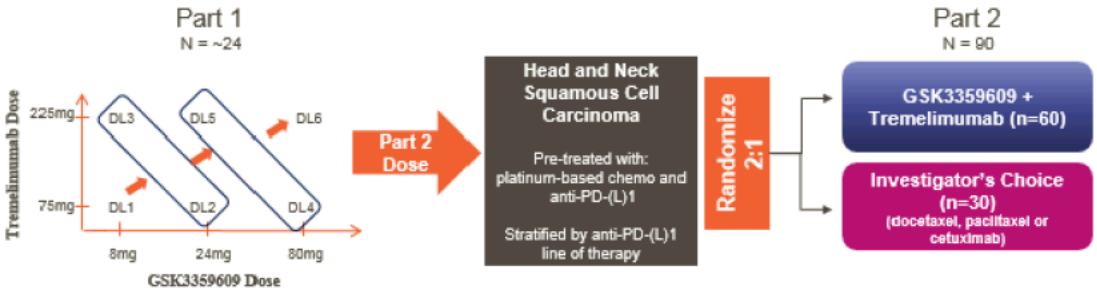
2.2.2. PART 2: Cohort Expansion

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• Evaluate clinical activity of GSK3359609 in combination with tremelimumab compared to SOC	• OS
Secondary Objectives	**Secondary Endpoints**
• Further evaluate the clinical activity of GSK3359609 in combination with tremelimumab compared to SOC	• ORR, DCR, PFS, TTR, DoR
• Further evaluate the PK properties of GSK3359609 and tremelimumab when administered in combination	• Cmax, Cmin, AUC (0-t) of GSK3359609 and tremelimumab as data permit
• Further evaluate immunogenicity of GSK3359609 and tremelimumab when administered in combination	• ADA incidence
• Further evaluate the safety and tolerability of GSK3359609 and tremelimumab when administered in combination	• Frequency and severity of AEs, AESI, SAEs and AE/SAEs leading to dose modifications/ delays/ withdrawals; changes in laboratory, vital signs, and ECG safety assessment parameters
Exploratory Objectives	**Exploratory Endpoints**
• Examine potential relationships between anti-cancer activity and changes in markers of target engagement immune cell profiles, immune activation and function or tumor biology post treatment compared to that at screening	• Immunophenotyping and functional analysis, anti-cancer activity parameters • Other biomarkers such as gene expression changes, relevant transcripts, TCR diversity, and/or soluble analytes
• Evaluate other measures of antitumor activity	• Evaluation of tumor growth kinetic parameters which may be measured by the

Objectives	Endpoints
	following methods: including, but not limited to, RECIST v1.1, uni-dimensional, bi-dimensional, and volumetric tumor measurements
• Explore relationship between antitumor activity, PK parameters, pharmacodynamic activity and other participant characteristics	• Antitumor activity (CR, PR, SD, PD), tumor kinetic parameters, PK parameters, pharmacodynamic activity, and other participant characteristics as data permit
• Examine potential relationships between anti-cancer activity and various biomarkers • Evaluate potential markers of sensitivity and/or resistance to the treatment	• Target expression, immune phenotypes, HPV positivity for HNSCC tumors, TCR (T cell receptor) sequencing, genetic polymorphisms in the target or other related gene expression and/or tumor mutational burden
• Evaluate disease and treatment related symptoms and impact on function and health-related quality of life	• Health-related quality of life as measured by the EORTC-QLQ-C30 and HN35, PROMIS-PF, and EQ-5D
• Evaluate participant-reported tolerability	• PRO-CTCAE and FACT GP5

OS = overall survival; SOC = standard of care; ORR = overall response rate; DCR = disease control rate; PFS = progression-free survival; TTR = time to response; Cmax = maximum observed concentration; Cmin = minimum observed concentration; AUC (0-t) = area under the concentration-time curve over the dosing interval; DoR = duration of response; TCR = T cell receptor; ADA = anti-drug antibodies; AEs = adverse events; SAEs = serious adverse events; RECIST = response evaluation criteria in solid tumors; PK = pharmacokinetic; EORTC QLQ-C30 and HN35 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 and head and neck cancer 35 module; EQ-5D = EuroQOL Group EQ-5D; FACT GP5 = Functional Assessment of Cancer Therapy – General Physical Well Being Item 5; PROMIS PF = Patient-Reported Outcome Measurement Information System – Physical Function; Impression of Change; PRO-CTCAE = Patient Reported Outcomes – Common Terminology Criteria for AEs

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	This study consists of 2 parts: • Part 1 is dose escalation and will enroll participants with advanced, selected solid tumors. Part 1 is designed to evaluate the safety and tolerability of escalating doses of GSK3359609 in combination with tremelimumab according to a bivariate Continual Reassessment Method (2D-CRM) design [Neuenschwander, 2008; Neuenschwander, 2014] to identify a single dose level/cohort for evaluation in Part 2. As shown in the figure above, dosing will begin on a cohort of participants at dose level (DL) 1 and continue using zone-based dose escalation rules whereby each zone must be cleared for safety prior to opening the next zone of DLs/cohorts. The totality of data will be used to determine whether to proceed to Part 2 and which dose level/cohort will be chosen to expand as the recommended phase 2 dose (RP2D). PK/pharmacodynamic cohort(s) may be initiated at any DL(s), once safety is cleared for that dose level, with mandatory paired tumor sample collections to inform on dose selection for Part 2 of the study. Paired tumor samples may also be collected in the dose escalation cohorts. • Part 2 is randomized expansion and will enroll participants with head and neck squamous cell carcinoma (HNSCC) who have progressed after receiving at least 1 platinum-based chemotherapy and at least one anti-PD-1/PD-L1 therapy, whether in combination or separately. Randomization is 2:1 to the RP2D and standard of care (Investigator's choice of paclitaxel, docetaxel or cetuximab) arms, respectively. In Part 2, participants will be stratified by line of anti-PD-(L)1 therapy (i.e., received in the first line vs. second line). • In both parts, there is a screening period (up to 45 days), treatment period (up to 2 years) and follow-up period (until death, study termination or treatment arm termination, whichever comes first; approximately 2 years). Participants deriving benefit from the treatment may be on study intervention beyond 2 years. The maximum duration of treatment with GSK3359609 is 2 years.

Overview of Study Design and Key Features	
	Participants who discontinue tremelimumab may continue treatment with GSK3359609. • Approximately 114 participants will be enrolled in this study; up to 24 in Part 1 and 90 in Part 2.
Dosing	• **Dosing Schedule:** GSK3359609 will be administered every 3 weeks and tremelimumab will be administered every 3 weeks for 6 doses, followed by every 12 weeks. GSK3359609 is to be administered first as a 30-minute IV infusion. Tremelimumab is to be administered as an IV infusion over 60 minutes beginning at least 1 hour and no more than 2 hours following the end of the GSK3359609 infusion. Standard of care agents (Investigator's choice of paclitaxel, docetaxel or cetuximab) should be administered as per local and Institutional guidelines. Paclitaxel or cetuximab given once a week and docetaxel given every 3 weeks. **Part 1 Dose Escalation:** Part 1 will initiate with 8 mg GSK3359609 in combination with 75 mg tremelimumab (termed dose level [DL]1), the planned lowest dose for each agent. The highest planned doses are 80 mg GSK3359609 and 225 mg tremelimumab (termed DL6). A total of 6 combination doses are planned for dose escalation. The planned dose levels of GSK3359609/tremelimumab are: 8 mg/75 mg (DL1); 24 mg/75 mg (DL2) ; 8 mg/225 mg (DL3); 80 mg/75 mg (DL4); 24 mg/225 mg (DL5); 80 mg/225 mg (DL6). **Part 2 Cohort Expansion**: A single dose combination of study intervention will be selected as the recommended Phase 2 dose (RP2D) and carried forward from Part 1 into Part 2, based on the totality of Part 1 data. Participants will receive either the RP2D combination of GSK3359609/tremelimumab or standard of care. Standard of care dosing is as follows: Docetaxel 75mg; Pacitaxel 80mg; Cetuximab 400mg loading dose followed by 250mg.
Schedule of Activities (SoA)	• Refer to Appendix 2: Schedule of Activities
Treatment Assignment	• Part 1 is a non-randomized open-label single-group treatment part with 1 arm. • Part 2 is a parallel-group open-label randomized part with 2 arms. Participants are randomized at a ratio of 2:1 to either the study intervention or SOC, respectively. Randomization & Medication Ordering System New Generation (RAMOS NG) is used for treatment assignment.
Interim Analysis	• Part 1: interim analyses will be performed to determine if a dose-escalation is appropriate and to support the dose-escalation decision following the completion of each dose cohort. The DLT information along with preliminary safety data, including AEs, changes in laboratory values and other safety parameters, and available

Overview of Study Design and Key Features	
	PK/pharmacodynamic data will be evaluated for each dose escalation cohort prior to making dose escalation decisions. • Part 2: no interim analysis for futility or efficacy will be performed.

2.4. Statistical Hypotheses

2.4.1. Part 1: Dose Escalation

No formal statistical hypotheses will be tested in relation to the primary objective in Part 1. Descriptive methods will used to analyse the data.

2.4.2. Part 2: Cohort Expansion

The primary endpoint for Part 2 is OS. A one-sided log-rank test will be performed at the 2.5% significance level to compare the overall survival between the study intervention and the SOC. Further details are provided in Section 7.1 of the RAP.

The null hypothesis is:

H0: The study intervention does not improve overall survival over the SOC, i.e. HR≥1.

The alternative hypothesis is:

H_A: The study intervention improves overall survival over the SOC, i.e. HR<1.

3. PLANNED ANALYSES

3.1. Interim Analyses

3.1.1. Part 1: Dose Escalation

In Part 1, interim analyses will be performed to determine if a dose-escalation is appropriate and to support the dose escalation decision recommended by the bivariate CRM analysis following the completion of each dose cohort, i.e. once all participants in a dose cohort complete the determinative 28 day DLT observation period, including replacement participants. For dose escalation phase, the Dose Limiting Toxicity (DLT) information along with preliminary safety data, including AEs, changes in laboratory values and other safety parameters, and available PK/pharmacodynamic data will be evaluated using unblinded data for all dose escalation cohorts in each zone (see Section 4.1 of the protocol) prior to making dose escalation decisions.

Review of preliminary data will be performed after completion of each cohort. Preliminary safety and study population data may include a demographic summary, adverse event (AE) summary, AE summary by maximum toxicity category, SAE listing, listing of AEs that are reported to be DLT's. No formal outputs will be produced by statistics and programming. For dose escalation decisions, reviews of Spotfire output will be performed.

Further, after the first instance of a DLT and for each subsequent cohort, the recommended dose from the bivariate CRM analysis and updated posterior estimates of the probabilities of being in each dose-toxicity range may be provided. The Fixed and Adaptive Clinical Trial Simulator (FACTS) (Version 6.1 or higher) software from Tessella will be used to perform bivariate CRM analyses. These posterior estimates will not be reported in the CSR.

To perform the bivariate CRM analysis, the priors for each pair of parameters (α, β) for the Bayesian logistic regression model for each drug are specified via a bivariate normal distribution, with a separate mean and standard deviation (s.d.) for ln(α) and ln(β), and a correlation term. The parameters (s.d.) of the model are

$\ln(\alpha_1)$=-3 (10), $\ln(\beta_1)$=1(10),

$\ln(\alpha_2)$=-3 (10), $\ln(\beta_2)$=1(10),

$\rho_1 = \rho_2$=0.1

where ln(α) and ln(β) for each drug are assumed to be distributed as bivariate normal with correlation ρ. The prior for the interaction term η is assumed to follow the standard normal distribution N(0,1).

Refer to Section 9.2.1 and Section 10.10.1 of the CSP for more details of the bivariate CRM model.

The bivariate CRM analysis will only provide guidance for dose escalation based on toxicity alone. The GSK study team, in collaboration with study investigators, will review all relevant data (using Spotfire visualisations and site feedback and any other relevant source of data) to support:

- whether the current dose had acceptable toxicity, and
- the decision regarding the next dose level based on the totality of the data including PK, pharmacodynamic/biomarker data when available.
- the decision of the recommended Phase 2 dose (RP2D) based on the totality of the data including but not limited to PK and pharmacodynamics/biomarkers data when available.

Once the total planned number of participants have completed the 28 day DLT observation period for Part 1, data from all dose levels will be reviewed in order to identify the R2PD. The totality of data, including safety/tolerability, PK, pharmacodynamic, and efficacy will be used to determine whether to proceed to Part 2 and which dose combination will be chosen as the RP2D. Outputs to facilitate this review are described in Section 13.10.

3.1.2. Part 2: Cohort Expansion

No formal interim analysis for futility or efficacy is planned to be performed in Part 2. The study team may evaluate safety, PK and Pharmacodynamic data and make the recommendation to discontinue the study at any time due to safety concerns.

3.2. Final Analyses

For participants who meet all eligibility criteria and enroll into the study, the maximum duration of treatment is expected to be two years. The maximum follow-up period for safety assessments will be 90 days from the date of the last dose of study treatment. The expected maximum follow-up period for survival and subsequent anti-cancer therapy will be two years from the date of the last dose of study treatment. Participants deriving benefit from study treatment may remain on study beyond 2 years.

All participants who permanently discontinue study treatment for any reason will be followed for survival, disease progression (if not already confirmed by iRECIST) and new anti-cancer therapy (including radiotherapy) every 12 weeks until death, termination of the overall study or an arm /cohort by the sponsor.

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. After 72 events have occurred for participants enrolled in Part 2, which is 80% of the total sample size of Part 2 or all participants have completed the study as defined in the protocol, whichever comes first. (This will no longer apply as study is terminating after Part 1)
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.

3. Randomization codes have been distributed according to RandAll NG procedures.

Note: the study is not blinded, therefore, criteria for unblinding do not need to be met.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility	• Screening Status
Enrolled	• All participants who passed screening and entered the study. • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study.	• Disposition
Intent-To-Treat (ITT)	• Part 2: All participants who are randomized in the trial. Note: Part 1 participants that were dosed at the dose level chosen for expansion in Part 2 will be excluded from the Part 2 ITT Population. Similarly, Part 2 participants will not be included in the corresponding Part 1 dose level. • Participants will be analysed based on the assigned/randomized treatment, regardless of actual treatment received. • This will be the primary population for efficacy analyses of Part 2. This population is not required for any Part 1 analyses.	• Part 2 Study Population • Part 2 Efficacy
All Treated	• All participants who receive at least 1 dose of SOC or tremelimumab or GSK3359609. • Participants will be assigned to the actual treatment that they received. If a participant is dosed with more than one study treatment, they will be assigned to the treatment/dose level that they received for ≥50% of the visits at which they were dosed. • Note: Part 1 participants that were dosed at the dose level chosen for expansion in Part 2 will be excluded from the Part 2 All Treated Population. Similarly, Part 2 participants will not be included in the corresponding Part 1 dose level.	• Part 1 Study Population • Part 1 Efficacy • Part 1 Safety • Part 2 Safety
Pharmacokinetic (PK)	• All participants from the All Treated population for whom at least one PK sample is obtained, analysed and measurable. This will be the primary population for PK analyses.	• PK
Pharmacodynamic (PD)	• All participants from the All Treated population for whom pre- and on-treatment paired tumour biopsies or pre- and on-treatment blood samples are obtained, analysed and measurable.	• PD/Biomarker
DLT Evaluable	• All Treated Population in Part 1 who complete the 28-day DLT observation period and complete two treatment administrations, or experience a DLT during the determinative 28-day period or as agreed upon by the study team	• Part 1 DLT

Refer Section 13.10: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

Important protocol deviations (including but not limited to deviations related to study inclusion/exclusion criteria, participant safety or interpretability of the trial data, or conduct of the trial) will be summarised and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan [V3.0].

- Data will be reviewed prior to freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised in the protocol deviations dataset. Although a per protocol population is not included, cases of site misconduct, any suspected fraudulent activity or other serious protocol deviations may warrant parameter, participant or site level exclusion from analysis populations. These will be captured in a note to file following study team review and agreement.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate summary and listing of all deviations from inclusion/exclusion criteria specified in the protocol will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

Protocol deviations related to the COVID-19 pandemic will contain the prefix COVID19.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions				
[RandAll NG]			Data Displays for Reporting	
Part	Code	Description	Description	Order in TLF
PART 1	A	GSK3359609 + Treme in Part 1	GSK3359609 8mg/ Treme 75mg	1
			GSK3359609 24mg/ Treme 75mg	2
			GSK3359609 8mg/ Treme 225mg	3
			GSK3359609 80mg/ Treme 75mg	4
			GSK3359609 24mg/ Treme 225mg	5
			GSK3359609 80mg/ Treme 225mg	6
PART 2	B	GSK3359609 + Treme (RP2D) in Part 2	*GSK3359609 xxmg/ Treme xxmg	7
	C	SOC in Part 2	SOC	8

*The selected RP2D dosing information will be displayed in the outputs, similarly to the corresponding dose level description in Part 1.

Data display descriptions will be derived using the RandAll data in combination with the treatment exposure, as applicable for each analysis population. The dose levels/treatment arms will be summarised using the treatment label descriptions above and listed in the order indicated in the table.

In order to identify the study part that screening failures were enrolled in; screening failures will be assigned to Part 1 or Part 2 based on the date of screening. Any participants with earliest study date (likely date of informed consent) after the date that

the last Part 1 participant completes the 28 day DLT observation period will be assigned to Part 2. All other participants will be assigned to Part 1.

Part 1 participants dosed at the RP2D meeting the additional Part 2 inclusion/exclusion criteria will not be included in the Part 2 analyses.

5.2. Baseline Definitions

For all endpoints (except as noted in baseline definitions below) the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits.

If time is not collected and it is not otherwise possible to determine whether the assessment was performed pre- or post-dose, Day 1 assessments are assumed to be taken prior to first dose and may be used as baseline. Furthermore, if there are multiple assessments on the same day, the mean of the pre-dose assessments performed on that day will be taken. The latest non-missing average prior to dosing on Day 1 will be used as baseline. For laboratory data, baseline will be the latest non-missing pre-dose value from central lab. If no central lab value is available, the latest non-missing pre-dose value from local lab will be used. For participants who did not receive study treatment during the study, baseline will be defined as the latest, non-missing value.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

Parameter	Study Assessments Considered as Baseline		Baseline used in data displays
	Screening	Day 1 (Pre-Dose)	
Disease Assessment	X		Screening
Vital Signs	X	X	Day 1 Pre-dose
ECOG PS	X	X	Day 1 Pre-dose
Physical Examination (including height and weight)	X	X	Day 1 Pre-dose if collected, otherwise, use screening
12-lead ECG	X	X	Day 1 pre-dose measurements
Echocardiogram/MUGA	X		Screening
Laboratory Assessment (including hematology, clinical chemistry and urinalysis)	X	X	Day 1 Pre-dose if collected, otherwise, use screening
Pancreatic Function laboratory testing	X	X	Day 1 Pre-dose if collected, otherwise, use screening
Thyroid Function, serum pregnancy, Hepatitis B, C, HIV, cardiac function, coagulation	X		Screening
Pharmacokinetics/ Pharmacodynamics/ Biomarker		X	Day 1
Patient reported outcomes: • EORTC QLQ-C30 • EORTC QLQ-HN35 • PROMIS – PF • FACT GP5 • PRO-CTCAE • EQ-5D		X	Day 1

5.3. Multicentre Studies

It is anticipated that participant accrual will be spread thinly across centres and summaries of data by centre are unlikely to be informative, therefore, all centres will be pooled prior to analysis and no controlling for centre-effect will be considered in the statistical analyses.

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

Randomization in Part 2 will be stratified by Line of anti-PD-(L)1 therapy. This will be based on the IxRS data. This stratification factor may be used in descriptive summaries and statistical analyses for Part 2 only. If appropriate, subgroup analyses may be performed. Further subgroup analyses based on the same strata identified in the eCRF data may be performed if the percentage of participants in the corresponding CRF and IxRS stratum differ by more than 5%. The strata will not be included as a covariate in any statistical analyses.

Category	Details
Strata	Line of anti-PD-(L)1 therapy: • Anti-PD-(L)1 therapy received as part of the first line treatment • Anti-PD-(L)1 therapy received as part of the second line treatment

5.4.2. Examination of Subgroups

No subgroup analysis is planned.

5.5. Multiple Comparisons and Multiplicity

There are no planned adjustments for multiple comparisons or multiplicity.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
13.3	Appendix 3: Assessment Windows
13.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
13.5	Appendix 5: Data Display Standards & Handling Conventions
13.6	Appendix 6: Derived and Transformed Data
13.7	Appendix 7: Reporting Standards for Missing Data
13.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

In this multicentre global study, enrolment will be presented by country and investigative site using the enrolled population where applicable.

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the All Treated population for Part 1 and the ITT population for Part 2, unless otherwise specified.

Study population analyses including analyses of participant's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, disease characteristics at initial diagnosis and at screening, prior anti-cancer therapy, surgical/medical procedures, substance use, duration of follow up, exposure and treatment compliance will be based on GSK Core and Oncology Data Standards. Separate displays will be presented for each study part, unless otherwise specified. Details of the planned displays are presented in Appendix 10: List of Data Displays.

6.2. Disposition of Participants

A summary of the number of participants in each of the analysis populations described in Section 4 will be provided, based on the screened population. A listing of participants excluded from each analysis populations will also be provided, based on the screened population. Number of participants based on the Enrolled population will be summarized by country and site for each study part. Participants planned and actual treatment received will be listed.

The number and percentage of participants who met eligibility criteria and entered the study, who failed screening for any reason and therefore were not entered into the study, and participants who met eligibility criteria but were not needed will be summarized for the screened population. Reasons for failure for those subjects who failed screening will also be summarized in the display and listed. A participant may have more than one reason for screen failure.

A summary of participant status (completed, ongoing, withdrawn) and reason for study withdrawal will be provided. This display will show the number and percentage of participants who have completed the study, are ongoing or have withdrawn from the study, including primary and secondary (if any) reasons for study withdrawal. Reasons for study withdrawal will be presented in the order they are displayed in the eCRF (Electronic Case Report Form).

For Part 1 participants will be considered to have completed the study if they fulfil one of two criteria:

1. Complete screening assessments, receive at least two doses of study treatment (or receive one dose but experience a dose limiting toxicity (DLT), are observed during the 28 day DLT observation period), and complete the treatment

discontinuation visit and the follow-up visit for safety (this will be considered 'completed follow-up')
2. Completed screening assessment and have died while receiving study treatment or during post-study treatment follow-up period for safety.

For Part 2, participants will be considered as completing the study if they complete screening assessments, receive at least one dose of study treatment, discontinue study treatment for reasons other than lost to follow-up or non-compliance, and complete the study treatment discontinuation visit and follow-up visits or have died while receiving study treatment or during post-treatment follow-up period.

In the event the Sponsor decides to close the study, participants receiving ongoing study treatment or ongoing in follow-up will be considered as completed the study (under 'completed follow-up' for Part 1 participants). The end of the study in this case is defined as the completion of the last participant's required visit.

A listing of reasons for study withdrawal will also be produced for the enrolled population.

A single, overall summary of the number and percentage of participants who entered, withdrew from and completed each study part will be displayed.

A summary of study treatment status will be provided. This display will show the number and percentage of participants who are ongoing or discontinued study treatment and a summary of the primary reasons for discontinuation of study treatment. Reasons for study treatment discontinuation will be presented in the order they are displayed in the eCRF.

A listing of reasons for treatment discontinuation will be generated. The listing will include date of discontinuation, last dose date, and primary reasons for study treatment discontinuation.

6.3. Protocol Deviations

Important protocol deviations will be summarized and listed and will include inclusion/exclusion deviations as well as other deviations. See Section 4.1 for details.

A separate listing of inclusion/exclusion criteria deviations as captured on the eCRF will also be provided.

6.4. Demographic and Baseline Characteristics

The demographic characteristics (e.g., age, race, ethnicity, sex, height, baseline body weight, and line of anti-PD(L)1 therapy [for Part 2 only]) will be listed and summarized. Age, height and weight will be summarized using the mean, standard deviation, minimum, median, and maximum. In addition, age will also be categorized and summarized by 18-64, 65-74, 75-84, and ≥85 and by 18-64 and ≥65. The count and percentage will be computed for race, ethnicity and sex. The summary of demographic data will be displayed for each cohort and overall.

A separate summary of age ranges based on the Enrolled population will be provided. Age will be summarized in categories: 18-64, 65-84, and ≥85. Race and racial combinations will also be summarized.

6.5. Concomitant Medications

Concomitant medications will be coded using GSK Drug coding dictionary and summarized and listed. The summary of concomitant medications will show the number and percentage of participants taking concomitant medications by Ingredient. Multi-ingredient products will be summarized by their separate ingredients rather than as a combination of ingredients.

In the summary of concomitant medications, each participant is counted once within each unique ingredient. For example, if a participant takes Amoxycillin on two separate occasions, the participant is counted only once under the ingredient "Amoxycillin". In the summary of concomitant medications, the ingredients will be summarized by the base only, using CMBASECD and CMBASE.

All medications, regardless of onset date will be included in the summary and listing. Blood products or blood supportive care products with onset date after the start of study treatment will be included in the summary tables. The frequency and percentage of participants using blood products and blood supportive care products after the start of study treatment will be provided. Supportive listings will also be provided.

6.6. Disease Characteristics

Disease history and characteristics at initial diagnosis and screening (where relevant: primary tumor type, lesion status, time since initial diagnosis in weeks, stage, time since last progression in weeks) will be summarized. Indicators (yes/no) for the following, collected at screening, will also be summarized: measurable disease, non-target lesions, and metastatic disease. Past and current medical conditions reported at screening will be summarized by cancer-related and non-cancer related categories. Disease history and characteristics, as well as these medical conditions, will be presented in data listings.

A summary and listing of disease burden at baseline will be provided. Information on sites of metastatic disease at screening will be summarized and listed.

6.7. Prior Anti-cancer Therapy

Prior anti-cancer therapy will be coded using GSK Drug coding dictionary, then summarized by type of therapy and listed. A listing of prior anti-cancer therapy will show the relationship between Anatomical Therapeutic Chemical (ATC) Level 1, ingredient, and verbatim text; therapies will be classified by type (chemotherapy, immunotherapy, hormonal therapy, radiotherapy, and biologic therapy, radioactive therapy, small molecule targeted therapy, vaccine).

A summary of the number of prior anti-cancer therapy regimens/lines by type will also be produced.

Prior cancer related surgeries will be summarized alongside type, and all prior surgical procedures will be and listed.

6.8. Subsequent Anti-cancer Therapies

The number and percentage of participants that received chemotherapy, immunotherapy, hormonal therapy, biologic therapy, radioactive therapy, small molecule targeted therapy, radiotherapy and cancer-specific surgery as post study treatment anti-cancer therapy will be summarized. Time from study treatment discontinuation to the first post study treatment anti-cancer therapy will also be included in this summary table.

Follow-up anti-cancer therapy will be coded using GSK Drug coding dictionary, then summarized by ingredient. A listing of the type of follow-up anti-cancer therapy received (chemotherapy, immunotherapy, hormonal therapy, biologic therapy, radioactive therapy, small molecule targeted therapy, radiotherapy and cancer-specific surgery and details of the anti-cancer therapy (radiotherapy site, surgical procedure, or drug name for chemotherapy, hormonal, immunotherapy, biologic therapy) for each participant will be provided.

6.9. Treatment Compliance and Exposure

Individual participant summary listings of study treatment exposure and dose modifications (e.g., number of dose reductions, dose delays, missed doses, dose interruptions and incomplete infusions) for each component will be provided.

Extent of exposure to GSK3359609, tremelimumab and SOC will be summarized and listed, separately.

The duration of exposure to study treatment in weeks, defined as (treatment stop date – treatment start date + 1) divided by 7, will be summarized. Descriptive statistics including mean, median, standard deviation, minimum, and maximum will be calculated for time on study treatment. Moreover, time on study treatment will be categorized in different time period: <9 weeks, 9 – 18 weeks, 18 – 24 weeks, 24 – 48 weeks and >= 48 weeks.

The cumulative dose, infusion dose intensity and relative dose intensity (%) will also be summarized for each drug component using mean, median, standard deviation, minimum, and maximum. The cumulative dose is the sum of the actual dose administered during each infusion for a participant throughout the study.

The dose intensity is calculated by cycles which consist of 3-week periods for GSK3359609, Tremelimumab and Docetaxel; and a 1 week period for Paclitaxel and Cetuximab. The dose intensity is calculated by cumulative dose divided by expected duration of exposure (last infusion date – first infusion date + cycle length in days)/cycle length in days). The relative dose intensity (%) is the dose intensity divided by planned dose per cycle.

Dose delays will be summarised by number of delays and reasons for the delays. Dose interruptions will be summarised by number of interruptions, duration of interruptions and reason for interruptions.

All dose interruptions, incomplete infusions, and dose delays will be listed separately. Any overdose will also be listed if applicable.

Dose modifications (dose interruptions and dose delays) and Dose limiting toxicity (DLT) will also be summarized and listed according to GSK Core Data Standards.

7. PRIMARY ENDPOINT ANALYSES

The primary endpoint analyses planned for Part 1 of the study can be found in Section 10: Safety Analyses.

The primary endpoint analyses for Part 2 are stated in the section below.

The primary population of interest for Part 2 will be the Intent-To-Treat (ITT) population summarized by randomized treatment arm. This will be the population for figures, listings and summaries of OS data.

7.1. Definition of Endpoints

Overall Survival (OS)

The endpoint for primary analyses for Part 2 is Overall Survival (OS), defined as the interval of time (in weeks) from randomization to the date of death due to any cause.

In the absence of confirmation of death, survival time will be censored at the last date the participant is known to be alive at (i.e. their last known alive date). Often, this will be the date of last contact. Participants lacking data beyond the date of randomization will have their survival times censored at the date of randomization. When calculating overall survival, all deaths following subsequent anti-cancer therapy will be included.

The distribution of OS for each treatment arm at the time of final analyses will be estimated using the Kaplan-Meier method. The median, 25^{th} and 75^{th} percentiles of OS will be estimated and corresponding 2-sided 95% confidence intervals will be estimated using the Brookmeyer-Crowley method (1982). The treatment difference in survival will be assessed by the stratified log-rank test.

7.2. Statistical Analyses / Methods

Overall Survival (OS)

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

OS will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

Statistical Methodology Specification

Endpoint / Variables
• OS
Model Specification
• OS will be estimated using Kaplan-Meier analysis for each study intervention (PROC LIFETEST). 95% Confidence intervals will be estimated using the Brookmeyer-Crowley method (1982). • Comparison of distributions of OS between study interventions will be based on the stratified log-rank test (PROC LIFETEST).
Model Results Presentation
• Kaplan-Meier estimates for the median overall survival and the first and third quartiles will be presented, along with 95% CIs. • The p-value from the stratified log-rank test will be reported.
Subgroup Analyses
• NA

7.3. Primary Exploratory Analysis

Calculation of Predictive Probability of Phase 3 success

Prior to calculating the predictive probability of success for the hypothetical Phase 3 study, the hazard ratio (HR) will be derived based on the ratio of the hazard rates in the study intervention and SOC observed from the Part 2 overall survival (OS) data. Final analysis will be performed after 72 events have occurred, which is 80% of the total sample size of Part 2. The predictive probability of Phase 3 success will be calculated as detailed below, assuming (proportional hazards?) the sampling behaviour of the observed log hazard ratio is well approximated by a normal distribution, and the unknown fixed true log hazard ratio is the same in phase 2 and phase 3. The ancillary pivotal quantity

$$\frac{\log\left(\widehat{HR}_{p3}\right) - \log\left(\widehat{HR}_{p2}\right)}{\sqrt{\widehat{\mathrm{SE}}_{p3}^2 + \widehat{\mathrm{SE}}_{p2}^2}} \sim N(0,1)$$

follows an asymptotic standard normal distribution, where $\widehat{\mathrm{SE}}_{p2}$ is an estimator for the standard error of $\log\left(\widehat{HR}_{p2}\right)$ and $\widehat{\mathrm{SE}}_{p3}^2 = \widehat{\mathrm{SE}}_{p2}^2 \left(\frac{1}{n_{p2}^T} + \frac{1}{n_{p2}^C}\right)^{-1} \left(\frac{1}{n_{p3}^T} + \frac{1}{n_{p3}^C}\right)$.

The two-sided $100(1-\alpha)\%$ prediction interval is

$$\log\left(\widehat{hr}_{p2}\right) \pm z_{\alpha/2} \sqrt{\widehat{se}_{p3}^2 + \widehat{se}_{p2}^2}$$

Intervals constructed in this manner will cover the as of yet unobserved phase 3 log hazard ratio estimate $100(1-\alpha)\%$ of the time. Using the estimated standard error from

phase 2, under the null hypothesis of equality of hazards in phase 3 the one-sided 2.5% alpha level logrank test (two-sided 5% test) is statistically significant if

$$Z_{p3} < -1.96 \quad or\ equivalently, \quad y = \log(\widehat{hr}_{p3}) < -1.96 * \widehat{se}_{p3}.$$

If $-1.96 * \widehat{se}_{p3}^2$ exceeds the one-sided upper 60% prediction limit (20% two-sided upper limit) we are no less than 60% confident in a successful phase 3 result. The confidence level in a successful phase 3 result is one minus the probability of the observed phase 2 result and an unsuccessful phase 3 result or something more extreme, and is given by

$$1 - \Phi\left(\frac{\log(\widehat{hr}_{p2}) - (-1.96 * \widehat{se}_{p3})}{\sqrt{\widehat{se}_{p2}^2 + \widehat{se}_{p3}^2}}\right)$$

$$\Phi\left(\frac{-\log(\widehat{hr}_{p2}) - 1.96 * \widehat{se}_{p3}}{\sqrt{\widehat{se}_{p2}^2 + \widehat{se}_{p3}^2}}\right)$$

where $\Phi(t)$ is the cdf of a standard normal distribution.

8. SECONDARY ENDPOINT ANALYSES

8.1. Efficacy Analysis

The secondary analyses for Part 1 will be performed for ORR and DCR. The secondary analyses for Part 1 will be based on the All Treated population, unless otherwise specified.

The secondary analyses for Part 2 will be performed for ORR, DCR, PFS, TTR and DoR. The secondary analyses for Part 2 will be based on the ITT population, unless otherwise specified.

Additional secondary endpoints for Part 2 can be found in Section 10: Safety Analyses.

8.1.1. Definition of Endpoints

Tumor response i.e., complete response (CR), partial response (PR), and stable disease (SD), and progressive disease (PD) will be based on the assessments from the investigators' assessment of objective evidence (e.g., radiological scan). Overall responses were measured in accordance with the RECIST v1.1 [Eisenhauer, 2009] and iRECIST [Seymour, 2017].

Lesion assessment method and timing, evaluation of disease, disease progression and response criteria will be conducted according to RECIST (version 1.1) and iRECIST as outlined in Appendix 7 of the protocol. iRECIST will be used to determine treatment decisions and RECIST v1.1 will be primarily used for the analysis of anti-cancer activity.

The secondary endpoints include the following:

Secondary Efficacy Endpoints	
Overall Response Rate (ORR)	For Part 1 and 2 ORR is defined as percentage of participants with a confirmed CR or PR as assessed by the investigator per either RECIST v1.1 or iRECIST criteria.
Disease Control Rate (DCR)	For Part 1 and 2 DCR is defined as the percentage of participants with confirmed CR or PR or at least 18 weeks of SD, as assessed by the investigator per RECIST v1.1 or iRECIST criteria.
Progression-Free Survival (PFS)	For Part 2, PFS is defined as the interval of time (in weeks) between the date of randomization and the first documented date of disease progression as assessed by the investigator per RECIST v1.1 and confirmed by iRECIST criteria, or the date of death due to any causes. Determination of dates of PFS events and dates for censoring are described in Table 1.
Time to Response (TTR)	TTR is defined, as the interval of time (in weeks) from first dose and the first documented evidence of confirmed CR or PR as the Best Overall Response (BOR), as assessed by the investigator per RECIST v1.1 or iRECIST criteria.

Secondary Efficacy Endpoints	
Duration of Response (DoR)	Duration of response is defined as the interval of time (in weeks) from first documented evidence of CR or PR to the time when disease progression is documented as assessed by the investigator per RECIST v1.1 and confirmed by iRECIST, or death due to any cause among participants with a confirmed PR or CR as the BOR. Censoring rule will follow those for PFS as specified in Table 1.

Best Overall Response (BOR) is defined as the best confirmed response (Complete Response (CR) > Partial Response (PR) > Stable Disease (SD) > Progressive Disease (PD) > Not Evaluable (NE)) from treatment start date until disease progression or initiation of new anti-cancer therapy, whichever is earlier, as assessed by the investigator per RECIST v1.1 and iRECIST Criteria.

With respect to best overall responses (BOR), RECIST v1.1 and iRECIST will be based on investigator assessments of overall response at each visit:

- To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after the first dose at a minimum of 9 weeks.
- If the minimum duration for SD is not met, BOR will depend on the subsequent assessments. For example, if an assessment of PD follows the assessment of SD and SD does not meet the minimum duration requirement the BOR will be PD. Alternatively, participants lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

In terms of RECIST v1.1, a confirmatory disease assessment of PR or CR will be performed no less than 4 weeks (28 days) after the criteria for response are first met. A status of SD or PD is not confirmed.

For iRECIST, a confirmatory disease assessment of PR or CR will be performed no less than 4 weeks (28 days) after the criteria for response are first met. In addition, a confirmatory disease assessment of PD will be performed no less than 4 weeks and up to 8 weeks later to confirm PD.

A summary of the assignments for progression and censoring dates for PFS and DoR are specified in the Table 1 below.

Table 1 Censoring Rules for PFS and DoR

Censoring Rules		
Situation	**Date of Event (Progression/Death) or Censoring**	**Outcome: Event (Progression/Death) or Censoring**
No (or incomplete) baseline tumor assessments and the participant has not died (if the participant has	Date of Randomization (Part 2)	Censored

Censoring Rules		
Situation	**Date of Event (Progression/Death) or Censoring**	**Outcome: Event (Progression/Death) or Censoring**
died, follow the rules for death indicted at the bottom of the table)		
No post-baseline assessments and the participant has not died (if the participant has died, follow the rules for death indicted at the bottom of the table)	Date of Randomization (Part 2)	Censored
Progression documented between scheduled visits	Date of assessment of progression[1]	Event
No progression *(or death)*	Date of last 'adequate' assessment of response[2]	Censored
New anti-cancer treatment started *(prior to documented disease progression).*[3]	Date of last 'adequate' assessment of response[2] *(on or prior to starting anti-cancer therapy)*	Censored
Death before first PD assessment (or Death at baseline or prior to any adequate assessments)	Date of death	Event
Death between adequate assessment visits	Date of death	Event

Censoring Rules		
Situation	**Date of Event (Progression/Death) or Censoring**	**Outcome: Event (Progression/Death) or Censoring**
Death or progression after more than one missed visit	Date of last 'adequate' assessment of response[2] *(prior to missed assessments)*: If the disease assessment is every 6 weeks, a window of 91 days ([12=6*2] weeks + 7 day window) will be used to determine whether there is extended time without adequate assessment. If the time difference between PD/death due to any cause and last adequate disease assessment is more than [91] days, PFS will be censored at the last adequate disease assessment prior to PD/death due to any cause. For scans conducted prior to 10 weeks, a window of 119 days [16 weeks + 7 day window) will be used to determine whether there is extended time without adequate assessment. For scans conducted after 52 weeks, a window of 175 days ([24=12*2] weeks + 7 day window) will be used to determine whether there is extended time without adequate assessment.	Censored

NOTES :

[1] The earliest of (i) Date of radiological assessment showing new lesion (if progression is based on new lesion); or (ii) Date of radiological assessment showing unequivocal progression in non target lesions, or (iii) Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)

[2] An adequate assessment is defined as an assessment where the investigator assessed response is CR, PR, or SD.
[3] If PD and New anti-cancer therapy occur on the same day, assume the progression was documented first (e.g. outcome is progression and the date is the date of the assessment of progression). If anti-cancer therapy is started prior to any adequate assessments, censoring date should be the date of first dose.

8.1.2. Statistical Analyses / Methods

Unless otherwise specified, endpoints / variables defined in this section will be summarised using descriptive statistics, graphically presented (where appropriate) and listed. For ORR, DCR, TTR, and DoR, 2-sided 95% exact confidence limits will be provided.

Details of the planned displays are provided in Section 13.10: List of Data Displays and will be based on GSK data standards and statistical principles.

Overall response rate (ORR)

The number and percentage of participants BOR will be summarized by cohort for Part 1 and treatment arm for Part 2. ORR will be reported per both RECIST v1.1 and iRECIST as defined in Section 8.1.1.

Participants with Not Evaluable or missing response will be treated as non-responders; i.e. they will be included in the denominator when calculating the percentage.

ORR and the associated 2-sided 95% exact confidence limits will be provided by cohort/treatment arm for each part.

Disease control rate (DCR)

The number and percentage of participants BOR will be summarized by cohort for Part 1 and treatment arm for Part 2. DCR will be reported per both RECIST v1.1 and iRECIST as defined in Section 8.1.1.

Participants with unknown or missing responses will be treated as non-responders, i.e., these participants will be included in the denominator when calculating percentages of response.

DCR will be summarized and the associated 2-sided 95% exact confidence limits will be provided separately by cohort/treatment arm for each part.

Progression Free Survival (PFS)

The distribution of PFS for each treatment arm will be estimated using the Kaplan-Meier method. Summaries of the number and percentage of participants experiencing a PFS event and the type of event will be provided along with the median, 25th and 75th percentiles of PFS will be estimated and corresponding 95% confidence intervals will be estimated using the Brookmeyer-Crowley method (1982).

The date of documented disease progression will be defined as the date of disease progression by iRECIST based on eCRF entries. If an assessment occurs over multiple

days, the earliest date of progression will be used; the date of death should be taken from the Record of Death page. Death on study due to any cause will be included.

Participants whose disease progressed or died after an extended period (two or more consecutive scheduled disease assessments) without adequate assessment will be censored at their date of last adequate assessment prior to progression or death even if subsequent information is available regarding progression or death. anti-cancer

For participants who receive subsequent anti-cancer therapy including radiotherapy and cancer-related surgery the following rules will apply:

- If the start date of anti-cancer therapy is partial (i.e. either missing the day but has the month and year available or missing both day and month), the imputation rules described in Appendix 7 will be applied. No imputation will be made for completely missing dates.
- If anti-cancer therapy is started without documented disease progression or is started prior to documented disease progression, then PFS will be censored at the date of the last adequate assessment that is no later than the date of initiation of anti-cancer therapy (i.e. if an assessment occurs on the same day as the start of new anti-cancer therapy the assessment will be used – as it will be assumed the assessment occurred prior to the administration of new anti-cancer therapy). The date of response at the last adequate assessment will be used as the censoring value.
- If a participant has only a baseline visit or does not have an adequate assessment that is no later than the date of initiation of anti-cancer therapy, PFS will be censored at the date of randomization.

If a participant has neither progressed nor died nor started new anti-cancer therapy, then PFS will be censored at the date of the last adequate assessment prior to PD or death or new anti-cancer therapy.

If there is no adequate baseline assessment, the participants will be censored at their date of first dose. Participants without any adequate post-baseline tumour assessments will be censored at the date of randomization.

Participants should not start subsequent anti-cancer therapy while on study. For participants who receive subsequent anti-cancer therapy the censoring rules described in Table 1 will apply.

Statistical Methodology Specification

Endpoint / Variables
• PFS
Model Specification
• Comparison of distribution of PFS between dose levels/treatment arms will be based on the log-rank test stratified by the randomization factor(s). • Hazard ratio for PFS and corresponding [95%] confidence interval will be estimated using the Cox's proportional hazard model stratified by the randomization factor(s) with dose level/treatment arm as the sole explanatory variable.

Model Checking & Diagnostics
• The proportional hazards assumption will be assessed using the following methods: ○ Kaplan-Meier plot by dose level/treatment arm ○ Plot of log(time) against log(-log(survival)) by dose level/treatment arm ○ Plot of Schoenfeld residuals for treatment ○ Evaluation of time-dependency of treatment effect by adding an interaction term of treatment and time in the Cox model. If the interaction term is significant ($p< 0.10$), it is considered that the proportional hazards assumption is violated. • If one or more of the tests above demonstrates clear violation of the proportional hazards assumption, it is considered the proportional hazards assumption does not hold. Hazard ratio and corresponding 95% CI estimated from the Cox model will still be reported. • Additional analysis of PFS based on RMST, which does not require the proportional hazard assumption, will be conducted and comparison of OS/PFS between dose levels/dose level/treatment arms will be based on the p-value from the RMST test instead of the log-rank test. • RMST at [pre-specified time point] will be estimated from the Kaplan-Meier curve for each dose level/treatment arm: $$\mu_{t^*} = \int_0^{t^*} S(t)\,dt$$ RMST difference at [pre-specified time] ($\hat{\Delta}_{t^*}$) between treatment arms will be estimated as: $$\hat{\Delta}_{t^*} = \int_0^{t^*} \left[\hat{S}_T(t) - \hat{S}_C(t)\right] dt$$ [95%] CI for RMST difference and the p-value will be estimated using the default settings in Proc RMSTReg.
Model Results Presentation
• If the proportional hazard assumption does not hold, plot of RMST difference and corresponding [95%] pointwise confidence interval will be generated.

Time to Response (TTR)

If there are sufficient number of responses, time to response will be summarized descriptively by treatment arm. TTR will be summarized and median, 25th and 75th percentiles will be estimated as well as KM estimates and corresponding 95% confidence intervals. This analysis will be performed in the subset of participants with a confirmed response of CR or PR as the BOR per RECIST v1.1 and iRECIST.

Duration of Response (DOR)

Duration of response will be summarized descriptively by treatment arm. DOR will be summarized and median, 25th and 75th percentiles will be estimated as well as KM estimates and corresponding 95% confidence intervals. This analysis will be performed in the subset of participants with a confirmed response of CR or PR per RECIST v1.1.

Censoring rules will follow those of the PFS as described in Table 1.

8.2. Pharmacokinetic Analyses

8.2.1. Endpoint / Variables

8.2.1.1. Drug Concentration

The GSK3359609 plasma concentration-time data will be summarized by planned time point and cohort. Standard summary statistics will be calculated (i.e. mean, standard deviation, median, minimum and maximum).

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 13.5.3 Reporting Standards for Pharmacokinetic)

8.2.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin Version 6.3 or higher. All calculations of non-compartmental parameters will be based on actual sampling times.

Pharmacokinetic parameters listed will be determined from the plasma concentration-time data, as data permits.

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-tau)	Area under the concentration-time curve from time zero to the pre-dose of the next dose. This will be calculated for Week 1 only.
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
tmax	Time to reach Cmax, determined directly from the concentration-time data.
Cmin	Observed trough concentration at the end of the dosing period (prior to the next dose) in Week 1 and Week 19 .

NOTES:
Additional parameters may be included as required.

8.2.2. Summary Measure

All derived PK parameters will be listed.

For each of these parameters, except tmax, the following summary statistics will be calculated for each dose level: median, minimum, maximum, arithmetic mean, 95% confidence interval for the arithmetic mean, standard deviation, coefficient of variation (CV = 100*(sqrt (exp(SD^2) - 1))) [NOTE: SD = SD of log transformed data]), geometric mean, 95% confidence interval for the geometric mean and standard deviation of logarithmically transformed data.

For tmax, median, maximum, minimum, arithmetic mean, 95% confidence interval, and standard deviation will be calculated. The first point, last point and number of points used in the determination of λz will be included on the listing of the derived parameters.

All PK parameters will be reported to at least 3 significant digits, but to no more significant digits than the precision of the original data.

8.2.3. Population of Interest

All pharmacokinetic analyses will be based on the PK population, unless otherwise specified. All summaries, figures and data listings will use cohort/treatment labels specified in Section 5.1.

8.2.4. Statistical Analyses / Methods

Details of the planned displays are provided in Section 13.10: List of Data Displays and will be based on GSK Data Standards and statistical principles.

The following pharmacokinetic statistical analyses will only be performed, if sufficient data is available (i.e. if participants have well defined plasma profiles).

8.2.4.1. Dose proportionality

If data permits, dose proportionality will be assessed using power model for:

- AUC(0- τ), Cmax, and Cmin in Week 1
- Cmax and Cmin in Week 19

Dose proportionality of GSK3359609 Cmax following single dose administration and AUC(0-τ) and Cmax following repeat dose administration will be evaluated using the power model as described below:

log (pharmacokinetic parameter) = a + b * log(dose)

where a is the intercept and b is the slope.

Both the intercept and slope will be fitted as fixed effects. If there is sufficient data, the model may also be fit with the intercept and/or slope as random effects depending on the ability of the model to converge and on estimation of variance-covariance matrix. The mean slope and corresponding 90% confidence interval will be estimated from the power model.

8.2.4.2. Accumulation

To assess accumulation, ANOVA with a fixed effect term for day and a random effect term for participant will be performed on log-transformed Ctrough for each treatment group (dose level) separately. The observed accumulation ratio (Ro) will be estimated by

exponentiating the difference in least squares means (Dose 6 – Dose 1) and the associated 90% confidence interval.

8.3. Immunogenicity Analyses

Immunogenicity/ Anti-drug antibodies (ADA) testing will occur in dosed participants then analyzed, summarized descriptively and listed.

Immunogenicity information will be listed by participant and a summary of the number of participants that are negative and positive for the presence of the antibodies will be provided at each timepoint and overall for the participant. Drug tolerance of the assays will be taken into account in categorizing results at each timepoint as positive, negative, or inconclusive. A positive result at any timepoint means that the participant's overall category is positive.

To assess immunogenicity of GSK3359609 and Treme, serum will be tested for the presence of anti-GSK3359609 antibodies and anti-Treme antibodies using antibody assays. For the binding assay, there will be 3-steps testing schema: screening, confirmation and titration steps. A screening assessment is performed which produces a result of positive or negative. For samples with a positive screening result, a confirmatory assay is then performed, which also produces a result of positive or negative. If a sample has a positive confirmation result, a titer value will also be obtained to quantify the degree of binding in the titration assay step. Participants will be viewed as positive for the binding assay if the confirmatory assay was positive.

For the incidence of patients with positive binding antibody, a table will be produced summarizing results for the binding antibody assay by dose level and visit. The table will include the number and proportion of participants in each result category for each visit (including TDV visit). Binding confirmatory assay results will be categorized as negative, transient positive (defined as a single positive immunogenic response that does not occur at the final/TDV assessment) or persistent positive (defined as a positive immunogenic response at least 2 consecutive assessments or a single result at the final/TDV assessment).

A separate table will be produced to summarize the median, min and max titer values among all visits by dose level and part.

9. EXPLORATORY ENDPOINT ANALYSIS

9.1. Efficacy Analysis

The exploratory analyses for Part 1 will be performed for PFS, OS, TTR and DoR. The exploratory analyses for Part 1 will be based on the All Treated population, unless otherwise specified.

Progression Free Survival (PFS)

For Part 1 participants, PFS duration is defined as the time from the date of first dose to first documented evidence of disease progression or death (regardless of cause of death), whichever comes first.

Summaries of the number and percentage of participants experiencing a PFS event and the type of event will be provided by cohort along with the median, 25^{th} and 75^{th} percentiles of PFS and corresponding 95% confidence intervals will be estimated using the Brookmeyer-Crowley method (1982).

Overall Survival (OS)

For Part 1, OS is defined as the interval of time (in weeks) from first dose to the date of death due to any cause.

Summaries of the number and percentage of participants experiencing a OS event and the type of event will be provided by cohort along with the median, 25th and 75th percentiles of OS and corresponding 95% confidence intervals will be estimated using the Brookmeyer-Crowley method (1982).

Time to Response (TTR) and Duration of Response (DoR)

Summaries of the number and percentage of participants experiencing a response event and the type of event will be provided by cohort along with the median, 25th and 75th percentiles of response and corresponding 95% confidence intervals will be estimated using the Brookmeyer-Crowley method (1982).

9.2. Pharmacodynamic and Biomarker Analyses

9.2.1. Endpoint / Variables

Data obtained from the pharmacodynamic samples will be descriptively and/or graphically summarized. These include serum sICOS, plasma cytokines, tumor biopsy material and protein expression by IHC.

9.2.2. Summary Measure

The results of these biomarker investigations will be reported separately from the main clinical study report. All endpoints of interest from all comparisons will be descriptively (absolute value/change from baseline) and/or graphically summarized or as appropriate to the data.

Exploratory analyses may be performed to examine potential relationships between anti-cancer activity and changes in markers of target inhibition or tumor biology (e.g., biomarkers, relevant transcripts, and/or proteins) or between anti-cancer activity and potential markers of sensitivity.

Additional exploratory analyses may be performed to further characterize the novel biomarkers.

9.2.3. Population of Interest

The pharmacodynamic analyses will be based on the PD population, unless otherwise specified.

9.3. Pharmacokinetic/Pharmacodynamic Analyses

If warranted, exploratory PK/Pharmacodynamic analyses will be conducted to inform dose selection decisions.

9.4. Pharmacogenetic Analyses

Further details on PGx analyses discussed in the protocol may be identified /addressed in a separate PGx RAP, if applicable.

9.5. Patient Reported Outcomes

Patient reported outcomes will not be analysed as data is not collected for part 1.

10. SAFETY ANALYSES

The safety analyses are the Primary analyses for Part 1 and Secondary for Part 2. All safety analysis will be based on the All Treated population, unless otherwise specified.

Changes from baseline in all serially collected safety endpoints (laboratory tests, vital signs, ECG parameters) will be summarized according to the scheduled, nominal visit at which they are collected and across all on treatment time points using a "worst-case" analysis. Data for vital signs and electrocardiograms (ECGs) will be summarized based on predetermined criteria identified to be of potential clinical concern (PCI).

10.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Section 13.10: List of Data Displays. All summaries analyses and listings will present all adverse events. AEs will be coded to the preferred term (PT) level using the Medical Dictionary for Regulatory Affairs (MedDRA version 20.1 or higher) and grouped by system organ class (SOC) and adverse events of special interest (AESI) groupings. AEs will be graded by the investigator according to the NCI-CTCAE version 5.0 or higher. Unless otherwise specified AEs will be presented for Parts 1 and 2 separately.

A summary of number and percentage of participants with any adverse events by maximum grade will be produced. The maximum grade throughout the duration of event rather than the severity grade at onset will be used to determine the severity grade recorded by a participant at each level of summarization. AEs will be sorted by System Organ Class (SOC) and Preferred term (PT) in descending order of total incidence. The summary will use the following algorithms for counting the participants:

- **Preferred term row**: Participants experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade/intensity.
- **System organ class (SOC) rows**: Each participant is counted only once at the maximum toxicity grade/intensity at each SOC level per dose level received, although they may have several different preferred term events within the same SOC.
- **Adverse events of special interest (AESI):** As defined in the protocol. Each participant is counted only once at the maximum toxicity grade/intensity at each dose combination received.
- **Any event row**: Each participant with at least one adverse event will be counted only once at the maximum grade/intensity no matter how many events they have.

The summary tables will be displayed in descending frequency of total incidence by SOC and Preferred Term (PT), and by alphabetic order when PT with equal incidence within the SOC. If maximum toxicity grade is missing but the toxicity grade at onset is available, then this will be used instead. If both are missing and there are no other events

with a toxicity grade for the participant, at each level of summarization, then this event will be displayed in an "unknown" row.

In addition, the number and percentage of participants with AEs (all grades) will be summarized and displayed in descending frequency of total incidence by SOC and PT.

A separate summary will be provided for study treatment related AEs. A study treatment related AE is defined as an AE for which the investigator classifies the relationship to any of the study treatments as "Yes" or as determined by the study team. A conservative (worst-case scenario) approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study treatment as 'Yes' if missing. The summary table will be displayed in descending frequency of total incidence by SOC and PT.

Summaries for treatment-related adverse events will be produced and summarized by frequency (number and percentage of total participants) and maximum severity (grade), by system organ class and preferred term. If listed in the NCI-CTCAE (version 5.0), these summaries will be by the maximum grade.

A summary of the number and percentage of participants and the number of occurrences of common non-serious AEs that occurred in strictly 5% of the participants or above will be provided (no rounding for the percentage will be used in terms of 5% threshold, e.g., event with 4.9% incidence rate should not be included in this table). The summary will be displayed by System Organ Class (SOC) and Preferred Term (PT) in descending order of total incidence.

A listing of all AEs will be provided.

10.2. Adverse Events of Special Interest Analyses

Current adverse events of special interest (AESIs) include AEs of any grade that may have a potential immunologic aetiology. AESIs have been selected based on pre-clinical and clinical experience across the ICOS program by the safety review team. AESIs for GSK3359609 are pneumonitis, colitis, hepatitis, endocrinopathies, myocarditis, nephritis and renal function, skin adverse reactions, and other potentially immune-mediated AEs, and infusion-related reactions as specified in Appendix 6 (Section 13.6.3).

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional AESIs, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team agreements in place at the time of reporting. The list of identified AESIs along with the MedDRA code can be found in Section 13.6.3. Summaries of the number and percentage of participants with these events will be summarized by TOI of AESIs, preferred term and maximum toxicity grade in one table.

In addition, AESIs will be listed separately.

10.3. Deaths and Serious Adverse Events

All deaths will be summarized based on the number and percentage of participants. This summary will classify participants by time of death relative to the last dose of medication (>30 days or ≤30 days) and by the primary cause of death in the order listed in the CRF. A supportive listing will be generated to provide participant-specific details on participants who died.

The incidence of deaths and the primary cause of death will be summarized.

A summary of the number and percentage of participants and the number of occurrences of serious, drug-related serious, fatal serious, and drug-related fatal serious adverse events will be created for disclosure requirements to regulatory agencies.

All SAEs will also be tabulated based on the number and percentage of participants who experienced the events. The summary tables will be displayed in descending order of total incidence by SOC and PT.

A study treatment-related SAE is defined as an SAE for which the investigator classifies the relationship to study treatment as "Yes". A worst case scenario approach will be taken to handle missing data, i.e. the summary table will include events with the relationship to study treatment as 'Yes' or missing.

Study treatment-related SAEs will be summarized by GSK3359609, tremelimumaband SOC separately.

SAEs are included in the listing of all adverse events. Separate supportive listings with participant-level details will be generated for:

- Fatal SAEs
- Non-Fatal SAEs

Separate supportive listings with participant-level details will be generated for fatal and non-fatal SAEs, respectively. The fatal and non-fatal SAEs will be listed by dose level for Part 1 and treatment arm for Part 2, including the relationship with treatment.

A listing of deaths will be generated to provide participant-specific details on participants who died.

10.4. Adverse Events Leading to Discontinuation of Study Treatment and/or Withdrawal from the Study and Other Significant Adverse Events

The following categories of AEs will be summarized separately in descending order of total incidence by PT only and separate supportive listings will be generated with participant level details for those participants:

- AEs leading to Discontinuation of Study Treatment
- AEs leading to Withdrawal from the Study

A summary of the number and percentage of participants with adverse events leading to permanent discontinuation of study treatment will be displayed by overall frequency.

Similar outputs will be produced for non-serious treatment-related adverse events and common (≥5 or ≥10%) adverse events as stated below:

- Common (>10%) AEs
- Common (≥5%) Grade 3-5 AEs
- Common (≥5%) treatment-related Grade 3-5 AEs
- Non-serious treatment-related AEs

10.5. Pregnancies

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. If participants become pregnant while on the study, the information will be included in the narratives and no separate table or listing will be produced.

10.6. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Section 13.10: List of Data Displays.

The assessment of laboratory toxicities will examine the laboratory tests listed in Appendix 2 in the protocol.

Laboratory grades will be evaluated using NCI-CTCAE v5.0. However, some tests are not graded using NCI-CTCAE. For hematology, Red Blood Cell (RBC) is not gradable by NCI-CTCAE v5.0. For clinical chemistry, BUN and creatinine clearance are not gradable by NCI-CTCAE v5.0. For sodium, potassium, calcium, glucose, and magnesium there will be two bi-directional parameters (hyper and hypo) created and the tests will be graded by NCI-CTCAE v5.0 in both directions.

Summaries of worst-case grade increase from baseline grade will be provided for all the lab tests that are gradable by NCI-CTCAE v5.0. These summaries will display the number and percentage of participants with a maximum post-baseline grade increasing from their baseline grade. Any increase in grade from baseline will be summarized along with any increase to a maximum grade of 3 and any increase to a maximum grade of 4. Missing baseline grade will be assumed as grade 0. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia separately.

For lab tests that are not gradable by NCI-CTCAE v5.0, summaries of worst-case changes from baseline with respect to normal range will be generated. Decreases to low, changes to normal or no changes from baseline and increases to high will be summarized

for the worst-case post-baseline. If a participant has a decrease to low and an increase to high during the same time interval, then the participant is counted in both the "Decrease to Low" categories and the "Increase to High" categories.

Separate summary tables for haematology, chemistry and urinalysis tests will be produced. Liver function, thyroid function and pancreatic laboratory tests will be included with chemistry tests. Cardiac function, coagulation will be included with haematology tests.

Hematology and clinical chemistry data will be summarized using frequencies and proportions according to the NCI-CTCAE (version 5.0) [NCI, 2017]. Laboratory test results outside the reference ranges that do not have an associated NCI-CTCAE criteria will be summarized using proportions.

Detailed derivation of baseline assessment is specified in Section 5.2.

Unscheduled data will only be included in "post-baseline" summaries for capturing a worst case across all scheduled and unscheduled visits after the first dose of study medication.

Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of participants with non-missing value at each visit.

Supporting listing of laboratory data for participants with grade 3 and above will be provided. A separate listing of laboratory data with character values will also be provided.

A character lab value starting with '<X' or '>X' will be displayed in listings but will not be imputed with a numeric value thus will not be included for summaries.

10.7. Liver Function Analyses

Summaries of hepatobiliary laboratory events including possible Hy's law cases will be provided in addition to what has been described above.

Possible Hy's law cases are defined as any ALT ≥3×ULN **and overall** bilirubin ≥2×ULN (with direct bilirubin ≥35% of total bilirubin, if direct bilirubin is measured) **OR** (ALT ≥3×ULN **and** INR >1.5, if INR is measured). Note that INR measurement is not required, and the threshold value stated will not apply to participants receiving anticoagulants.

A listing of liver function tests for participants meeting Hy's law will be generated. A listing of participants with liver function test toxicity grade ≥3 will also be provided.

Summaries of hepatobiliary laboratory events including possible Hy's law cases will be provided in addition to what has been described above.

Possible Hy's law cases are defined as all events of ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN and International Normalized Ratio (INR)>1.5,

which may indicate severe liver injury. An e-DISH plot of maximum post baseline total bilirubin versus maximum post baseline ALT will be created.

Liver function test (LFT) patient profiles plots for participants experiencing an ALT, AST or total bilirubin of toxicity grade 2 or above will be produced. A trellis display of LFT shifts from baseline to maximum values will be provided. Each dose level will be presented in a separate row and each liver function test in a separate column. A matrix display of maximum post-baseline values of each of the LFT tests will also be produced with different symbols for each dose level.

A summary of the number of participants with on-treatment liver re-challenges, adaptations and recovery will be provided. A re-challenge is defined as an ALT elevation, followed by interruption of study treatment, and subsequently an ALT value of Grade 1 or below on or prior to re-starting study treatment, where the ALT elevation means ALT>3xULN and ≤3xULN at baseline. An adaptation is defined as an ALT elevation followed by an ALT assessment returning to baseline grade or below without any interruption to study treatment between the ALT elevation and normalization. A recovery is defined as an ALT elevation followed by an ALT Grade 1 or below for 2 consecutive visits or Grade 1 or below for one visit if participant discontinued study treatment and there is no data available.

10.8. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. LVEF and Performance status will be summarized and listed based on GSK Oncology Data Standard. The details of the planned displays are presented in Section 13.10: List of Data Displays.

Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of participants with non-missing value at each particular visit.

10.8.1. Vital Signs

Values of vital signs (Systolic and diastolic blood pressure (BP), heart rate, temperature and weight) as well as the change from baseline will be summarized by scheduled visit using mean, median, standard deviation, minimum and maximum.

In addition, vital signs values will be categorized (inclusively) as follows:

- Systolic BP (mmHg): Grade 0 (<120), Grade 1 (120-139), Grade 2 (140-159) and Grade 3 (≥160)
- Diastolic BP (mmHg): Grade 0 (<80), Grade 1 (80-89), Grade 2 (90-99), and Grade 3 (≥100)
- Heart rate (beats/min): <60, 60-100, and >100
- Temperature (°C): ≤35, >35-<38, ≥38

Summaries of increase in systolic and diastolic blood pressure from the baseline with respect to the categories defined above will be performed. These summaries will display the number and percentage of participants with increase to grade 2 and increase to grade 3 in the worst case post-baseline.

10.8.2. Performance Status

ECOG performance status will be summarized at baseline and each post-baseline scheduled visit. Summaries will use frequency and percentage of participants at each planned assessment time. A summary of change from baseline by scheduled visits will be performed, as well as the worst case post-baseline and the best case post-baseline changes during the study (improved, no change, deteriorated).

A supporting listing will also be provided.

10.8.3. ECG

ECG is only standardly collected at the screening visit (within 30 days prior to first dose of study treatment) and Day 1, then is only required during the treatment phase if clinically indicated. The ECG findings will therefore only be summarized using mean, median, standard deviation, minimum and maximum at the screening and baseline (day 1) visits. No post-baseline and change from baseline summaries will be provided but all values collected will be listed.

10.8.4. LVEF

ECHO/MUGA is only standardly collected at the screening visit (within 30 days prior to first dose of study treatment) and is only required during the treatment phase if clinically indicated. The LVEF (%) will therefore only be summarized using mean, median, standard deviation, minimum and maximum at the screening visit. No post-baseline and change from baseline summaries will be provided but all values collected will be listed.

11. ADDITIONAL ANALYSES DUE TO THE COVID-19 PANDEMIC

Listings will be produced to summarize the COVID-19 pandemic study/visit impact and any assessment and diagnosis information.

Visits and assessments missed due to the COVID-19 pandemic, together with visits conducted remotely, will be listed by participant.

A participant is defined as having a suspected, probable or confirmed COVID-19 infection during the study if the answer is “Confirmed”, “Probable” or “Suspected” to the case diagnosis question from the COVID-19 coronavirus infection assessment eCRF.

A listing of participants with a suspected, probable or confirmed COVID-19 infection, and of COVID-19 test results will be based on GSK Core Data Standards.

In addition to the overall summary of important protocol deviations, a listing of protocol deviations related to COVID-19 will also be produced.

12. REFERENCES

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13. APPENDICES

13.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

There is no planned per protocol analysis for this study.

13.2. Appendix 2: Schedule of Activities

See Section 1.3 of the protocol.

13.3. Appendix 3: Assessment Windows

13.3.1. Definitions of Assessment Windows for Analyses

Not applicable.

13.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

13.4.1. Study Phases

Adverse events, serious adverse events, death, laboratory data, vitals, ECG, echocardiogram (ECHO), Eastern Cooperative Oncology Group (ECOG) result, and other safety domains will be assigned to the study phases defined below. Partial dates will be imputed into full dates, if applicable, for slotting data to the appropriate categories below. Flag variables (time in relation to study phase) indicating the study time periods will be added to the ADaM variable APHASE, and the treatment emergent AE flag will be created to ADAE variable TRTEMFL.

Assessments and events will be classified according to the time of occurrence relative to Study Treatment Start Date.

Study Phase	Definition
Pre-Treatment	Date < Study Treatment Start Date
On-Treatment	Study Treatment Start Date ≤ Date ≤ Study Treatment Stop Date + 30 days
Post-Treatment	Date > Study Treatment Stop Date + 30 days

13.4.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before 28 days prior to screening visit
Concomitant	Any medication that is not a prior

13.4.2. Treatment Emergent Flag for Adverse Events

Not applicable.

13.5. Appendix 5: Data Display Standards & Handling Conventions

13.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: US1SALX00259
HARP Compound	: Compound: GSK3359609, study: 207871
Analysis Datasets	
• Analysis datasets will be created according to according to CDISC standards (SDTM IG Version 3.2 and ADaM IG version 1.1).	
Generation of RTF Files	
• RTF files will be generated for IA and SAC.	

13.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  ◦ 4.03 to 4.23: General Principles
  ◦ 5.01 to 5.08: Principles Related to Data Listings
  ◦ 6.01 to 6.11: Principles Related to Summary Tables
  ◦ 7.01 to 7.13: Principles Related to Graphics
• Do not include participant level listings in the main body of the GSK Clinical Study Report. All participant level listings should be located in the modular appendices as ICH or non-ICH listings.
• All data displays (Tables, Figures & Listings) will use the term "Subject" which reflects CDISC and GSK Data Display Standards terminology

Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's. • Summary Statistics: values will be reported relative to the precision on the eCRF. Min and max will be to the same as the raw data, mean and median to 1 extra decimal place, standard deviation to 2 extra decimal places. • Listings: values will be displayed to the same precision on the eCRF.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  ◦ Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  ◦ The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:

○ Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). ○ Unscheduled or unplanned readings will be presented within the participant's listings.
Unscheduled Visits
• All unscheduled visits will be included in listings. • Unscheduled visits will not, be included in summary tables and/or figures, except for worst case summary tables and/or figures.
Descriptive Summary Statistics
Continuous Data: Refer to IDSL Statistical Principle 6.06.1
Categorical Data: N, n, frequency, %
Graphical Displays
• Refer to IDSL Statistical Principals 7.01 to 7.13.

13.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to SOP 00000314000: Non-Compartmental Analysis of Clinical Pharmacokinetic Data. Note: Concentration values will be imputed as per GUI_51487 (v4.0)
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 (v4.0) for descriptive summary statistics/analysis and summarized graphical displays only.
NONMEM/Pop PK File	Not applicable.
NONMEM/PK/PD File	Not applicable.
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by Programmer	The following PK parameters will be derived by the Programmer: Cmax, tmax, Cmin, AUC(0-t), AUC(0-τ),
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to GUI_51487 (v4.0)
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to GUI_51487

13.6. Appendix 6: Derived and Transformed Data

13.6.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • If there are two values within a time window (as per Appendix 3: Assessment Windows) the value closest to the target day for that window will be used. If values are the same distance from the target, then the mean will be taken. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day for Safety
• Calculated as the number of days from First Dose Date: o Ref Date = Missing → Study Day = Missing o Ref Date < First Dose Date → Study Day = Ref Date - First Dose Date o Ref Date ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1
Study Day for Efficacy
• Calculated as the number of days from First Dose Date (Part 1)/Randomization Date (Part 2): o Ref Date = Missing → Study Day = Missing o Ref Date < First Dose Date/Randomization Date → Study Day = Ref Date - First Dose Date/Randomization Date o Ref Date ≥ First Dose Date/Randomization Date → Study Day = Ref Date - First Dose Date/Randomization Date + 1
Change from Baseline
• Change from Baseline = Post-Baseline Visit Value – Baseline • % Change from Baseline= 100 x (Post-Baseline Visit Value – Baseline) / Baseline • Maximum Increase/Decrease from Baseline = maximum (Increase/Decrease from Baseline) • If either the Baseline or Post-Baseline Visit Value is missing, Change from Baseline and % Change from Baseline is set to missing
Date of Response
• For post-baseline disease assessments, the date of response (PR or better) is assigned to the latest date of disease assessments; for other response categories (SD, NE, PD), the date of response is assigned to the earliest date of disease assessments.
Date of New Anti-Cancer Therapy
• Derived as the earliest date of new anti-cancer therapy, radiotherapy (where applicable) or cancer-related surgical procedure (where applicable) • Missing or partial dates will be imputed for derivation of new anti-cancer therapy following rules specified in Appendix 7: Reporting Standards for Missing Data.
Time to Death (OS)
• OS (weeks) = [death date – date of randomization +1]/7.

Duration and Elapsed Time

- Durations (e.g., the duration of an adverse event, duration of exposure, etc.) are calculated as the stop date minus the start date plus one.
- For elapsed time (e.g., the time since initial diagnosis):
  - If the reference date is on or after the event date, then the elapsed time is the reference date minus the event date + 1
  - If the reference date is before the event date, then the elapsed time is the reference date minus the event date
- For time to event (TTE) durations such as PFS
  - To report in months, divide the number of days by 30.4375
  - To report in weeks, divide the number of days by 7
  - To report in years, divide the number of days by 365.25.

  These algorithms for time to event return decimal numbers and ignore the actual numbers of days in the months or years between start date and stop date. The "year" used in these algorithms is 365.25 days long, and the "month" is one twelfth of that year.
- For converting all other durations (e.g., duration of adverse events, duration of exposure, age) to weeks, months or years use the following:
  - To report the duration in weeks divide the number of days by 7
  - To report the duration in months use: (YEAR(stopdate + 1) – YEAR(startdate)) * 12 + (MONTH(stopdate + 1) – month(startdate) – 1) + (DAY(stopdate + 1) > = DAY(startdate))
  - To report the duration in years use:intck('year', startdate, stopdate + 1) – (month(stopdate + 1) < month(startdate) or (month(stopdate + 1) = month(startdate) and day(stopdate + 1) < day(startdate)))

  These algorithms return whole numbers for months and years, accurately accounting for the actual numbers of days in the months or years between the start date and the stop date.

13.6.2. Study Population

Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Weeks = [Treatment Stop Date – (Treatment Start Date) + 1]/7** • The cumulative dose will be based on the formula: **Cumulative Dose = Sum of (the dose administered during each infusion)** • The dose intensity is the cumulative actual dose divided by the number of cycles across the entire treatment period. **Dose Intensity = Cumulative Dose/((last infusion date – first infusion date + days in cycle)/days in cycle)** • The relative dose intensity (%) is the infusion dose intensity divided by planned dose per week. **Relative Dose Intensity = Dose Intensity/(Planned Dose/weeks in cycle)** Cycle lengths are as follows: For GSK3359609, Tremelimumab and Docetaxel 3 weeks For Paclitaxel and Cetuximab 1 week.
Time since Initial Diagnosis
• Calculated as the number of Days from the Date of Initial Diagnosis: o Randomization/First Dose Date = Missing → Elapse Time = Missing o Date of Initial Diagnosis = Completely/partially Missing → Elapse Time = Missing o Otherwise → Elapse Time = Randomization/First Dose Date – Date of Initial Diagnosis + 1

13.6.3. Safety

Adverse Events					
Adverse Events of Special Interest (AESI)					
TOI List Name	**Dictionary**	**Code**	**Dictionary Version**	**Status**	**Type**
ICOS Colitis	MedDRA	319004	23.0	Active	Study Specific TOI
ICOS Endocrinopathies	MedDRA	319007	23.0	Active	Study Specific TOI
ICOS Hepatitis	MedDRA	319005	23.0	Active	Study Specific TOI
ICOS Infusion Related Reactions	MedDRA	319013	23.0	Active	Study Specific TOI
ICOS Myocarditis	MedDRA	319011	23.0	Active	Study Specific TOI
ICOS Nephritis and Renal Function	MedDRA	319009	23.0	Active	Study Specific TOI
ICOS Other Immune Mediated Adverse Events	MedDRA	319012	23.0	Active	Study Specific TOI
ICOS Pneumonitis	MedDRA	319003	23.0	Active	Study Specific TOI
ICOS Skin Adverse Reactions	MedDRA	319010	23.0	Active	Study Specific TOI

Duration of AE

- Calculated as the number of days from AE Start Date to AE Stop Date:
- AE Start Date = Missing → Elapse Time = Missing
- AE Stop Date = Missing → Elapse Time = Missing
- Otherwise → Elapsed Time = AE Stop Date – AE Start Date + 1

ECHO/MUGA

- Change from Baseline for cardiac data, e.g., Left Ventricular Ejection Fraction (LVEF), will be calculated based on the same modality (ECHO or MUGA) throughout the study for each participant. Post-baseline assessments with a different cardiac scan modality will not be used to calculate change from Baseline.

Clinical Laboratory
Laboratory Parameters

• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value.
  • Example 1: 2 Significant Digits = '< x ' becomes x – 0.01
  • Example 2: 1 Significant Digit = '> x' becomes x + 0.1
Example 3: 0 Significant Digits = '< x' becomes x – 1

ECG Parameters
Corrected QT Intervals
• When not entered directly in the eCRF, corrected QT intervals using Fredericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements. • If RR interval (msec) is provided then missing corrected QT intervals using Fredericia's (QTcF) formula will be derived as: $$QTcF\ (msec) = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

13.6.4. Pharmacokinetic

Refer to Section 9.3.

13.7. Appendix 7: Reporting Standards for Missing Data

13.7.1. Premature Withdrawals

Element	Reporting Detail
General	• For Part 1 dose escalation phases of the study, participants will be considered as completing the study if they complete screening assessments, receive at least two doses of study treatment or receive one dose but experience a DLT, are observed during the 28 day DLT observation period, and complete the treatment discontinuation visit and the follow-up visit for safety or have died while receiving study treatment or during post-study treatment follow-up period for safety. • For Part 1, if a participant withdraws from the study before the completion of the 28 day DLT evaluation period for reasons other than DLT, then the participant may be replaced. • For Part 2, participants will be considered as completing the study if they complete the screening assessments, and receive at least one dose of study intervention or SOC, and discontinue study intervention or SOC for reasons other than lost to follow-up or non-compliance, and complete the follow-up visit for safety (if required), and are followed until death, or complete screening. assessments and have died while receiving study intervention or SOC or during the post-study follow-up period for safety. • A participant will be considered to have withdrawn from the study if the participant has not died and is lost to follow-up, has withdrawn consent, at the investigator's discretion is no longer being followed or if the study is closed/terminated. • The end of the study is defined as the completion of the last participant's required visits post study treatment discontinuation. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

13.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: ○ These data will be indicated by the use of a "blank" in participant listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

13.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays. • Imputed partial dates will not be used to derive study day, duration (e.g., duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.
•</td></tr>
<tr><td>Birth Date</td><td>• As only the year of birth is being collected within the EDC system, participant birth date and month will be defaulted to '30/JUN'. For example, if birth year is 1989 then birthdate will be 30/Jun/1989.</td></tr>
<tr><td>Adverse Events</td><td>• Imputations in the adverse events dataset are used for slotting events to the appropriate study time periods and for sorting in data listings.
• Partial dates for AE recorded in the CRF will be imputed using the following conventions:
<table>
<tr><td>Missing start day</td><td>• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = 1st of month.
• Else if study treatment start date is not missing:
o If month and year of start date = month and year of study treatment start date then
▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month.
▪ Else set start date = study treatment start date.
o Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = January 1.
• Else if study treatment start date is not missing:
o If year of start date = year of study treatment start date then
▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1.
▪ Else set start date = study treatment start date.
o Else set start date = January 1.</td></tr>
<tr><td>Missing stop day</td><td>o Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used.</td></tr>
<tr><td>Missing stop day and month</td><td>No Imputation</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table></td></tr>
<tr><td>Concomitant Medications/Medical History</td><td>• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
<table>
<tr><td>Missing start day</td><td>• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = 1st of month.
• Else if study treatment start date is not missing:
o If month and year of start date = month and year of study treatment start date then
▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month.
▪ Else set start date = study treatment start date.
o Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = January 1.
• Else if study treatment start date is not missing:</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>

If year of start date = year of study treatment start date then

If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1.
Else set start date = study treatment start date.

Else set start date = January 1.

</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year)</td></tr>
<tr><td>Missing end day and month</td><td>A '31' will be used for the day and 'Dec' will be used for the month.</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
The recorded partial date will be displayed in listings.
</td></tr>
<tr><td>Date of Initial Diagnosis</td><td>

If both month and day are missing, first of January will be used
If only day is missing, first of the month will be used

</td></tr>
<tr><td>Last Recurrence/ Progression Prior to Enrollment</td><td>

If both month and day are missing, first of January will be used
If only day is missing, first of the month will be used
If the entire date is missing, no imputation will be performed

</td></tr>
<tr><td>Covariates for efficacy analysis (Prior Anti-cancer Therapy/Radiotherapy/Surgical Procedures)</td><td>

Completely missing start or end dates will remain missing, with no imputation applied.
If partial start date contains a year only set to January 1st.
If partial start date contains a month and year set to the 1st of the month.
No imputation for partial end dates will be performed.

</td></tr>
<tr><td>New Anti-Cancer Therapy/ Radiotherapy/ Surgical Procedures/Crossover for Efficacy Evaluation (e.g., response rate, time to event)</td><td>

Partial start dates for follow-up anti-cancer therapy, radiotherapy (where applicable), surgical procedures (where applicable), or crossover (when applicable) will be imputed in order to define censoring rules for progression-free survival, response rate, or duration of response (i.e. start date for new anti-cancer therapy/crossover). Dates will only be imputed when a month and year are available, but the day is missing. The imputed dates will not be stored on the anti-cancer therapy, radiotherapy, or surgical procedure datasets. The following rules will be used to impute the date when partial start dates are present on anti-cancer therapy radiotherapy, and/or surgical procedures datasets.
No Imputation for completely missing start dates.
No imputation for missing start day and month (note the eCRF should only allow for missing day).
If only day is missing:

If partial start date falls in the same month as the last dose of study treatment, then assign to earlier of (date of last dose of study treatment+1, last day of month).
If partial start date falls in the same month as the participant's last disease assessment and the participant's last disease assessment is progressive disease (PD), then assign to earlier of (date of last disease assessment+1, last day of month).
If both rules above apply, then assign to the later date of the two dates
Otherwise, impute missing day to the first of the month.
No imputation for completely or partial missing end dates will be performed.

</td></tr>
<tr><td>Exposure End Dates</td><td>

In general, complete missing dates are not imputed. However, missing exposure end dates for participants who are still on study treatment at the time of an

</td></tr>
</table>

Element	Reporting Detail
	analysis will be imputed. For imputation of missing exposure end date at an interim analysis when participants are still on treatment, the following conventions will be applied: o If exposure end date is missing, then assign exposure end date as the earliest of: the date of the data cutoff, the date of withdrawal from the study, or the death date. o The imputed exposure end date will be used to calculate cumulative dose and exposure duration. o The imputed exposure end date will be stored in the exposure analysis dataset and an exposure end date imputation flag variable will be derived indicating which exposure end date records are imputed. o Imputed exposure end dates will also be stored on the study treatment end date variable.

13.8. Appendix 8: Values of Potential Clinical Importance

To identify laboratory values of potential clinical importance, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v5.0) will be used to assign grades for laboratory parameters including clinical chemistry, hematology, liver function tests, thyroid function tests, pancreatic enzyme tests, QTcF values, vital signs (heart rate, blood pressure, temperature) and LVEF.

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern. The laboratory reference ranges will be provided on the listings of laboratory data. Clinical laboratory test results outside of the reference range will be flagged in the listings.

Liver Function			
Test Analyte	**Units**	**Category**	**Potential Clinical Importance Range**
ALT/SGPT	U/L	High	> 3x ULN
AST/SGOT	U/L	High	> 3x ULN
AlkPhos	U/L	High	> 2.5x ULN
Total Bilirubin when Liver Function Test is normal; increase by factor	µmol/L	High	> 1.5xULN
Total Bilirubin + increase in Liver function test	µmol/L U/L	High	1.51xULN T. Bilirubin ≥2x ULN Liver function test

13.8.1. ECG

ECG Parameter	Units	Potential Clinical Importance Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec	> 450	≤ 480
	msec	>480	≤ 500
	msec	> 500	
Absolute PR Interval	msec	< 110	> 220
Absolute QRS Interval	msec	< 75	> 110
Change from Baseline			
Increase from Baseline QTcF	msec	> 30	≤ 60
	msec	> 60	

13.8.2. Vital Signs

Vital Sign Parameter (Absolute)	Units	Potential Clinical Importance Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	≥120	<140
	mmHg	≥140	<160
	mmHg	≥160	
Diastolic Blood Pressure	mmHg	≥ 80	< 90
	mmHg	≥ 90	< 100
	mmHg	≥ 100	
Heart Rate	bpm	< 60	> 100
Body temperature	°C	≤ 35	≥ 38

13.9. Appendix 9: Abbreviations & Trade Marks

13.9.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine aminotransferase
ANOVA	Analysis of Variance
A&R	Analysis and Reporting
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a participant across all treatments
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
BOR	Best Overall Response
BUN	Blood urea nitrogen
CC	Critical Component
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CL	Clearance
Cmax	Maximum observed concentration
Cmin	Minimum Observed Concentration;
CPMS	Clinical Pharmacology Modelling & Simulation
CR	Complete response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTR	Clinical Trial Register
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DLT	Dose-limiting toxicity
DoR	Duration of response
DP	Decimal Places
ECG(s)	Electrocardiogram(s)
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
EORTC QLQ-C30 and H&N35	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 and Head and Neck Cancer 35 Module
EQ-5D	EuroQOL Group EQ-5D
FACT GP5	Functional Assessment of Cancer Therapy – General Population
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
HNSCC	Head and Neck Squamous Cell Carcinoma

Abbreviation	Description
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
iRECIST	Modified RECIST v1.1 for Immune-based Therapeutics
kg	Kilogram(s)
LVEF	Left ventricular ejection fraction
λz	Apparent terminal phase elimination rate constant
mg	Milligram
msec	Millisecond
MTD	Maximum tolerated dose
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
ORR	Overall Response Rate
OS	Overall Survival
PCI	Potential Clinical Importance
PD	Progressive Disease
PD-1	Programmed death receptor protein-1
PD-L1	Programmed death-ligand 1
PDMP	Protocol Deviation Management Plan
PFS	Progression Free Survival
PK	Pharmacokinetic
PR	Partial Response
PRO-CTCAE	Patient Reported Outcomes Version of the Common Terminology Criteria for Adverse Events
PROMIS-PF	Patient-Reported Outcome Measurement Information System – Physical Function;
QC	Quality Control
QTc	Corrected QT interval duration
QTcF	Frederica's QT Interval Corrected for Heart Rate
R2PD	Randomized phase 2 dose
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SAE	Serious adverse event(s)
SD	Stable Disease
SAS	Statistical Analysis Software
SDSP	Study Data Standardization Plan
SDTM	Study Data Tabulation Model
SOC	System Organ Class / Standard of Care
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
tmax	Time of occurrence of Cmax
TTR	Time to Response
ULQ	Upper Limit of quantification
ULN	Upper Limit of Normal
V	Volume
WBC	White blood cell

13.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
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WinNonlin

13.10. Appendix 10: List of Data Displays

13.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays. Part 1 outputs only will be generated:

Section	Tables	Figures
Study Population	1.1 to 1.n	1.1 to 1.n
Efficacy	2.1 to 2.n	2.1 to 2.n
Safety	3.1 to 3.n	3.1 to 3.n
Pharmacokinetic	4.1 to 4.n	4.1 to 4.n
Population Pharmacokinetic (PopPK)	5.1 to 5.n	5.1 to 5.n
Pharmacodynamic and / or Biomarker	6.1 to 6.n	6.1 to 6.n
Pharmacokinetic / Pharmacodynamic	7.1 to 7.n	7.1 to 7.n
Section	**Listings**	
ICH Listings	1 to x	
Other Listings	y to z	

13.10.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Section 13.11: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Population Pharmacokinetic (PopPK)	POPPK_Fn	POPPK_Tn	POPPK_Ln
Pharmacodynamic and / or Biomarker	PD_Fn	PD_Tn	PD_Ln
Pharmacokinetic / Pharmacodynamic	PKPD_Fn	PKPD_Tn	PK/PD_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

13.10.3. Deliverables

Delivery [Priority] [1]	Description
SAC [1]	Final Statistical Analysis Complete

NOTES:

1. Indicates priority (i.e. order) in which displays will be generated for the reporting effort

13.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	All Treated	ES8	Summary of Subject Status and Reason for Study Withdrawal - Part 1	ICH E3, FDAAA, EudraCT	SAC [1]
1.2.	All Treated	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment - Part 1	ICH E3 Note: page by treatment, list only primary reasons that appear in the data, as specified in the CRF. Present reasons in the order collected on the CRF. Add total column. Separate treatment discontinuation forms collected for each drug, so repeat this table by drug within the same table. If reasons for discontinuation differ within a patient, footnotes should be added to identify these patients after queries are raised. Those with missing relatedness will be assumed to be related to treatment in the summary and footnotes to clarify added. If no patients have missing relatedness, remove footnote.	SAC [1]
1.3.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure – Part 1	Journal Requirements	SAC [1]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.4.	Enrolled	NS1	Summary of Number of Participants by Country and Site ID – Part 1	EudraCT/Clinical Operations	SAC [1]
Protocol Deviation					
1.5.	All Treated	DV1	Summary of Important Protocol Deviations – Part 1	ICH E3	SAC [1]
Population Analysed					
1.6.	Screened	SP1	Summary of Study Populations – Part 1	IDSL	SAC [1]
Demographic and Baseline Characteristics					
1.7.	All Treated	DM1	Summary of Demographic Characteristics – Part 1	ICH E3, FDAAA, EudraCT Note: 2 age group categories are defined. One is required for FDAAA disclosure and the other for study specific requirements.	SAC [1]
1.8.	Enrolled	DM11	Summary of Age Ranges – Part 1	EudraCT Age categories: 18-64, 65-84 and ≥85	SAC [1]
1.9.	All Treated	DM5	Summary of Race and Racial Combinations – Part 1	ICH E3, FDA, FDAAA, EudraCT	SAC [1]
Prior and Concomitant Medications					
1.10.	All Treated	MH1	Summary of Past Medical Conditions – Part 1	ICH E3	SAC [1]
1.11.	All Treated	MH1	Summary of Current Medical Conditions – Part 1	ICH E3	SAC [1]
1.12.	All Treated	CM1	Summary of Concomitant Medications – Part 1	ICH E3	SAC [1]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure and Treatment Compliance					
1.13.	All Treated	OEX5	Summary of Exposure to Study Treatment by Component – Part 1	ICH E3	SAC [1]
1.14.	All Treated	OEX9	Summary Listing of Overall Exposure and Dose Modifications by Component – Part 1	IDSL	SAC [1]
Disease Characteristics					
1.15.	All Treated	DC1	Summary of Disease Characteristics at Initial Diagnosis – Part 1	ICH E3 Note: List all applicable categories as per CRF in the order presented in CRF. Some parameters (TNM staging) may only be applicable to Part 2. Remove from Part 1.	SAC [1]
1.16.	All Treated	DC2	Summary of Disease Characteristics at Screening – Part 1	ICH E3 Note: Number of IO therapies to be included. Missing row only when missing data is present	SAC [1]
1.17.	All Treated	MD1	Summary of Metastatic Disease at Screening – Part 1		SAC [1]
1.18.	All Treated	LA1	Summary of Disease Burden at Baseline – Part 1	ICH E3	SAC [1]
Anti-Cancer Therapy					
1.19.	All Treated	AC1	Summary of Prior Anti-Cancer Therapy – Part 1	IDSL	SAC [1]
1.20.	All Treated	AC3	Summary of Number of Prior Anti-Cancer Therapy Regimens – Part 1	IDSL	SAC [1]
1.21.	All Treated	FAC1	Summary of Follow-up Anti-Cancer Therapy – Part 1	IDSL	SAC [1]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Substance Use					
1.22.	All Treated	SU1	Summary of Substance Use – Part 1	IDSL	SAC [1]
Follow-up					
1.23.	All Treated	FAC2	Summary of Duration of Follow-up – Part 1		SAC [1]

13.10.5. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Response					
2.1.	All Treated	RE8b	Investigator-Assessed Best Percent Reduction from Baseline in Tumor Measurement (iRECIST) – Part 1		SAC [1]
2.2.	All Treated	RE8b	Plot of Percent Change over Time from Baseline in Tumor Measurement – Part 1	Differentiate dose levels by color	SAC [1]

13.10.6. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	All Treated	AE5B	Summary of All Adverse Events by Maximum Grade by System Organ Class and Preferred Term – Part 1	ICH E3	SAC [1]
3.2.	All Treated	AE3	Summary of Common (>10%) Adverse Events by Overall Frequency – Part 1	ICH E3	SAC [1]
3.3.	All Treated	AE3	Summary of Common (>=5%) Grade 3-5 Adverse Events by Overall Frequency – Part 1	ICH E3	SAC [1]
3.4.	All Treated	AE5B	Summary of All Treatment-Related Adverse Events by System Organ Class and Preferred Term and Maximum Grade – Part 1	ICH E3 Note: 1. Include All Treated participants in Part 1 2. Page by dose level/treatment arm 3. Only include programmatically derived treatment-related events 4. order by frequency, instead of alphabetically.	SAC [1]
3.5.	All Treated	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subject and Occurrences) – Part 1	FDAAA, EudraCT	SAC [1]
3.6.	All Treated	AE3	Summary of Common (>=5%) Treatment-Related Grade 3-5 Adverse Events by Overall Frequency – Part 1	ICH E3	SAC [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.7.	All Treated	AE3	Summary of Non-Serious Treatment-Related Adverse Events by Overall Frequency – Part 1		SAC [1]
3.8.	All Treated	AE3	Summary of Adverse Events Leading to Dose Reductions – Part 1		SAC [1]
Adverse Events of Special Interest					
3.9.	All Treated	ESI1	Summary of Characteristics of AE of Special Interest – Part 1		SAC [1]
3.10.	All Treated	AE5B	Summary of Adverse Events of Special Interest by Sub Class, Preferred Term and Maximum Toxicity Grade – Part 1		SAC [1]
3.11.	All Treated	AE13	Summary of Adverse Event Overview – Part 1	Note: For combination therapy, participants should contribute to each "study treatment" row if they meet the condition on either GSK3359609 or tremelimumab CRF forms. Assume missing relatedness is related to treatment for each applicable drug.	SAC [1]
Serious and Other Significant Adverse Events					
3.12.	All Treated	AE5B	Summary of Serious Adverse Events by System Organ Class and Preferred Term and Maximum Grade – Part 1	Note: Same as above	SAC [1]
3.13.	All Treated	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) – Part 1	FDAAA, EudraCT	SAC [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.14.	All Treated	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment by System Organ Class and Preferred Term – Part 1	IDSL	SAC [1]
3.15.	All Treated	AE1	Summary of Adverse Events Leading to Withdrawal from Study by System Organ Class and Preferred Term – Part 1	IDSL	SAC [1]
3.16.	All Treated	AE3	Summary of Serious Adverse Events – Part 1		SAC [1]
3.17.	All Treated	AE3	Summary of Serious Treatment-Related Adverse Events by Overall Frequency – Part 1		SAC [1]
3.18.	All Treated	AE3	Summary of Fatal Adverse Events – Part 1		SAC [1]
3.19.	All Treated	AE3	Summary of Fatal Adverse Events Related to Study Treatment – Part 1		SAC [1]
Deaths					
3.20.	All Treated	DTH1A	Summary of Deaths – Part 1	IDSL This summary will classify subjects by time of death relative to the last dose of medication (>30 days or ≤30 days).	SAC [1]
Laboratory: Chemistry					
3.21.	All Treated	LB1	Summary of Chemistry Changes from Baseline – Part 1	ICH E3	SAC [1]
3.22.	All Treated	LB16	Summary of Worst Case Chemistry Results by Maximum Grade Increase Post-Baseline Relative to Baseline - Part 1	ICH E3	SAC [1]
3.23.	All Treated	LB15	Summary of Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline - Part 1	ICH E3	SAC [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Hematology					
3.24.	All Treated	LB1	Summary of Hematology Changes from Baseline - Part 1	ICH E3	SAC [1]
3.25.	All Treated	LB16	Summary of Worst Case Hematology Results by Maximum Grade Increase Post-Baseline Relative to Baseline - Part 1	ICH E3	SAC [1]
3.26.	All Treated	LB15	Summary of Worst Case Hematology Results Relative to Normal Range Post-Baseline Relative to Baseline - Part 1	ICH E3	SAC [1]
Laboratory: Hepatobiliary (Liver)					
3.27.	All Treated	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting – Part 1	IDSL	SAC [1]
3.28.	All Treated	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities – Part 1	IDSL	SAC [1]
ECG					
3.29.	All Treated	EG1	Summary of ECG Findings – Part 1	IDSL	SAC [1]
Vital Signs					
3.30.	All Treated	VS1	Summary of Change from Baseline in Vital Signs – Part 1	ICH E3	SAC [1]
3.31.	All Treated	VS3	Summary of Vital Sign Results Relative to Normal Range Post-Baseline Relative to Baseline– Part 1	IDSL	SAC [1]
3.32.	All Treated	VS6	Summary of Vital Sign Results by Maximum Grade Increase Post-Baseline Relative to Baseline– Part 1	IDSL	SAC [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Dose Modifications					
3.33.	All Treated	ODMOD2	Summary of Dose Interruptions by Component – Part 1	ICH E3	SAC [1]
3.34.	All Treated	ODMOD3	Summary of Dose Delays by Component – Part 1	ICH E3	SAC [1]
Dose Limiting Toxicity (DLT)					
3.35.	DLT Evaluable	AE19	Summary of Dose-Limiting Toxicities – Part 1	ICH E3	SAC [1]
Performance Status					
3.36.	All Treated	PS1A	Summary of ECOG Performance Status – Part 1	ICH E3	SAC [1]
3.37.	All Treated	PS3A	Summary of Change in ECOG Performance Status from Baseline – Part 1		SAC [1]
Immunogenicity					
3.38.	All Treated	IMM1	Summary of Positive Immunogenicity Results for Anti-GSK3359609– Part 1		SAC [1]
3.39.	All Treated	IMM1	Summary of Positive Immunogenicity Results Anti-Tremelimumab– Part 1		SAC [1]

13.10.7. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
3.1.	All Treated	AE10	Plot of Common (>10%) Adverse Events – Part 1	IDSL	SAC [1]
Laboratory					
3.2.	All Treated	LIVER14	Scatter Plot of Maximum vs. Baseline for ALT – Part 1	IDSL	SAC [1]
3.3.	All Treated	LIVER9	Scatter Plot of Maximum Bilirubin versus Maximum ALT (eDISH) – Part 1	IDSL	SAC [1]
Exposure					
3.4.	All Treated	OEX12	Plot of Duration of Study Treatment Part 1		SAC [1]

13.10.8. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK					
4.1.	PK	PK01	Summary of GSK3359609 Plasma Pharmacokinetic Concentration-Time Data – Part 1	IDSL	SAC [1]
4.2.	PK	PK01	Summary of Tremelimumab Plasma Pharmacokinetic Concentration-Time Data – Part 1	IDSL	SAC [1]
4.3.	PK	PK06	Summary of Derived GSK3359609 Pharmacokinetic Parameters (non-transformed and log-transformed) – Part 1	IDSL	SAC [1]
4.4.	PK	PK06	Summary of Derived Tremelimumab Pharmacokinetic Parameters (non-transformed and log-transformed) – Part 1	IDSL	SAC [1]
4.5.	PK	Non-standard PK_T1	Summary of the Analysis of GSK3359609 Accumulation – Part 1	See Appendix 11	SAC [1]
4.6.	PK	Non-standard PK_T1	Summary of the Analysis of Tremelimumab Accumulation – Part 1	See Appendix 11	SAC [1]
4.7.	PK	Non-standard PK_T2	Results of the Power Model Analysis of Dose Proportionality of GSK3359609 Pharmacokinetic Parameters – Part 1	See Appendix 11	SAC [1]
4.8.	PK	Non-standard PK_T2	Results of the Power Model Analysis of Dose Proportionality of Tremelimumab Pharmacokinetic Parameters – Part 1	See Appendix 11	SAC [1]

13.10.9. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK					
4.1.	PK	PK16a and PK16b	Individual GSK3359609 Plasma Concentration-Time Plot by Subject (Linear and Semi-Log) – Part 1	IDSL Paginate by Subject	SAC [1]
4.2.	PK	PK16a and PK16b	Individual Tremelimumab Plasma Concentration-Time Plot by Subject (Linear and Semi-Log) – Part 1	IDSL Paginate by Subject	SAC [1]
4.3.	PK	PK17	Mean GSK3359609 Plasma Concentration-Time Plots (Linear and Semi-log) – Part 1	IDSL	SAC [1]
4.4.	PK	PK17	Mean Tremelimumab Plasma Concentration-Time Plots (Linear and Semi-log) – Part 1	IDSL	SAC [1]
4.5.	PK	PK18	Median GSK3359609 Plasma Concentration-Time Plots (Linear and Semi-log) – Part 1	IDSL	SAC [1]
4.6.	PK	PK18	Median Tremelimumab Plasma Concentration-Time Plots (Linear and Semi-log) – Part 1	IDSL	SAC [1]

13.10.10. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure – Part 1	Journal Guidelines	SAC [1]
2.	Enrolled	ES2	Listing of Reasons for Study Withdrawal– Part 1	ICH E3	SAC [1]
3.	All Treated	SD2	Listing of Reasons for Study Treatment Discontinuation – Part 1	ICH E3	SAC [1]
4.	All Treated	TA1	Listing of Planned and Actual Treatments – Part 1	IDSL	SAC [1]
Protocol Deviations					
5.	All Treated	DV2	Listing of Important Protocol Deviations – Part 1	ICH E3	SAC [1]
6.	All Treated	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations – Part 1	ICH E3	SAC [1]
Populations Analysed					
7.	Screened	SP3	Listing of Subjects Excluded from Any Population – Part 1	ICH E3	SAC [1]
Demographic and Baseline Characteristics					
8.	All Treated	DM2	Listing of Demographic Characteristics – Part 1	ICH E3	SAC [1]
9.	All Treated	DM9	Listing of Race – Part 1	ICH E3	SAC [1]
Prior and Concomitant Medications					

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
10.	All Treated	CM3	Listing of Concomitant Medications – Part 1	IDSL	SAC [1]
Exposure and Treatment Compliance					
11.	All Treated	OEX8B	Listing of Exposure to GSK3359609 – Part 1	ICH E3	SAC [1]
12.	All Treated	OEX8B	Listing of Exposure to Tremelimumab – Part 1	ICH E3	SAC [1]
Dose Modifications					
13.	All Treated	ODMOD11A	Listing of Dose Interruptions – Part 1	ICH E3	SAC [1]
14.	All Treated	ODMOD12A	Listing of Dose Delays – Part 1	ICH E3	SAC [1]
15.	All Treated	ODMOD14a	Listing of Incomplete Infusions– Part 1		SAC [1]
Response					
16.	All Treated	LA5	Listing of Investigator-Assessed Lesion Assessments (RECIST v1.1) – Part 1		SAC [1]
17.	All Treated	LA5	Listing of Investigator-Assessed Lesion Assessments (iRECIST) – Part 1		SAC [1]
18.	All Treated	RE5	Listing of Investigator-Assessed Responses (without or with confirmation) (RECIST v1.1) – Part 1		SAC [1]
19.	All Treated	RE5	Listing of Investigator-Assessed Responses (without or with confirmation) (iRECIST) – Part 1		SAC [1]
Time to Event					

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
20.	All Treated	TTE9	Listing of Time to Response – Part 1		SAC [1]
21.	All Treated	TTE9	Listing of Progression Free Survival (RECIST v1.1) – Part 1		SAC [1]
22.	All Treated	TTE9	Listing of Progression Free Survival (iRECIST) – Part 1		SAC [1]
23.	All Treated	TTE9	Listing of Overall Survival – Part 1		SAC [1]
Adverse Events					
24.	All Treated	AE8	Listing of All Adverse Events – Part 1	ICH E3 Note 1. Include All Treated subjects in Part 1 2. Page by dose level/treatment arm, no need to include "overall/total" repeat as this duplicates data. 3. 3 Include all events, regardless of treatment-emergence 4. "Actions taken" should be clear which drug it applies to, for combination therapy.	SAC [1]

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events of Special Interest					
25.	All Treated	AE8	Listing of AE of Special Interest – Part 1	Note: Use AESI spreadsheet to identify AESIs. Check this is aligned with protocol defined AESIs. Replace SOC with AESI and AESI subclass .The sort order will be Centre ID, Unique Subject ID, Subject ID, AE Start date and then by AESI, AESI subclass , PT and Verbatim Text.	SAC [1]
Serious and Other Significant Adverse Events					
26.	All Treated	AE8	Listing of Fatal Serious Adverse Events – Part 1	ICH E3	SAC [1]
27.	All Treated	AE8	Listing of Non-Fatal Serious Adverse Events – Part 1	ICH E3	SAC [1]
28.	All Treated	AE14	Listing of Reasons for Considering as a Serious Adverse Event – Part 1	ICH E3	SAC [1]
29.	All Treated	AE8	Listing of Adverse Events Leading to Withdrawal from Study - Part 1	ICH E3	SAC [1]
30.	All Treated	AE8	Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment – Part 1	ICH E3	SAC [1]

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
31.	All Treated	AE8	Listing of Other Significant Adverse Events – Part 1	ICH E3	SAC [1]
Dose-Limiting Toxicities					
32.	All Treated	AE8	Listing of Dose-Limiting Toxicities (DLT) – Part 1	Note. Present any DLTs that occur for the all treated population. Do not restrict to a 28 day period.	SAC [1]
Deaths					
33.	All Treated	DD3	Listing of Deaths – Part 1	ICH E3	SAC [1]
Hepatobiliary (Liver)					
34.	All Treated	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events -Part 1	IDSL	SAC [1]
35.	All Treated	SU2	Listing of Substance Use for Subjects with Liver Stopping Events – Part 1	IDSL	SAC [1]
All Laboratory					
36.	All Treated	LB5	Listing of All Laboratory Data for Subjects with Any Value Outside of Normal Range– Part 1	ICH E3	SAC [1]
37.	All Treated	LB14	Listing of Laboratory Data with Character Results – Part 1	ICH E3	SAC [1]
ECG					
38.	All Treated	EG3	Listing of ECG Values of Potential Clinical Importance – Part 1	IDSL	SAC [1]

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
39.	All Treated	EG5	Listing of All ECG Findings for Participants with an Abnormal ECG Finding – Part 1	IDSL	SAC [1]
Vital Signs					
40.	All Treated	VS4	Listing of Vital Signs of Potential Clinical Importance – Part 1	IDSL	SAC [1]
ECOG					
41.	All Treated	PS5A	Listing of ECOG Performance Status – Part 1		SAC [1]

13.10.11. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Disease Characteristics					
42.	All Treated	DC3	Listing of Disease Characteristics at Initial Diagnosis -Part 1		SAC [1]
43.	All Treated	DC4	Listing of Disease Characteristics at Screening-Part 1		SAC [1]
44.	All Treated	MD2	Listing of Metastatic Disease at Screening - Part 1		SAC [1]
Anti-Cancer Therapy					
45.	All Treated	AC6	Listing of Prior Anti-cancer Therapy -Part 1		SAC [1]
46.	All Treated	FAC3	Listing of Follow-Up Anti-Cancer Therapy -Part 1		SAC [1]
Surgical Procedures					
47.	All Treated	SP1	Listing of Prior Surgical Procedures – Part 1		SAC [1]
Substance Use					
48.	All Treated	SU2	Listing of Substance Use – Part 1		SAC [1]
Protocol Deviations					
49.	All Treated	DV2	Listing of All COVID-19 Related Protocol Deviations – Part 1		SAC [1]
50.	All Treated	PAN7	Listing of Visits impacted by COVID-19 Pandemic – Part 1		SAC [1]

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
51.	All Treated	PAN12	Listing of COVID-19 Assessments and Symptom Assessments for Subjects with COVID-19 Adverse Events – Part 1		SAC [1]
Immunogenicity					
52.	All Treated	IMM2	Listing of Immunogenicity Results – Part 1		SAC [1]
PK					
53.	PK	PK07	Listing of GSK3359609 Plasma Pharmacokinetic Concentration-Time Data - Part 1	IDSL	SAC [1]
54.	PK	PK07	Listing of Tremelimumab Plasma Pharmacokinetic Concentration-Time Data - Part 1	IDSL	SAC [1]
55.	PK	PK13	Listing of Derived GSK3359609 Plasma Pharmacokinetic Parameters - Part 1	IDSL	SAC [1]
56.	PK	PK13	Listing of Derived Tremelimumab Plasma Pharmacokinetic Parameters - Part 1	IDSL	SAC [1]

13.11. Appendix 11: Example Mock Shells for Data Displays

Data Display Specification will be made available on request

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