Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for A Phase I Open Label Study of GSK3359609 Administered Alone and in Combination with Anticancer Agents in Participants with Selected Advanced Solid Tumors
Compound Number	:	GSK3359609
Effective Date	:	06 May 2022

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol TMF-11734800.
- This RAP is intended to describe the requirements during the study that include support for dose escalation decisions to progress to the next dose level or transition to expansion phase, including determination of the MTD or MAD for GSK3359609 or futility analysis for expansion phase of GSK3359609 delivered as monotherapy or in combination.
- This RAP will be provided to the study team members to convey the content of the reporting efforts, specifically Statistical Analysis Complete (SAC) for the final analysis.

RAP Author(s):

PPD
Study Statistician, RD Clinical Statistics

RAP Team Approvals:

Reviewer	Date	Approval Method
PPD Principal Programmer RD Clinical Programming	25APR2022	Email
PPD Clinical Pharmacology Manager RD CPMS	25APR2022	Email
PPD Value Evidence and Outcomes	22APR2022	Email
PPD RD Clinical Science	22APR2022	Email
PPD RD Clinical Safety	25APR2022	Email

Clinical Statistics and Clinical Programming Line Approvals:

Approver	Date	Approval Method
PPD Statistics Leader RD Clinical Statistics	06 May 2022	eTMF
PPD Programming Leader RD Clinical Programming	06 May 2022	eTMF

TABLE OF CONTENTS

PAGE

1. INTRODUCTION

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

Revision Chronology:		
2015N238345_00	26-JAN-2016	Original
2015N238345_01	14-MAR-2016	Amendment No. 1
2015N238345_02	14-NOV-2016	Amendment No. 2
2015N238345_03	13-DEC-2017	Amendment No. 3
2015N238345_04	30-OCT-2018	Amendment No. 4
2015N238345_06	14-MAR-2019	Amendment No. 5
2015N238345_11	27-FEB-2020	Amendment No. 6
2015N238345_13	08-APR-2020	Amendment No. 7
2015N238345_15	09-OCT-2020	Amendment No. 8
TMF-11734800	20-AUG-2021	Amendment No. 9

Note: Country specific amendments are not listed here since all changes were later incorporated into the global protocol amendments.

This RAP will cover all of the individual CSR cycles compiled throughout the study with the support of documents such as a list of TLFs and mock shells within each reporting effort (\arwork\gsk3359609\mid204691). The cohorts included within each cycle are:

CSR Cycle	**Study Cohort Numbers**[1]
CSR Cycle 1	100, 300, 202, 401
CSR Cycle 2	201, 600
CSR Cycle 3	All remaining cohorts

1. See Section 5.1.1 for description for each cohort number.

CSR Cycles 2 and 3, following the decision to discontinue the asset, will be a reduced set of displays compared to the analysis described in this document, as indicated in the supporting mock shell document.

The above table corresponds to data processing cycles. The actual organization of binders in the GSK archive and the themes of CSR's will reflect the division of data into pharmacokinetics/pharmacodynamics, including safety and preliminary efficacy. The efficacy data is intended to be the output of all the expansion cohorts. In turn, the data dissemination plan includes 2 publications, the first based on dose escalation, pharmacokinetics, and safety and the second based on analysis of clinical efficacy.

The mapping of cohorts in the CSR documents and the subsequent publications is summarized in the following table:

Binder/ CSR Document	**Cohorts**
Dose Escalation- PK-PD-Safety	100, 201, 300, 600, 500-510
Dose Expansion – Preliminary Efficacy	All remaining cohorts

1.1. RAP Amendments

Revision chronology:

RAP Section	Amendment Details
Reporting and Analysis Plan_Study204691_Final_Vn 07APR2020	
Reporting and Analysis Plan_Study204691_Amendment1_Final_V1 [18OCT2020]	
5.1	• Refined definition and scope of analyses for efficacy analysis cohort
9.5	• Updated PRO section for future analyses
Multiple sections	• Updates to output descriptions based on new IDSL standards
Multiple sections	• Additions of text clarity
Reporting and Analysis Plan_Study204691_Amendment2_Final_V1 [TBC]	
Multiple sections	• Updates in line with Protocol Amendment 9
Multiple sections	• Updates to cover differing display approaches across CSR cycles
Multiple sections	• Removal of individual crossover outputs. Addition of crossover/re-treatment listing
Section 5.4.2	• Confirmation of subgroups and ranges
Section 7.5	• Addition of listings for impact of Covid-19
Section 8.3.2.5	• Update TTR to RECIST v1.1 (as per other time to event)
CCI [redacted]	
Section 9.6	• Removal of all PRO analyses except compliance
Multiple sections	• Additions of text clarity and corrections

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the current protocol.

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

Objectives	Endpoints
Part 1 GSK3359609 (feladilimab) Monotherapy	
Primary	
• To determine the safety, tolerability, MTD or the MAD of GSK3359609 (feladilimab)	• AEs, SAEs, DLTs, changes in safety/laboratory assessment parameters, dose modifications
Secondary	
• To determine the recommended dose of GSK3359609 (feladilimab) for further exploration	• AEs, SAEs, DLTs, changes in safety/laboratory assessment parameters, dose modifications, PK, pharmacodynamic activity, antitumor activity
• To evaluate the antitumor activity of GSK3359609 (feladilimab)	• ORR[1], DCR[1], PFS[1], OS, TTR[1,2], DoR[1,2]
• To characterize the PK properties of GSK3359609 (feladilimab)	• Plasma PK parameters such as Cmax, Ctau, AUC (0-τ) as data permit
• To determine immunogenicity	• ADA incidence by dose level/dose
• **Exploratory**	

CCI

[redacted]

Objectives	Endpoints
CCI [redacted]	

Abbreviations: ADA=anti-drug antibody; AE=adverse events; AUC=area under the curve; Cmax= maximum observed concentration; Ctau=minimum observed concentration; DCR=disease control rate; DLT=dose limiting toxicity; DNA=deoxyribonucleic acid; DoR=duration of response; CCI [redacted] IHC=immunohistochemistry; irRECIST=immune-related RECIST; MAD=maximum administered dose; MTD=maximum tolerated dose; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic; CCI [redacted] RECIST=Response Evaluation Criteria in Solid Tumors; RNA=ribonucleic acid; SAE=serious adverse events; TTR=time to response

1. irRECIST is the primary measure of clinical activity for response endpoints (i.e., ORR, DCR); RECISTv1.1 guidelines are used for PFS, DoR, TTR and disease assessments.
2. TTR and DoR will be evaluated if data permit. Refer to Protocol Section 10.7.2.1 for further details on the possible analysis of antitumor activity in the dose escalation cohorts.

Objectives	Endpoints
Part 2 GSK3359609 (ICOS) in Combination with Pembrolizumab or GSK3174998 (anti-OX40)	
Primary	
• To determine the safety, tolerability, MTD or the MAD of GSK3359609 (feladilimab) in combination with pembrolizumab or GSK3174998 (anti-OX40)	• AEs, SAEs, DLTs, changes in safety/laboratory assessment parameters, dose modifications
Secondary	
• To determine the recommended dose(s) and schedule of GSK3359609 (feladilimab) in combination with pembrolizumab or GSK3174998 for further exploration	• AEs, SAEs, DLTs, changes in safety/laboratory assessment parameters, dose modifications, PK, pharmacodynamic activity, antitumor activity
• To determine the recommended dose(s) of GSK3359609(feladilimab) and GSK3174998 in combination	
• To evaluate the antitumor activity of GSK3359609 (feladilimab) in combination with pembrolizumab or GSK3174998	• ORR[1], DCR[1], PFS[1], OS, TTR[1,2] DoR[1,2]
• To characterize the PK properties of GSK3359609 (feladilimab), pembrolizumab or GSK3174998 when administered in combination	• GSK3359609 (feladilimab), GSK3174998, and pembrolizumab PK parameters such as Cmax, Ctau, AUC (0-τ) as data permit
• To determine immunogenicity of GSK3359609 (feladilimab), pembrolizumab or GSK3174998 when administered in combination	• ADA incidence of each drug by dose level/dose
• **Exploratory**	
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

Abbreviations: ADA=anti-drug antibody; AE=adverse events; AUC=area under the curve; Cmax= maximum observed concentration; Ctau=minimum observed concentration; CPS=combined positive score; DCR=disease control rate; DLT=dose limiting toxicity; DNA=deoxyribonucleic acid; DoR=duration of response; CCI [redacted] HNSCC=head and neck squamous cell carcinoma; IHC=immunohistochemistry; irRECIST=immune –related RECIST; MAD=maximum administered dose; MTD=maximum tolerated dose; ORR=overall response rate; OS=overall survival; PD-L1= programmed cell death receptor 1-ligand 1; PFS=progression-free survival; PK=pharmacokinetic; CCI [redacted] RECIST=Response Evaluation Criteria in Solid Tumors; RNA=ribonucleic acid; SAE=serious adverse events; TTR=time to response

1. irRECIST is the primary measure of clinical activity for response endpoints (i.e., ORR, DCR); RECISTv1.1 guidelines are used for PFS, DoR, TTR and disease assessments.
2. CCI [redacted]

Objectives	Endpoints
Part 2A GSK3359609 (feladilimab) Combination with Chemotherapies (±Pembrolizumab)	
Primary	
• To determine the safety, tolerability, of GSK3359609 (feladilimab) in combination with standard of care chemotherapies ± pembrolizumab	• AEs, SAEs, changes in safety/laboratory assessment parameters, dose modifications
Secondary	
• To determine the recommended dose of GSK3359609 (feladilimab) for further exploration	• AEs, SAEs, DLTs, changes in safety/ laboratory assessment parameters, dose modifications, PK, pharmacodynamic activity, antitumor activity
• To characterize the PK properties of GSK3359609 (feladilimab), chemotherapies and pembrolizumab	• Plasma PK parameters such as Cmax, and Ctau as data permit
• To determine immunogenicity of GSK3359609 (feladilimab) and pembrolizumab	• ADA incidence by dose level/dose
• **Exploratory**	

CCI

[redacted]

Abbreviations: ADA=anti-drug antibody; AE=adverse events; Cmax= maximum observed concentration; Ctau=minimum observed concentration; DCR=disease control rate; DLT=dose limiting toxicity; DNA=deoxyribonucleic acid; DoR=duration of response; irRECIST=immune –related RECIST; ORR=overall response rate; OS=overall

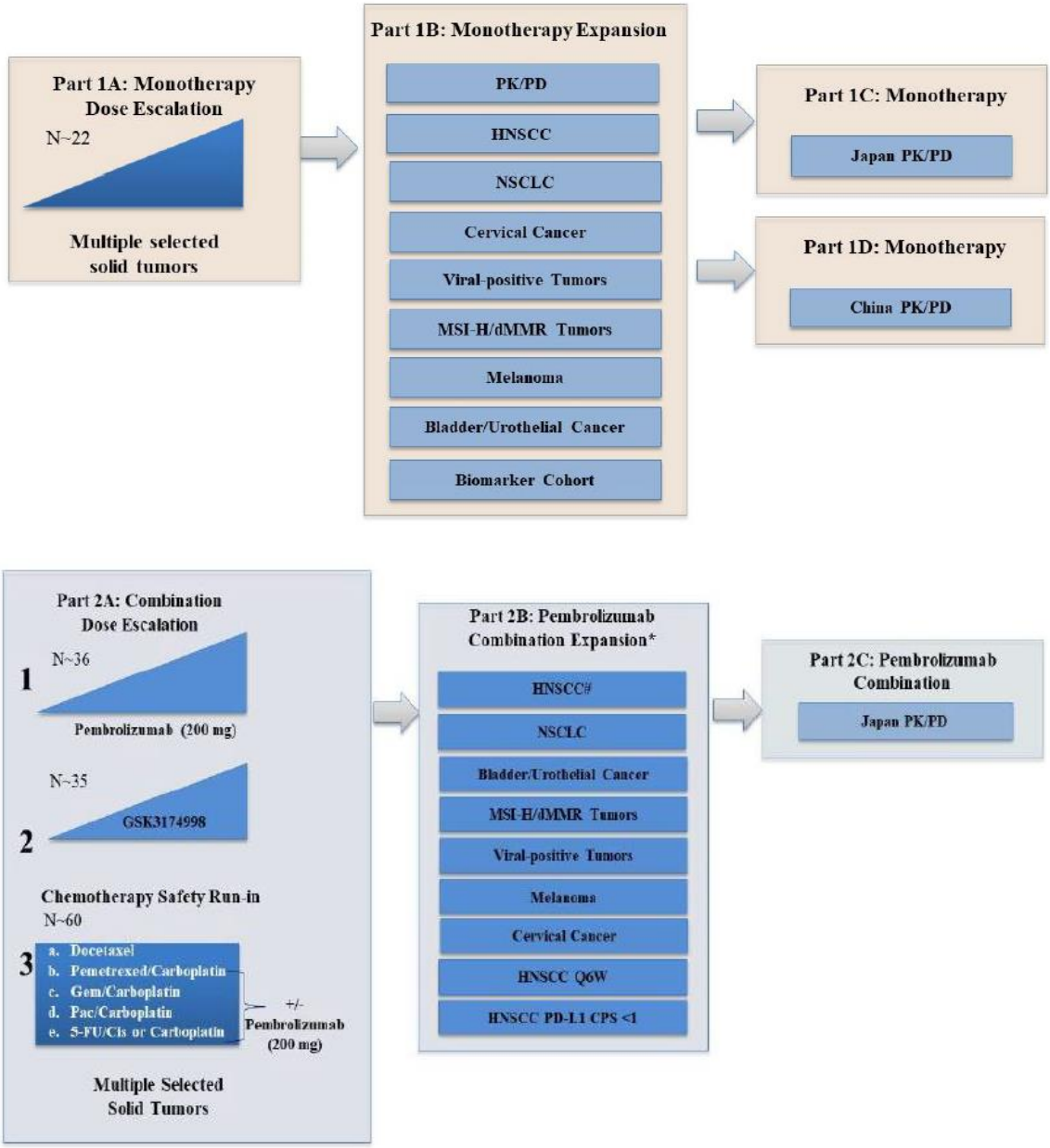
survival; PFS=progression-free survival; PK; pharmacokinetic; RECIST=Response Evaluation Criteria in Solid Tumors; RNA=ribonucleic acid; SAE; serious adverse events; TTR=time to response

1. irRECIST is the primary measure of clinical activity for response endpoints (i.e., ORR, DCR); RECISTv1.1 guidelines are used for PFS, DoR, TTR and disease assessments.
2. TTR and DoR will be evaluated if data permit; Refer to Protocol Section 10.7.2.1 for further details.

2.3. Study Design

Figure 1 Study Design

Overview of Study Design and Key Features



Abbreviations: 5-FU=fluorouracil; Cis=cisplatin; dMMR= deficient mismatch repair; Gem=gemcitabine; IHC = immunohistochemistry; MSI-H= microsatellite instability-high; NSCLC=non-small cell lung cancer; Pac=paclitaxel; PD-L1=programmed death; HNSCC= head and neck squamous cell cancer.
#: a subset of HNSCC participants will be randomly assigned to one of 3 doses of GSK3359609 (feladilimab) (refer to Table 6 of protocol) in combination with 200mg of pembrolizumab
*Participants enrolled in the Part 2B cohorts (GSK3359609 (feladilimab)/pembrolizumab combination) may be stratified by PD-L1 IHC status and prior PD-1/L1 treatment

1. The number of participants allocated to any Part is an estimate.
2. The number of cohorts indicated in any Part is an estimate.
3. Expansion cohorts may increase enrollment following outcome of interim analyses (refer to

Overview of Study Design and Key Features	
Protocol Section 10.6 for details); enrollment in the overall population will not exceed 867 participants except by a Protocol amendment. 4. Participants enrolled in Part 1 (GSK3359609 (feladilimab) monotherapy) upon disease progression may be permitted to receive GSK3359609 (feladilimab) in combination with pembrolizumab (defined as crossover). Note: Within Protocol Amendment 7, three additional combinations with GSK3359609 (feladilimab) were added: dostarlimab or dostarlimab plus cobolimab or bintrafusp alfa (M7824). These were removed within the current protocol and therefore will not be mentioned in further sections. However, any data collected for the few participants enrolled into these cohorts will be listed as well as displaying the number of participants within each cohort in the summary of study populations table. GSK3359609 (feladilimab) will be written as GSK3359609 throughout the remainder of the document.	

Design Features	• As illustrated in Figure 1, the study will be conducted in two parts (Part 1 GSK3359609 monotherapy and Part 2 GSK3359609 combination therapy) whereby each part consists of a dose escalation phase (A) followed by a cohort expansion phase (B).
	• In Part 1 of the study, all participants will receive GSK3359609 monotherapy.
	• In Part 2, participants will be enrolled into expansion cohorts defined by tumor histology or by a specific characteristic.
	• In Part 2A of the study, participants will receive GSK3359609 in combination with:
	  • Pembrolizumab
	  • Standard of care chemotherapy regimens (Docetaxel, Pemetrexed/Carboplatin, Paclitaxel/Carboplatin, Gemcitabine/Carboplatin, Fluorouracil (5-FU)/Carboplatin, Fluorouracil (5-FU)/Cisplatin) with and without pembrolizumab
	  • GSK3174998 (OX40)
	• In Part 2B all participants will receive GSK3359609 in combination with pembrolizumab
	• In Part 2C (Japanese expansion cohort) participants will receive GSK3359609 at one of the three defined dose levels (0.3, 1, 3 mg/kg) in combination with 200mg of pembrolizumab.
	• Participants receiving GSK3359609 monotherapy (Part 1) except the Japan and China PK/pharmacodynamic cohorts (Part 1C and Part 1D) may be allowed to crossover to receive GSK3359609 in combination with pembrolizumab provided the participant has documented objective progression and should not have experienced any drug-related AEs ≥Grade 3 or SAEs of any Grade.
	• Each part and phase of the study includes a screening period, a treatment period, and a follow-up period. For participants who meet all eligibility criteria and register into the study, the maximum duration of treatment with GSK3359609 is expected to be two years; in those participants who receive combination therapy, the maximum duration of treatment with GSK3359609 in combination with pembrolizumab (±chemotherapy) or GSK3174998 is expected to be two years.
	• The duration of chemotherapy treatment will be according to institutional practice but should be a minimum of 4 cycles (cycle=21 days); the maximum duration of GSK3359609 and pembrolizumab treatment is expected to be 2 years; thus, if the course of chemotherapy treatment is completed after a minimum of four cycles or discontinued prior to completion of a minimum of 4 cycles, GSK3359609 and pembrolizumab treatment may continue.
	• The maximum follow-up period for safety assessments will be 90 days from the date

Overview of Study Design and Key Features	
	of the last dose of study treatment. The expected maximum follow-up period for survival and subsequent anticancer therapy will be two years from the date of the last dose of study treatment. • All participants who permanently discontinue study treatment for any reason will be followed for survival and new anticancer therapy (including radiotherapy) every 12 weeks until death, termination of the overall study or a cohort by the sponsor or until the participant has been followed for two years. • Participants who attain a CR and discontinue study treatment prior to completing 35 cycles OR in participants with RECISTv1.1 confirmed SD, PR or CR who discontinue study treatment after completing 35 cycles of study treatment may be eligible to receive up to an additional 18 cycles (approximately 1 year) of study treatment upon disease progression within the initial treatment phase. Maximum treatment duration for participants participating in HNSCC Q6W Dosing cohort is 8 cycles (approximately 1 year) for both GSK3359609 and pembrolizumab. This is termed re-treatment or second course treatment.
Dosing	• The weight-based dose levels of GSK3359609 monotherapy in Part 1A are displayed in Table 1 in protocol. Dose range in unit (mg/kg) starts from 0.001, then 0.003, 0.01, 0.03, 0.1, 0.3, 1.0, 3.0 to 10.0 Q3W. • The starting dose of GSK3359609 in combination with pembrolizumab (fixed at 200 mg) for Part 2A will be two dose levels below a dose that was shown to be tolerated and at which a pharmacodynamics effect was observed during monotherapy in Part 1A. • The starting dose of 80 mg Q3W GSK3359609 will be combined with standard of care chemotherapy regimens in Part 2A. A reduced dose of GSK3359609 (24 mg) may also be used. Chemotherapy will only be provided for 4-6 cycles (according to standard practice). Treatment with docetaxel and pemetrexed may continue beyond 6 cycles according to standard practice. Participants will be split into those receiving 200mg pembrolizumab or not. • Part 2A GSK3174998 and GSK3359609 combination dose escalation phase will initiate at starting doses of 8 mg Q3W for GSK3359609 and GSK3174998 and increase up to 24 and 80 mg Q3W in a staggered approach across the two treatments. • Any dose level(s)/doses in the dose escalation phases (Part 1A and Part 2A) may be selected for expansion of the study in Part 1B (GSK3359609 monotherapy) and Part 2B (GSK3359609 in combination with pembrolizumab fixed at 200 mg) with 3 weekly cycles. • The Part 1B Biomarker Cohort will have a fixed dose of 24mg Q3W. • The Part 2B HNSCC Q6W cohort will investigate GSK3359609 at an alternative dosing schedule of once every 6 weeks; participants will be randomly assigned to GSK3359609 doses of 48 mg or 160 mg Q6W in combination with pembrolizumab 400 mg administered at the schedule of Q6W. • In Part 1C (Japanese PK/PD cohort) and Part 1D (Chinese PK/PD cohort) participants will receive GSK3359609 monotherapy at selected previously defined escalation dose levels Q3W. • In Part 2C (Japanese expansion cohort) participants will receive GSK3359609 at selected previously defined escalation dose levels in combination with 200mg of pembrolizumab Q3W.
Time &	• Refer to Appendix 2: Schedule of Activities

Overview of Study Design and Key Features	
Events	
Treatment Assignment	• Participants enrolled in Part 1 of the study will be assigned to receive GSK3359609 monotherapy in an open-label fashion. Participants enrolled in Part 2 of the study will be assigned to a combination treatment either in the order in which screening assessments are completed or in the order in which dose escalation phase for each combination agent has been initiated.
Interim Analysis	• The data collected on the study will be reviewed on a regular ongoing basis. Available safety and PK/pharmacodynamic data will be reviewed after completion of each dose level. For dose expansion cohorts (aggregating dose escalation cohort and PK/PD cohort), continuous assessment of efficacy and safety data will be performed to ensure futility and safety across the cohorts. Actual decisions will depend on the totality of the data and any emerging pembrolizumab clinical trial data. Full details will be provided in the documents area of each specific interim analysis study area.

2.4. Statistical Hypotheses / Statistical Analyses

2.4.1. Part 1A and Part 2A Dose Escalation/Safety Run-in

In Part 1A and Part 2A, the primary aims are determining the recommended dose or doses for further exploration, the safety profile, and the pharmacology of GSK3359609 monotherapy and in combination with pembrolizumab, chemotherapy (±pembrolizumab), or GSK3174998 in participants with advanced solid malignancies. Descriptive methods will be used in analyses of the data obtained from this study. No formal statistical hypotheses are being tested.

2.4.2. Part 1B GSK3359609 Monotherapy Expansion/ Part 2B GSK3359609 Combination with Pembrolizumab Expansion of PD-1/L1 Experienced Participants

The assumptions for the secondary endpoint of overall response rate (ORR) underlying the design are detailed below:

The null hypothesis for the secondary endpoint ORR is:

H_0: p=10%.

The alternative hypothesis is:

HA: p=30%.

In the Part 1B Biomarker Cohort, the null hypothesis for the difference in ORR of GSK3359609 in the biomarker positive population (i.e., ICOS high) and

biomarker negative population (i.e., ICOS low) is given below:

The null hypothesis is:

H0: $p_H - p_L \leq 0\%$

The alternative hypothesis is:

HA: $p_H - p_L > 0\%$,

where p_H represents ORR in the ICOS high population and p_L represents ORR in the

ICOS low population.

2.4.3. Part 2B GSK3359609 Combination with Pembrolizumab Expansion of PD-1/L1 Naïve Participants

For each cohort, the aim is to test the null hypothesis that the ORR for the combination is equal to the historical response rate of monotherapy pembrolizumab which is expected to be between 15% to 40% according to tumor types selected for the study. In the KEYNOTE-001 trial, the reported pembrolizumab monotherapy ORR was 19.4% in 495 NSCLC participants across different histologies and PD-L1 status [Garon, 2015].

Overall, the aim of each expansion cohort is to detect an improvement in the ORR of the combination therapy compared with pembrolizumab monotherapy in the range of 20% over the null, with power of at least 80% and no more than a 10% type 1 error rate.

- **PD-1/L1 naïve Expansion Cohorts (HNSCC, NSCLC PD-L1 <50%, Bladder/Urothelial and Viral-positive Cancers)**

The null hypothesis for ORR is:

H_0: p=20%

The alternative hypothesis is:

H_A: p=40%

- **PD-1/L1 Treatment-Naïve HNSCC PD-L1 CPS <1 Cohort**

The null hypothesis for proportion of participants with a change in PD-L1 CPS status from <1 to ≥1 is:

H0: p=10%

The alternative hypothesis is:

HA: p=40%

- **PD-1/L1 naïve Expansion Cohort (NSCLC PD-L1 ≥50% and MSI-H/dMMR Cancers)**

The null hypothesis for ORR is:

H0: p=30%

The alternative hypothesis is:

HA: p=50%

3. PLANNED ANALYSES

3.1. Interim Analyses

During the dose escalation phases of the study, no formal interim analyses will be performed. Available safety and PK/pharmacodynamic data will be reviewed after completion of each dose level. This review will support the decision to escalate to the dose level using the corresponding dose-escalation guidelines based on Modified Toxicity Probability Interval (mTPI) or 2D-CRM design and totality of data across all tumor types will be considered in decision making. The Steering Committee will guide the transition of the study from dose escalation to cohort expansion for both monotherapy and combination therapy, refer to Section 4.1.1.5 in the protocol for further details.

Within the dose expansion (DE) phase of the study,

- after a minimum of 10 evaluable participants in one of the DE cohorts have been enrolled in one dose/dose level in a cohort, the number of observed best unconfirmed responses as well as other available data will be used for futility analysis according to the rules summarized in protocol Section 10.6.
- continuous assessment of efficacy and safety will be performed after first interim analysis (based upon a minimum of 10 evaluable participants in at least one of the disease-specific cohorts with available unconfirmed overall response data).
- administrative interim analysis (inflection point) will include:
    - safety data accumulated to the inflection point analysed by dose level.
    - efficacy data accumulated to the inflection point analysed by tumor type, PD-1/L1 treatment (naïve/experienced), and prior anti-cancer therapy status.
    - efficacy analysis summarized by sub-tumor type if data permit, such as (1) EGFR/ALK/ROS1 mutated patients in NSCLC; (2) Ocular in Melanoma patients; (3) Squamous in HNSCC patients.
    - efficacy analyses summarized within three different cohorts, (1) regimen cohort; (2) combined cohort; (3) analysis cohort as indicated in the specifications document (\arwork\gsk3359609\mid204691) provided for each reporting effort.

Presented in Table 1, Table 2 and Table 3 are the futility interim analysis decision rules for the 10th to 30th evaluable participants by specifying the number of participants with an unconfirmed ORR per irRECIST for continuing enrollment or stopping for futility when total sample size is up to 30. The efficacy analysis cohort used for interim analysis is defined by using disease specific regimen cohort, in addition to pooling participants from DE and PK/PD regimen cohorts where primary tumor type and/or histology is the same at the recommended dose level (primarily 0.1 mg/kg for monotherapy and 0.3 mg/kg for combination therapy).

Table 1 Futility Boundary for Monotherapy Expansion Cohorts and PD-1/L1 Experienced Pembrolizumab Combination Therapy Expansion Cohorts

Number of Participants[a]	Number of Responders					
	0	1	2	3	4	5
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						
29						
30						

a. Shaded regions indicate enrollment pause based on meeting futility

Table 2 Futility Boundary for PD-1/L1 Naïve Pembrolizumab Combination Therapy Expansion Cohorts (HNSCC, NSCLC PD-L1 <50%, Bladder/Urothelial Cancer and Viral-positive Cancer)

Number of Participants[a]	Number of Responders							
	1	2	3	4	5	6	7	8
10								
11								
12								
13								
14								
15								
16								
17								
18								
19								
20								

Number of Participants[a]	Number of Responders							
	1	2	3	4	5	6	7	8
21								
22								
23								
24								
25								
26								
27								
28								
29								
30								

a. Shaded regions indicate enrollment pause based on meeting futility

Table 3 Futility Boundary for PD-1/L1 Naïve Pembrolizumab Combination Therapy Expansion Cohort (NSCLC with PD-L1≥50% and MSI-H/ dMMR Cancers)

Number of Participants[a]	Number of Responders											
	1	2	3	4	5	6	7	8	9	10	11	12
10												
11												
12												
13												
14												
15												
16												
17												
18												
19												
20												
21												
22												
23												
24												
25												
26												
27												
28												
29												
30												

a. Shaded regions indicate enrollment pause based on meeting futility

3.2. Final Analyses

Final analyses will be performed on a selected group (i.e., subset) of cohorts and groups will be reported in CSR cycles on a rolling basis as outlined in Section 1.

The planned analyses for primary, secondary, and key exploratory endpoints will be performed at each CSR cycle after the completion of the following sequential steps:

1. All required database cleaning activities have been completed and final database release (DBR) have been declared by Data Management on the participant data within the selected cohorts. Note: Database freeze (DBF) will be declared at study conclusion for *all* cohorts
2. Randomization codes (where applicable) have been distributed according to RandAll NG procedures.

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.	• Disposition • Demographics
All Treated	• All participants who received at least one dose of study treatment.	• Study Population • Efficacy • Safety
All Evaluable	• Participants in All Treated who had at least one post baseline disease assessment or have progressed, died, or permanently discontinued from treatment.	• Efficacy in interim analyses of efficacy cohorts (pooling of DE+PK/PD participants with similar histologies and same dose level).
Crossover	• Participants who were treated in monotherapy and then crossover to the combination therapy with pembrolizumab.	• Study Population
Re-treatment	• Participants who responded on their original treatment and were re-treated following progression.	• Study Population
Pharmacokinetic	• Participants in the All Treated Population for whom a PK sample is obtained and analysed.	• PK
Pharmacodynamic	• Participants in the All Treated Population for whom pre- and on-treatment paired and evaluable tumor biopsies or pre- and on-treatment blood samples were obtained and analyzed for biomarkers.	• N/A: Will be determined and used by the EMU (biomarker) group only. Will not be part of the CSRs.
DLT Evaluable	• All Treated Population in the dose escalation phase or PK/PD cohorts, who completed the 28-day DLT observation period or experienced a DLT during the determinative period (28 days).	• DLT (including Parts 1A, 2A, 1C, 1D, 2C)

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarized 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 [14OCT2021 Version 7].

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations are captured and categorized on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate listing of all inclusion/exclusion criteria deviations will also be provided for the All Treated Population. This will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

For participants who were treated in monotherapy and then crossed over to the combination therapy with pembrolizumab or those who responded to therapy on their original treatment and were re-treated following progression, only the data prior to crossover/re-treatment will be included throughout the analysis unless otherwise stated.

5.1.1. Study Population

Study population will be displayed by study part and regimen cohort and will be labelled and separated as follows:

		Cohort Descriptions		
Cohort [RandAll NG]		Data Displays for Reporting		
Regimen Code	Description	Study Part	Description	Order in TLF
100	Part 1A-Dose Escalation 0.001 mg/kg	Monotherapy Part 1	DE	1
201	Part 1B-Cohort Expansion 1		PK/PD	2
204	Part 1B-Cohort Expansion 4		CERVICAL 1.000 mg/kg	3
202	Part 1B-Cohort Expansion 2		HNSCC 1.000 mg/kg	4
203	Part 1B-Cohort Expansion 3		NSCLC 0.300 mg/kg	5
203	Part 1B-Cohort Expansion 3		NSCLC 1.000 mg/kg	6
207	Part 1B-Cohort Expansion 7		MELANOMA 0.300 mg/kg	7
207	Part 1B-Cohort Expansion 7		MELANOMA 1.000 mg/kg	8
206	Part 1B-Cohort Expansion 6		MSI-H/DMMR 0.300 or 1.000 mg/kg	9
208	Part 1B-Cohort Expansion 8		BLADDER/UROTHELIAL 0.300 or 1.000 mg/kg	10
205	Part 1B-Cohort Expansion 5		VIRAL-POSITIVE 1.000 mg/kg	11
290	Biomarker, Part 1		BIOMARKER 24 mg	12
700	Part 1C - GSK3359609 (Japan PK/PD cohort)		GSK3359609 (JAPAN PK/PD COHORT)	13
800	Part 1D-China PK/PD Cohort		GSK3359609 (CHINA PK/PD COHORT)	14
300	Part 2A-Dose Escalation: pembrolizumab	Part 2 Combination with Pembrolizumab	DE	1
407	Part 2B-Cohort Expansion 7		CERVICAL 0.300 mg/kg	2
408	Part 2B-Cohort Expansion 8		HNSCC 0.100 mg/kg	3
401	Part 2B-Cohort Expansion 1		HNSCC 0.300 mg/kg	4
408	Part 2B-Cohort Expansion 8		HNSCC 1.000 mg/kg	5
408	Part 2B-Cohort Expansion 8		HNSCC 3.000 mg/kg	6
402	Part 2B-Cohort Expansion 2		NSCLC 0.300 mg/kg	7
406	Part 2B-Cohort Expansion 6		MELANOMA 0.300 mg/kg	8
406	Part 2B-Cohort Expansion 6		MELANOMA 1.000 mg/kg	9
405	Part 2B-Cohort Expansion 5		MSI-H/DMMR 0.300 mg/kg	10

Cohort [RandAll NG]		Cohort Descriptions		
		Data Displays for Reporting		
Regimen Code	**Description**	**Study Part**	**Description**	**Order in TLF**
403	Part 2B-Cohort Expansion 3		BLADDER/UROTHELIAL 0.300 mg/kg	11
404	Part 2B-Cohort Expansion 4		VIRAL-POSITIVE 0.300 mg/kg	12
409	Part 2B-Cohort Expansion 9		HNSCC_CPS<1	13
410	Part 2B-Cohort Expansion 10		HNSCC 48 mg	14
410	Part 2B-Cohort Expansion 10		HNSCC 160 mg	15
600	Combination Dose Escalation - GSK3174998, all dose levels		DE_OX40	16
701	Part 2C - GSK3359609/Pembrolizumab (Japan PK/PD cohort)		GSK3359609/ PEMBROLIZUMAB (JAPAN PK/PD COHORT)	17
500	Chemotherapy: DOCETAXEL	Part 2 Combination with Chemotherapies (±Pembrolizumab)	GSK3359609 + CHEMOTHERAPY	1
501	Chemotherapy: PEMETREXED/CARBOPLATIN			
502	Chemotherapy: PACLITAXEL/CARBOPLATIN			
503	Chemotherapy: GEMCITABINE/CARBOPLATIN			
504	Chemotherapy: Fluorouracil / Cisplatin			
505	Chemotherapy: Fluorouracil / Carboplatin			
506	Chemotherapy: Pemetrexed / Carboplatin / Pembrolizumab		GSK3359609 + PEMBROLIZUMAB + CHEMOTHERAPY	2
507	Chemotherapy: Paclitaxel / Carboplatin / Pembrolizumab			
508	Chemotherapy: Gemcitabine / Carboplatin/ Pembrolizumab			
509	Chemotherapy: Fluorouracil / Cisplatin / Pembrolizumab			
510	Chemotherapy: Fluorouracil / Carboplatin / Pembrolizumab			

For chemotherapy, due to the low numbers of participants, cohorts will be grouped into chemotherapy cohorts with and without pembrolizumab. The only table displayed by regimen cohort will be the summary of study populations.

5.1.2. Safety

Safety tables and figures for CSR cycles 1 and 2 will be displayed by regimen cohort as indicated for Study Population in Section 5.1.1 as well as by dose level received. For the CSR cycle 3, since little difference was seen between the dose levels in the first CSR cycles, Study Parts 1A, 1B, 2A and 2B will be displayed by regimen cohort or chemotherapy group only. However, the data from the regional study parts 1C, 1D and 2C will continue to be displayed by regimen cohort and dose level.

Listings will display both regimen cohort and dose level throughout.

5.1.3. Efficacy

For CSR Cycle 1, efficacy will be presented by efficacy analysis cohorts. Efficacy analysis cohorts are defined by tumor histology and/or by a specific tumor-agnostic characteristic. These cohorts are comprised of participants from the dose expansion phase (e.g., 1B, 2B) as well as participants from the dose escalation phase (e.g., 1A, 2A) if the cohort criteria are met. Efficacy for dose escalation cohorts will not be presented separately. Efficacy cohorts may be further classified according to prior PD-1/L1 therapy as detailed in Section 5.4.2. Differences between the regimen cohorts and the efficacy analysis cohorts will be provided in the footnotes of efficacy outputs at the CSR.

For CSR Cycle 2 and 3, efficacy will be displayed by regimen cohort as indicated for Study Population in Section 5.1.1. Study parts 1C, 1D and 2C will not be included and the Chemotherapy cohorts will only be displayed in the response listing. For Part 2 Combination with Pembrolizumab, the tumor types Bladder/Urothelial, Cervical, HNSCC, Melanoma and NSCLC will be further classified according to prior PD-1/L1 therapy.

5.1.4. PK

PK concentration and parameter summary tables and figures and CCI tables will be displayed by study cohort and dose level. Study cohort is the same as regimen cohort described for Study Population in Section 5.1.1 but without the split by dose. The PK parameter analyses tables will be pooled across appropriate study cohorts within dose level to increase the sample size. The PK parameter summary tables may also pool across study cohorts.

Listings will display both regimen cohort and dose level throughout.

5.2. Baseline Definitions

For all endpoints (except as noted in baseline definitions) 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, Day 1 assessments are assumed to be taken prior to first dose and 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.

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

Parameter	Study Assessments Considered as Baseline (Part 1 and Part 2)		Baseline Used in Data Display
	Screening	Day 1 (Pre-Dose)	
[Efficacy]			
Tumor imaging/Clinical exam	X		Screening
[Safety]			
Hematology/Clinical Chemistry/Urinalysis	X	X	Day 1 (if performed, otherwise Screening)
Thyroid	X		Screening
Troponin		X	Day 1
Physical Exam	X	X	Day 1
ECOG PS	X	X	Day 1
Vital signs	X	X	Day 1
12-lead ECG	X	X	Day 1
[Other]			
PRO (patient reported outcome)		X	Day 1
PK/Immunogenicity		X	Day 1
Biomarker/PD	X	X	Screening[1]

1. Based on screening unless visit has been classified as tumor imagining /clinical exam, then Day 1.

Only for Part 1, ECG is collected in triplicate at selected time points (see Table 25 in the protocol for details); in these cases, the mean of the available values will be used as baseline (even if less than 3). All values collected need to be prior to treatment start.

5.3. Multicentre Studies

In this multicentre global study, enrollment will be presented by country and investigative site. Data from all study sites will be integrated and no controlling for center-effect will be considered in the statistical analyses.

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

There are no planned covariates or strata considered for this study.

5.4.2. Examination of Subgroups

Efficacy for participants in combination with pembrolizumab (Part 2) will be summarized by prior PD-1/L1 treatment (Naïve, Experienced) for selected cohorts as detailed in Section 5.1.3. Efficacy for participants within selected cohorts will also be summarized by HPV status (HPV+, HPV-, Non-oropharynx, Unknown) if the sample size permits.

Additionally, key efficacy tables will be repeated by PD-L1 IHC Status and ICOS IHC intra tumoral result status. The following cut offs will be used for PD-L1 IHC status:

Cohort	CPS or TPS	Reference line(s)	Cut off
Bladder/Urothelial	CPS	10	<10 >=10
NSCLC	TPS	50	<1 1-49 >=50
HNSCC[1]	CPS	1 & 20	<1 1-19 >=20
Cervical	CPS	1	<1 >=1

1. HNSCC includes all doses from the cohorts HNSCC 0.3 mg/kg, HNSCC Randomized and HNSCC Q6W. HNSCC CPS<1 is not included since all participants fall into the <1 category.

The following cut offs will be used for ICOS IHC status of ICOS-High and ICOS-Low/Neg respectively:

Cohort	Part 1	Part 2
Bladder/Urothelial	>=10, <10	>=10, <10
NSCLC	>=10, <10	>=5, <5
HNSCC	>=10, <10	>=5, <5
Cervical	>=10, <10	>=10, <10
Melanoma[1]	>=10, <10	>=5, <5

1. Includes the Melanoma Biomarker 24mg regimen cohort.

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
Section 11.3	Appendix 3: Assessment Windows
Section 11.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
Section 11.5	Appendix 5: Data Display Standards & Handling Conventions
Section 11.6	Appendix 6: Derived and Transformed Data
Section 11.7	Appendix 7: Reporting Standards for Missing Data
Section 11.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population displays will be based on the All Treated Population and displayed by regimen cohort as specified in Section 5.1.1, unless otherwise stated.

Study population analyses including analyses of participant's disposition, protocol deviations, demographic and baseline characteristics, prior therapy, medical condition, concomitant medications and exposure will be based on GSK Core Data Standards.

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 using the Enrolled Population. A summary will also be provided for the number and percentage of participants in each of the subgroups defined in Section 5.4 for the All Treated Population. In addition, the number and percentage of participants treated by country and center will be summarized using the Enrolled Population and well as the All Treated Population if these populations are different. A summary table and listing identifying reasons for screening failures will be presented based on the Screened Population.

A summary of study treatment status will be provided. The display will show the number and percentage of participants who are ongoing or discontinued study treatment, with a summary of the primary reasons for discontinuation of study treatment. Participants in the crossover or retreatment phase will be included in an ongoing at crossover/re-treatment row. For participants in Part 2, study treatment status for each additional treatment and primary reasons for discontinuation for each will also be displayed. Reasons for study treatment discontinuation will be presented in the order they are displayed in the eCRF.

A listing of study treatment discontinuation for each treatment will be generated. The listing will include last dose date, date of decision to receive no future study treatment and additional specified reasons for study treatment discontinuation.

A summary of study status and reason for study withdrawal will be provided. The study status display will show the number and percentage of participants who withdrew from the study without meeting the above criteria, including primary reasons for study withdrawal. The number and percentage of participants who died, completed the study and those ongoing on study treatment, at crossover/re-treatment or in follow up will also be presented. Reasons for study withdrawal will be presented in the order they are displayed in the eCRF. A listing of reason for study withdrawal will also be provided.

Using the All Treated population, listings will also be provided detailing planned and actual treatments, and participants excluded from any population. Additionally, a listing with the participants who crossover to combination with pembrolizumab or are re-treated with their original treatment will be displayed with the start and end dates of each stage provided.

Duration of follow-up in months, defined as the time from randomization or treatment start to last contact or death, will be summarized by minimum, median, maximum and first and third quartiles. This will include the time after crossover or re-treatment if applicable.

6.3. Demographic and Baseline Characteristics

The demographic characteristics age (years), race, ethnicity, sex, baseline height (cm), baseline body weight (kg) and body mass index (BMI; kg/m^2) will be summarized and listed for the All Treated Population. As full date of birth is not provided, age will be derived at the time of screening using the year of birth imputed with 30^{th} June. Age, height, weight and BMI will be summarized using the mean, standard deviation, minimum, median, and maximum. In addition, age will also be categorized and summarized by 18-64, 65-84, and ≥85 years for both the All Treated population as part of the demography summary table, and also separately for the All Enrolled Population for compliance with Regulatory requirements. The number and percentage of participants will be computed for sex and ethnicity. Race and racial combinations will be summarized and listed.

Disease history and characteristics at initial diagnosis and at screening will be reported for the All Treated Population. It includes details of the tumor under study such as the primary tumor type and where applicable primary tumor location (e.g., oral cavity for HNSCC), the histology, the histologic grade, stage at initial diagnosis, presence of measurable disease at screening, presence of non-target lesions at screening, time since initial diagnosis in days, time from last progression in days, the number of prior anticancer therapy and radiotherapy regimens received and the intent of the anticancer therapy (i.e. adjuvant or metastatic). Durations will be derived with respect to the date of first dose. If the participant has metastatic disease at screening, then time from date of initial diagnosis to date of diagnosis of metastatic disease in days will also be derived.

Disease burden at baseline, including number of organs involved, location of organs involved and the sum of measurable target lesions at baseline will be reported for the All Treated Population

Indicators (yes/no) for the following, collected at screening, will also be summarized: Measurable disease, non-target lesions, prior adjuvant/neo-adjuvant, EGFR/ALK/ROS1 mutation, BRAF mutation, MSI-H, HPV and metastatic disease as well as the number of prior advanced/metastatic anti-cancer therapies. Disease history and characteristics, including dates and additional specified text, will be presented in data listings.

Predefined medical conditions (angina pectoris, diabetes, hypertension, hyperlipidemia, myocardial infarction, stroke) and other medical conditions will be collected at screening. These conditions will be summarized by whether they are past or current. In addition, separate summaries will be provided for past and current cancer related medical conditions. All medical conditions will be listed.

Prior anticancer therapies will be coded using GSK Drug coding dictionary version 1.4 or higher and summarized and listed for the All Treated Population. Therapies will be classified by general type (chemotherapy, immunotherapy, hormonal therapy, biologic

therapy, small molecule targeted therapy, bis-phosphate, vaccine, surgery, radiotherapy and unknown) as well as by immunotherapy type (CTLA-4, PD-1/L1, other immunotherapy) and the number and percentage of participants with each type will be displayed. A summary of the number of prior anticancer therapy regimens/lines by type, the intent of the therapy (e.g., neo-adjuvant, adjuvant etc) will also be provided.

Prior anticancer radiotherapy will be listed as well as prior cancer related surgeries.

Additional baseline listings and summaries will be provided for substance (tobacco and alcohol) use.

6.4. Concomitant Medications

Concomitant medications will be coded using GSK Drug coding dictionary version 1.4 or higher, summarized, and listed for the All Treated Population. 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. The ingredients will be summarized by the base component, using CMBASECD and CMBASE. Anatomical Therapeutic Chemical (ATC) classification Level 1 (Body System) information will be included in the dataset created but will not appear on the listing or summary.

In the summary of concomitant medications, each participant is counted once within each unique ingredient. For example, if a participant takes Amoxicillin on two separate occasions, the participant is counted only once under the ingredient “Amoxicillin”. All medications, regardless of onset date will be included in the summary and listing.

Blood products (including platelets or red blood cells) or blood supportive care products (growth factor support) with onset date after the start of study treatment will also be summarized if data permit. The number and percentage of participants receiving each type of blood product and blood supportive care products after the start of study treatment will be provided. Supporting listings will also be provided.

6.5. Extent of Exposure

Extent of exposure to GSK3359609 monotherapy, GSK3359609 in combination with pembrolizumab, GSK3359609 in combination with chemotherapy±pembrolizumab and GSK3359609 in combination with GSK3174998 will be displayed for each drug component separately for the All Treated Population.

The duration of exposure to study treatment in weeks for each participant and treatment, is defined as treatment stop date – treatment start date + 1 /7. For participants on a combination therapy this will considered the first and last treatment date across all treatments. For a participant who moves to crossover treatment or re-treatment, the treatment stop date for the original treatment will be the last available treatment stop date prior to crossover/re-treatment.

Duration of exposure to study treatment by dose level will be presented graphically (i.e., duration of treatment plots). A horizontal bar graph of duration of treatment will be

produced to display duration of treatment in weeks for each participant. Participants without a stop date will be indicated as ongoing.

The number of infusions administered for each drug component (prior to any crossover therapy) will also be determined and summarized with mean, median, standard deviation, minimum, and maximum as well as the number and percentage of participants who received a given number of infusions for each drug component. This will be categorized into <4, 4 – 10, and >10 infusions and summarized.

The infusion dose intensity (mg/cycle) will also be listed and summarized for each drug component within the original treatment using mean, median, standard deviation, minimum, and maximum. The dose intensity is calculated by 3-week period (cycles) as the cumulative dose divided by expected duration of exposure (last infusion date – first infusion date + 21)/21). The cumulative dose (mg) is the sum of the actual dose administered during each infusion for a participant throughout the study. A listing of expected duration, dose intensity and a summary of dose modifications by participant will be provided. A listing will also be provided for dose scheduled and received as well as cumulative dose at each time point.

Dose modifications will also be summarized. Duration of dose delay is defined as period from the expected start date of dose to actual start date of current dose. Calculation: (actual start date of current dose - expected start date of dose). Expected start date of dose = actual start date of previous dose + 21. Dose delays will be summarized by the number of participants with any delay, the total number of dose delays per category (0, 1, 2, ≥3 and Not Evaluable) and the delay duration in intervals of 1-21, 22-42 and >42 days.

For participants with dose modifications of reduction, missed dose or dose escalation separate summary tables will be produced for each category of modification and for each drug component showing the number of participants with any modifications, the number of dose modifications per category (0, 1, 2, ≥3 and Not Evaluable) and the reasons for the modifications. A separate listing containing further details including primary reason for the modification, will be produced for each dose modification category.

For participants with incomplete infusions or infusion interruptions separate summary tables will be produced for each of the two modification categories and for each drug component showing the number of participants with any modifications, the number of dose modifications per category (0, 1, 2, ≥3) and the reasons for the modifications. A listing containing further details including primary reason for the modification, will be produced for each of the two modification categories.

6.6. Subsequent Anticancer Therapies

Follow-up anticancer therapies will be coded using GSK Drug coding dictionary version 1.4 or higher and summarized and listed for the All Treated Population. Therapies will be classified by general type (chemotherapy, immunotherapy, hormonal therapy, biologic therapy, surgery and radiotherapy) and the number and percentage of participants with each type will be displayed. Time from study treatment discontinuation to the first post-study treatment anticancer therapy as determined for efficacy will also be included in this summary table.

7. PRIMARY ENDPOINTS ANALYSES

The safety analyses will be based on the All Treated population. Data will be displayed as specified in Section 5.1.2.

7.1. 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. 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). AEs will be graded by the investigator according to the NCI-CTCAE version 4.0 or higher.

An overview of the number and percentage of participants experiencing any AE, any AE leading to permanent discontinuation of study treatment and any AE leading to dose interruption/delay will be produced. The reasons of infusion interrupted but completed and infusion stopped early and not completed will be combined into the dose interruption/delay category. Where multiple action taken options are selected for an AE, within and across drug components, all will be included in the summary to indicate how many participants experienced each. The table will also include the number and percentage of participants experiencing any SAE, any SAE related to study treatment, any fatal SAE and any fatal SAE related to study treatment.

A summary of the number and percentage of participants with any AE by maximum severity grade will be produced with an additional column grouping AEs of grade 3 to 5. 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. The summary will use the following algorithms for counting the participant:

- **Preferred term row**: Participants experiencing the same AE preferred term several times with different grades will only be counted once with the maximum severity grade per dose level received.
- **System organ class (SOC) rows:** Each participant is counted only once at the maximum severity grade at each SOC level per dose level received, although they may have several different preferred term events within the same SOC.
- **Any event row**: Each participant with at least one AE will be counted only once at the maximum grade, for each dose level received, no matter how many events they have.

The summary table 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. An alternative option will be to display descending frequency of PT. If maximum severity grade is missing but the severity grade at onset is available, then this will be used instead. If both are missing and there are no other events with a severity 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 PT and also 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 PT. Additional summary tables for study treatment-related AEs will be provided of the number and percentage of participants for study treatment related AEs with an outcome of fatal by PT, for any study treatment related AE by PT and maximum severity grade and also by SOC, PT and maximum severity grade.

A summary of non-serious AEs that occurred in strictly 5% of the participants or above in any dose level within the cohort and for the All Treated Population 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 in descending frequency of total incidence by SOC and PT and will show both the number of participants and occurrences. The 'ANY EVENT' rows will include the number of participants meeting the 5% threshold.

Additional tables for common AEs will be produced by PT, for all AEs experienced by 5% or more of the total within a cohort and for the All Treated Population, grade 3-5 AEs experienced by 2% or more of the total within a cohort and for the All Treated Population and also for study treatment related grade 3-5 AEs experienced by 2% of more of the total within a cohort and for the All Treated Population. The 'ANY EVENT' row of these tables will be based on the full set of participants meeting the AE rather than the subset of participants with "common" adverse events that meet the threshold. Any percentage which rounds to the threshold (e.g., 4.99%) will be included.

A plot of the percentage of participants experiencing the most common (>=5%) adverse events by maximum severity grade will be produced by regimen cohort**.**

All AEs will be listed. Additionally, a listing of participant IDs for each individual AE will be produced as well as a listing showing the relationship between MedDRA SOC, PT, and Verbatim Text for each AE. Finally, a listing of adverse events recorded as DLTs will be provided for dose escalation cohorts only.

7.2. Adverse Events of Special Interest Analyses

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

Potential AESIs are selected using lists of terms of interest, determined by clinical/safety review to identify each type of event. These are provided in Appendix 6 (Section 11.6.4) and the preferred terms within each AESI terms of interest list will be reviewed and updated on an ongoing basis based on MedDRA dictionary updates.

Summaries of the number and percentage of participants with these events will be summarized by subclass of AESIs, preferred term and maximum severity grade in one table. A similar table will be produced for serious AESIs. The AESIs identified through this process will be listed.

AESIs are also identified on the CRF by the investigator. These will be listed separately.

7.3. Deaths and Serious Adverse Events

All deaths will be summarized based on the number and percentage of participants for the All Treated population. This summary will classify participants by time of death relative to the last dose of GSK3359609 (>30 days or ≤30 days) and by the primary cause of death in the order listed in the eCRF. Participants who either progressed on monotherapy and crossed over to combination therapy with Pembrolizumab or responded on their original treatment and were re-treated following progression will be classified as 'Alive at crossover/re-treatment' as applicable in the summary table. A supportive listing will also be generated to provide specific details for participants who died.

All SAEs will be tabulated based on the number and percentage of participants who experienced the events. Additionally, separate summaries will be provided for study treatment related SAEs, fatal SAEs, study treatment related fatal and non-fatal SAEs and common (>=2 events) grade 3-5 SAEs. The summary tables will be displayed in descending frequency of total incidence by PT. Additional tables will be produced displaying SAEs in descending frequency of total incidence by SOC and PT, using alphabetic order when PTs with equal incidence occur within the SOC as well as SAEs by maximum toxicity and descending frequency of PTs.

Finally, a table will be provided summarizing the number of occurrences as well as the number of participants with SAEs, the number of treatment-related SAEs, fatal SAEs and treatment-related fatal SAEs. In the table, this information will be provided for all event types and for each PT. A study treatment related SAE is defined as an SAE for which the investigator classifies the relationship to study treatment as "Yes" or determined by the study team. 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' if missing.

SAEs are included in the listing of all AEs. Separate supportive listings with participant-level details will be generated for non-fatal SAEs and the reasons for considering each SAE as serious.

7.4. Adverse Events Leading to Discontinuation of Administered Treatment

AEs leading to discontinuation of study treatment will be summarized separately in descending frequency of total incidence by PT only. In addition, AEs leading to discontinuation of study treatment will be listed.

7.5. Events of Clinical Interest Analyses

These are selected events considered of clinical interest recorded during the time period beginning with the administration of study treatment through to 30 days following discontinuation of study treatment. Events of clinical interest (ECI) include:

1. Overdose of study drug(s) (GSK3359609 and pembrolizumab (Part 2 only)) that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) laboratory value that is greater than or equal to 3 times the upper limit of normal and an elevated total bilirubin laboratory value that is greater than or equal to 2 times the upper limit of normal and, at the same time, an alkaline phosphatase laboratory value that is less than 2 times the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.
3. Infection with COVID-19 coronavirus, whether suspected based on exposure history and clinical signs and symptoms or confirmed by laboratory test in the context of exposure history and clinical signs and symptoms. Reporting will follow WHO and GSK guidelines.

The events will be determined from AE tables and liver result tables. Additionally, listings of the COVID-19 related PDs and assessments and symptoms of COVID-19 AEs will be provided.

7.6. 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.

7.7. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of hematology, chemistry, cardiac function, thyroid function, and urinalysis tests will be based on GSK Core Data Standards. Displays will be based on the All Treated population and data will be displayed as specified in Section 5.1.2.

The assessment of laboratory toxicities will examine the laboratory tests listed in protocol Table 28. For laboratory tests which are gradable, values will be graded and reported

using the Common Terminology Criteria for Adverse Events (CTCAE v4.0). In some cases, there will be two bi-directional parameters (hyper- and hypo-) created and the tests will be graded by CTCAE v4.0 in both directions.

Summaries of worst-case grade increase from baseline grade will be provided for all the laboratory tests that are gradable by CTCAE v4.0. These summaries will display the number and percentage of participants in each baseline grade category versus the number in each maximum grade category at each scheduled visit and for the worst-case post-baseline. The worst-case summary will use all available scheduled and unscheduled visits post-baseline. Missing baseline grade will be assumed as grade 0. For laboratory tests that are graded for both low and high values, summaries will be displayed separately and labeled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

For laboratory tests that are not gradable by CTCAE v4.0, 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 at each scheduled visit as well as for the worst-case post-baseline. Participants with missing baseline value are assumed to have normal baseline value. If a participant has a decrease to low and an increase to high during the same scheduled visit or for worst-case, then the participant is counted in both the "Decrease to Low" categories and the "Increase to High" categories. The worst-case summary will use all available scheduled and unscheduled visits post-baseline to determine if the participant has at least one low and/or high value for each laboratory test.

For the following laboratory parameters, every participant will be assessed separately for low and/or high values. The following groups indicate whether laboratory severity grades are assessed according to a low value, high value, or separately for both low and high values.

- **Low Value**: Maximum Severity (Grade 4) for the following laboratory tests: white blood cells (WBC), neutrophils, platelets, and albumin; Normal Range for the laboratory tests: RBC, haematocrit, total protein and basophils
- **High Value**: Maximum Severity (Grade 4) for the following laboratory tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase and creatinine; Normal Range for the laboratory tests: blood urea nitrogen (BUN), and eosinophils.
- **Low and High Values**: Potassium, sodium, glucose, and calcium, haemoglobin, lymphocytes will be assessed for the maximum severity grade for both low and high values. Monocytes will be assessed for the Normal Range for both low and high values. For these laboratory parameters, every participant will be assessed separately for high and low values (i.e., separate summary on severity grade/normal range will be produced for high glucose (hyperglycemia) and low glucose (hypoglycemia), high potassium (hyperkalemia) and low potassium (hypokalemia), high sodium (hypernatremia) and low sodium (hyponatremia), high calcium (hypercalcemia) and low calcium (hypocalcemia), high hemoglobin (hemoglobin increased) and low hemoglobin (anemia), high lymphocytes (lymphocyte count increased) and low

lymphocytes (lymphocyte count decreased) and high monocytes (monocytosis) and low monocytes (monocytopenia).

Separate tables for hematology, and chemistry laboratory tests will be produced. Cardiac function tests will be included with hematology laboratory tests and thyroid function tests will be included with chemistry laboratory tests. Unless otherwise specified, the denominator for calculating percentages at each scheduled visit will be based on the number of participants with a non-missing value at each visit. The denominator for worst-case will be the number of participants with a non-missing post-baseline value.

Additionally, summary tables for hematology (and cardiac function) and chemistry (and thyroid function) will summarize the change from baseline at each scheduled visit using mean, median, standard deviation, minimum and maximum.

All laboratory data will be listed. A supporting listing of laboratory data for participants with any value outside the normal range or of potential clinical importance will also be provided.

7.7.1. Analyses of Liver Function Tests

Summaries of hepatobiliary laboratory events including possible Hy's law cases will be provided in addition to liver monitoring/stopping events, if data permits. In addition, a listing of participants meeting hepatobiliary laboratory criteria post-baseline, a liver stopping event profile and a listing of liver monitoring/stopping event reporting will be provided. Finally, an e-DISH plot of maximum post baseline total bilirubin versus maximum post baseline ALT will be created.

7.8. 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. Displays will be based on the All Treated population and data will be displayed as specified in Section 5.1.2.

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

7.8.1. ECG

The key ECG measurement taken in this study will be the uncorrected QT interval (msec). The QT correction (QTc) will then either be calculated automatically or it will be calculated manually using the Fridericia formula (QTcF (msec)). In the case QTcF is required to be calculated manually, RR interval (msec) will also be recorded on the eCRF. Additionally, an overall interpretation of the ECG reading will be provided (normal, abnormal not clinically significant, abnormal clinically significant, no result and unable to evaluate).

For Part 1 only, on Day 1 the ECG measurements will be performed in triplicate at pre-dose (within 60 minutes prior to start of GSK3359609 infusion) and at the following

times following the end of infusion: 30 minutes, 4 hours and 24 hours. On Day 22 measurements will be performed in triplicate at pre-dose and on Day 85 measurements will be performed in triplicate at pre-dose and 30 minutes following the end of infusion. All other ECG measurements in Part 1 and all ECG measurements in Part 2 are performed as single measurements at pre-dose only.

For the numeric results recorded in triplicate, the mean of the available values (even if less than 3 are available) will be taken and used throughout the table and figure summaries. All available values will be provided on listings. For the overall interpretation, the worst of the recorded readings will be used in the order from worst to best to missing as: abnormal clinically significant, abnormal not clinically significant, normal, unable to evaluate, no result.

A summary of the number and percentage of participants who had each of the ECG findings will be displayed for baseline and by each scheduled visit and assessment time as well as for the worst-case post-baseline. The worst-case summary will use all available scheduled and unscheduled visits post-baseline to determine the worst finding. A summary of the change from baseline will also be provided at each scheduled visit and assessment time using mean, median, standard deviation, minimum and maximum.

The QTc values based on Fridericia formula will be rounded to an integer and the values will be categorized into the following ranges: Grade 0 (<450), Grade 1 (450-480), Grade 2 (481-500), and Grade 3 (≥501). Summaries of grade increases relative to baseline will be provided for the categories of 'No Change or Decrease to <450', 'Any Increase ≥450', 'Increase to ≥450 to ≤480', 'Increase to ≥481 to ≤500' and 'Increase to ≥501'.

QTcF shifts from the baseline value to the worst-case post-baseline value will be plotted with the baseline value displayed on the x axis. The figure will have reference lines at 480 and 500 msec on both axes. The change from baseline in QTcF values will be categorized into the clinical concern ranges: 31-60 and >60 msec. A summary of change from baseline in QTcF value will display the number and percentage of participants with a change within each range for the worst-case post-baseline. Participants with missing baseline values will be excluded from all the QTcF summaries.

Listings of abnormal ECG findings and a listing of ECG values will be provided.

7.8.2. Vital Signs

Change from baseline values of vital signs (Systolic and diastolic blood pressure (BP), pulse rate, temperature and weight) will be summarized by scheduled visit using mean, median, standard deviation, minimum and maximum. If more than one measurement is collected within a visit, then the mean will be taken and used in the summary. Listings of all vital signs values by participant and visit will be provided.

In addition, vital signs values will be categorized 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)
- Pulse rate (beats/min): Low (<60), Normal (60-100), and High (>100)

Summaries of increase in systolic and diastolic blood pressure from baseline with respect to the categories defined above will be performed. These summaries will display the number and percentage of participants with any grade increase (i.e., increase of grade 1-3), an increase of grade 2-3 and then separately, increases to grade 1, grade 2 and grade 3 and for the worst-case post-baseline.

Pulse rate is summarized for the worst-case pulse rate category experienced relative to the normal range post-baseline. Participants are counted in the worst-case category that their value changes to (low, normal or high) unless there is no change in their category. Participants whose value category is unchanged (e.g., High to High), or whose value became normal, are recorded in the "To Normal or No Change" category. Participants are counted twice if the participant has values that changed 'To Low' or 'To High', so the percentages may not add to 100%. Participants with missing baseline data are assumed to have normal baseline values.

7.8.3. LVEF

ECHO/MUGA is only standardly collected at the screening visit (within 28 days prior to first dose of study treatment) and is only required during the treatment phase if clinically indicated. All values collected will be listed.

7.8.4. Performance Status

ECOG performance status will be summarized using the number and percentage of participants with each status at baseline and each post-baseline scheduled visit as well as the last assessment post baseline, best case post baseline and worst-case post baseline. Additionally, a summary of change from baseline, categorized into improved, no change, deteriorated (ordered best to worse), will be performed by scheduled visits, as well as the last assessment post baseline, best case post baseline and worst-case post baseline.

The last assessment post baseline will be the grade recorded at the last visit after treatment start and prior to crossover (if applicable). The best- and worst-case post baseline will be the minimum and maximum grade respectively, recorded after treatment start and prior to crossover (if applicable). For the change from baseline table, the grade identified will be used to compare to baseline and determine the change category.

A supporting listing will also be provided.

8. SECONDARY ENDPOINTS ANALYSES

8.1. Pharmacokinetic Analyses

Pharmacokinetic parameters will be calculated by, or under the auspices of, CPMS, Quantitative Science, GlaxoSmithKline.

Statistical analysis of GSK3359609, pembrolizumab, chemotherapy and GSK3174998 pharmacokinetic parameters, as data permits, will be performed by, or under the direct auspices of Oncology Statistics and Programming, GlaxoSmithKline.

The pharmacokinetic (PK) analyses will be based on the PK Concentration, and PK Parameter populations, unless otherwise specified.

Table 4 provides an overview of the planned Pharmacokinetic analyses.

Table 4 Overview of Planned Pharmacokinetic Analyses

Endpoint / Parameter/ Display Type	Untransformed							Log-Transformed						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
PK Concentrations														
Plasma GSK3359609 Concentrations				Y	Y	Y	Y					Y	Y	
Plasma Pembrolizumab Concentrations				Y	Y		Y					Y		
Plasma GSK3174998 Concentrations				Y	Y	Y	Y					Y	Y	
PK Parameters														
Plasma GSK3359609 Parameters				Y			Y	Y			Y	Y	Y	
Plasma Pembrolizumab Parameters				Y			Y	Y			Y			
Plasma GSK3174998 Parameters				Y			Y	Y			Y	Y	Y	

NOTES :

- T = Table, F = Figure, L = Listings, Y = Display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual participant observed raw data.

8.1.1. Endpoint / Variables

8.1.1.1. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 11.5.3 Reporting Standards for Pharmacokinetic).

Drug concentration-time data will be listed for each participant and summarized by descriptive statistics at each time point by regimen cohort and dose level. Additionally, individual, mean and median concentration plots will be provided for treatment Cycle 1 data.

8.1.1.2. 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 Phoenix WinNonlin 6.3 or higher (CERTARA, NJ). All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed in Table 5 may be determined from the concentration-time data, as data permits.

Table 5 Pharmacokinetic Parameters

Parameter	Parameter Description
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
Tmax	Time to reach Cmax, determined directly from the concentration-time data.
Ctau	Concentration at the end of dosing interval.
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-τ)	Area under the concentration-time curve over the dosing interval.
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
λz	apparent terminal phase elimination rate constant (single dose)
$t_{1/2}$	Apparent terminal phase half-life will be calculated as: $t_{1/2} = \ln 2 / \lambda z$
CL	systemic clearance of parent drug

NOTES:

- Additional parameters may be included as required.

8.1.2. 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 (STD), coefficient of variation (%CV = 100*(sqrt (exp(STD^2) – 1))) [NOTE: STD = STD of natural log ($\log_e$) transformed data]), geometric mean, 95% confidence interval for the geometric mean and standard deviation of natural 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.

8.1.3. Population of Interest

The secondary pharmacokinetic analyses will be based on the Pharmacokinetic population, unless otherwise specified.

8.1.4. Statistical Analyses / Methods

Dose Proportionality:

If more than two dose levels are required to reach RP2D within the dose escalation cohorts, dose proportionality of GSK3359609 AUC(0-τ), Ctau and Cmax will be evaluated at Cycle 1. Regimen cohorts with the same dose levels may be combined to increase the number of participants included in the model.

GSK3359609 and GSK3174998 AUC(0-τ), Ctau and Cmax will be assessed separately for dose proportionality using the power model as described below:

$y = \alpha * dose^{\beta}$

where y denotes the pharmacokinetic parameter and α is an intercept term. Dose proportionality in this model equates to β=1. A point estimate and 90% confidence interval will be derived for β. βwill be estimated by regressing the log_e-transformed PK parameter on log_e dose.

$Log_e(PK\ parameter) = \alpha + \beta * log_e(dose)$

The power model will be fitted by restricted maximum likelihood (REML) using SAS Proc Mixed. Both the intercept and slope will be fitted as random effects. If the model with random intercept and slope fails to converge, the model will be refitted with slope as a fixed effect. If the mixed effects model still does not converge then a fixed effects power model will be fitted. The mean slope will be estimated from the power model and the corresponding 90% confidence interval calculated.

Additionally, dose proportionality for GSK3359609 and GSK3174998 at Cycle 1 will be assessed using Analysis of Variance (ANOVA) models for log_e-transformed, dose-normalized AUC(0-τ), Ctau and Cmax with a fixed effect term for treatment group (dose level). Differences in least squares means between each dose and the reference dose will be calculated. These differences and the corresponding 90% CIs will be back-transformed (exponentiated). The reference dose will be chosen based on the lowest clinically relevant dose over which PK can be adequately described and all other doses will be test doses. PK parameters will be dose-normalized prior to log_e-transformation by multiplying by reference dose/dose.

Accumulation

To assess accumulation of GSK3359609, Pembrolizumab and GSK3174998, where data allow, ANOVA with a fixed effect term for day and a random effect term for participant

will be performed on $\log_e$-transformed Ctau for each treatment group (dose level) separately. The observed accumulation ratio (Ro) will be estimated by exponentiating the difference in least squares means (e.g., end of cycle concentration Ctau after 6 cycles (Day 106) – Cycle 1 end of cycle Ctau) and the associated 90% confidence interval.

8.2. Population Pharmacokinetic Analyses

Population PK analyses may be conducted under the direction of CPMS, Quantitative Sciences, GSK. The data from this study may be combined with the data from other studies for a population PK analysis, which may be reported separately.

8.3. Efficacy Analyses

The All Evaluable population will be used at the time of the interim analysis. For final analysis, the All Treated Population will be used. Data will be displayed as specified in Section 5.1.3.

Table 6 provides an overview of the planned efficacy analyses. All efficacy data and calculated endpoints will be listed.

Table 6 Overview of Planned Efficacy Analyses

Endpoint / Parameter	Absolute						
	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
Tumor Measurement (CT or MRI Scan Assessments)							
Best tumor percentage change from baseline (irRECIST)					Y		
Best tumor percentage change from baseline (RECIST1.1)					Y		
Endpoints based on Best Overall Response (confirmed and unconfirmed)							
Overall Response Rate (ORR) (irRECIST)				Y			Y
Overall Response Rate (ORR) (RECIST1.1)				Y			Y
Disease Control Rate (DCR) (irRECIST)				Y			Y
Disease Control Rate (DCR) (RECIST1.1)				Y			Y
Survival							
Overall Survival (OS)	Y	Y					Y
Time to Event							
Progression Free Survival (PFS) (RECIST1.1)	Y	Y					Y
Time to Response (TTR) (RECIST 1.1)	Y	Y					
Duration of Response (DOR) (RECIST1.1)	Y	Y					

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e., modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e., descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual participant observed raw data.

8.3.1. Endpoints / Variables

Tumor response i.e., complete response (CR/irCR), partial response (PR/irPR), and stable disease (SD/irSD), and progressive disease (PD/irPD) will be based on the assessments from the investigators' review of objective evidence (e.g., radiological scan). Overall responses were measured in accordance with the RECIST v1.1 and irRECIST.

Assessments start at Week 9 for all but the 5-FU/Platinum chemotherapy combination cohort which start at Week 18. Assessments will then be performed every 9 weeks from the start of treatment until Week 54 then every 12 weeks thereafter until disease progression; participants who discontinue for reasons other than progression will be followed for progression until the start of subsequent anticancer therapy every 9 weeks until Week 54 then every 12 weeks thereafter. Participants who attain a CR and met the requirements defined in Section 5.4 of the protocol for early discontinuation of study treatment and discontinue study treatment will undergo disease assessments every 12 weeks until progression.

Participants who crossover from monotherapy to the combination therapy, disease assessments subsequent to crossover will be disregarded in the summarization of monotherapy.

The efficacy endpoint analysis will be based on ORR, DCR, PFS, OS, DOR and TTR. The response endpoints ORR and DCR will be primarily based on irRECIST but may be repeated by RECIST v1.1. The survival endpoints of PFS, TTR and DOR will be by RECIST v1.1 only.

8.3.2. Summary Measure

Lesion assessment method and timing, evaluation of disease, disease progression and response criteria will be conducted according to RECIST (version 1.1) and irRECIST [Wolchok, 2009; Nishino, 2013] as outlined in Appendix 6 of the protocol. The irRECIST guidelines will be used to determine treatment decisions and will be used for the primary analysis of anticancer activity.

Best Overall Response

Best overall response (BOR) will be derived to calculate the efficacy endpoints. Best overall response is defined as the best response recorded from enrollment/randomization into a cohort until the criteria for progression are met (taking into account any requirement for confirmation), the initiation of new anticancer therapy/crossover or death, whichever is earliest. The order from best to worst of the available responses is CR/irCR, PR/irPR, stable disease (SD/irSD), progressive disease (PD/irPD) and not evaluable (NE).

- To be assigned a status of SD/irSD, follow-up disease assessment(s) must have met the SD/irSD criteria at a minimum of 8 weeks (56 days) from baseline. Note that duration of stable disease (SD for RECIST/irSD for irRECIST) is measured from the date of first dose in non-randomized cohorts or the date of randomization in randomized cohorts until the last adequate non-PD/irPD response.

- If the minimum of 8 weeks (56 days) for SD/irSD is not met, the best overall response will depend on the subsequent assessments. If an assessment of PD follows the assessment of SD and SD does not meet the minimum 8-week requirement the best response will be PD. Alternatively, participants with no further adequate assessments, after an SD assessment not meeting the minimum time criteria, will be considered not evaluable.
- A participant without any adequate post-baseline assessments will have a BOR of NE.

The number and percentage of participants for each available BOR will be provided, both with and without confirmation, and for RECIST v1.1 and irRECIST.

RECIST (version 1.1) Criteria

Best overall response will be derived for RECIST v1.1 with confirmation of CR/PR and without. Best overall response without confirmation can be based on just one occurrence of the best available response available for the participant. For the derivation with (consecutive) confirmation, these additional points need to be considered:

- To be assigned a status of confirmed CR/PR, a confirmatory disease assessment should be performed no less than 4 weeks (28 days) after the criteria for response are first met.
- Responses of CR/PR that do not meet the requirements of confirmed CR/PR are still eligible to be considered SD if it has met the SD duration criteria.
- Assessments that are not done or are not evaluable can be disregarded when checking for confirmation. For example, a participant with PR-NE-PR is a confirmed response.

Confirmed best overall response per RECIST v1.1 will be derived according to Table 7.

Table 7 Best Overall Response per RECIST 1.1

Overall Response First time point	Overall Response Subsequent Time Point (minimum of 28 days later)	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[1]
CR	SD	SD provided minimum criteria for SD duration met[2], otherwise PD
CR	PD	SD provided minimum criteria for SD duration met[2], otherwise PD
CR	NE	SD provided minimum criteria for SD duration met[2], otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met[2], otherwise PD
PR	NE	SD provided minimum criteria for SD duration met[2], otherwise NE
NE	NE	NE

[1] If CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the participant had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.
[2] Minimum criteria for SD disease duration is at least 56 days to qualify as SD for BOR.
Note: If Best Overall Response is CR or PR, the participant is classified as a responder for the ORR analysis.

irRECIST Criteria

The principle of deriving BOR, with and without confirmation, per irRECIST (irBOR) closely follows RECIST v1.1. The exception is that participants with disease progression by RECIST version 1.1 guidelines are required to have a confirmatory disease assessment at least 4 weeks after disease progression was declared in order to confirm disease progression by irRECIST guidelines. Additionally, unconfirmed irPD will not override a subsequent irBOR of irSD, irPR, or irCR, meaning that irPR or irSD can be assigned as irBOR, providing that the criteria for confirmation of irPD are not met.

If irBOR is irPD and is confirmed consecutively, irBOR will be termed as irCPD even if there are subsequent irSD, irPR, or irCR after the confirmed irCPD. If irBOR is irPD but not confirmed, and there is no subsequent irSD, irPR, or irCR (e.g., NE or lost follow-up), the irBOR will be termed as irUPD.

If irBOR is irPD but not confirmed and there is no subsequent irSD, irPR, or irCR (e.g., NE or lost follow-up) due to study conclusion, the confirmed BOR will be termed as irCPD.

Both irCPD and irUPD will be categorized as irPD in the summary of confirmed irBOR.

8.3.2.1. ORR and DCR

Overall response rate (ORR) and disease control rate (DCR) per RECIST v1.1 criteria are defined below. ORR and DCR per irRECIST criteria are defined similarly.

- ORR is defined as the percentage of participants achieving a (confirmed) CR/PR as BOR, as assessed by the investigator per RECIST 1.1 criteria.
- DCR is defined as the percentage of participants achieving a (confirmed) CR/PR, or SD as BOR, as assessed by the investigator per RECIST 1.1 criteria. A status of SD will be assigned if the follow-up disease assessment has met the SD criteria at least once after the date of first dose/randomization at a minimum of 8 weeks (56 days; minimum of 9 weeks minus one-week visit window).
- DCR with SD durability is defined as the percentage of participants achieving a (confirmed) CR/PR, or SD≥18 weeks. A status of SD≥18 weeks will be assigned if the follow-up disease assessment has met the SD criteria at least once after the date of first dose/randomization at a minimum of 17 weeks (119 days) considering a one-week visit window.

The number and percentage of participants achieving ORR and DCR (9 and 18 weeks) will be provided for both RECIST v1.1 and irRECIST. Percentages will be calculated using the number of participants within each cohort. The 2-sided 95% exact (Clopper-Pearson) confidence limits for the binomial proportion will also be included.

8.3.2.2. Progression-Free Survival

PFS is defined as the interval between the date of first dose of study treatment (or date of randomization for randomized cohorts) and the date of disease progression (taking into account any requirement for confirmation when needed) according to radiological response from investigator assessment, or death due to any cause, whichever occurs earlier.

Participants whose disease progressed or who 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. For this type of censoring due to extended time without an adequate assessment, the date of 'last adequate disease assessment' will be defined as the date of the last radiological assessment by investigator that shows no disease progression prior to the missing assessments, the start date of new anticancer therapy or crossover, the date of first progression, or the date of death, whichever is the earliest.

Extended time without adequate assessment
As the assessment schedule changes through the course of the study (i.e., every 9 weeks until Week 54 then every 12 weeks thereafter until disease progression). Specifically, participants who attain a CR and met the requirements defined in Section 5.4 in the protocol for early discontinuation of study treatment and discontinue study treatment will undergo disease assessments every 12 weeks until progression. The following rules will be used for identifying the duration of extended time without adequate assessment.

- If PFS event is on or prior to Week 64, then a participant will be identified as an extended loss to follow up if the participant did not have an adequate disease assessment during the time period of 140 days (18 weeks + two one-week windows) prior to PFS event;

- Else if PFS event is after Week 64 and on or prior to Week 67, then a participant will be identified as an extended loss to follow up if the participant did not have an adequate disease assessment during the time period of 154 days (20 weeks + two one-week windows) prior to PFS event;

- Else if PFS event is after Week 67 and on or prior to Week 77, then a participant will be identified as an extended loss to follow up if the participant did not have an adequate disease assessment during the time period of 168 days (22 weeks + two one-week windows) prior to PFS event;

- Else if PFS event is after Week 77, then a participant will be identified as an extended loss to follow up if the participant did not have an adequate disease assessment during the time period of 182 days (24 weeks + two one-week windows).

Crossover/Anticancer Therapy
For participants who receive subsequent anticancer therapy including radiotherapy and cancer-related surgery or crossover from monotherapy to combination therapy the following rules will apply:

- If the start date of anticancer therapy/crossover 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 anticancer therapy/crossover 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 (last assessment with any investigator radiological response excluding NE) that is on or before the date of initiation of anticancer therapy/crossover. The date of response at the last adequate assessment will be used as the censoring date.
- If a participant has only a baseline visit or does not have an adequate assessment that is on or before the date of initiation of anticancer therapy/crossover, PFS will be censored at the date of first dose or randomization.

If a participant has neither progressed nor died nor started new anticancer therapy nor crossed over, then PFS will be censored at the date of the last adequate assessment.

If there is no adequate baseline assessment, the participants will be censored at their date of first dose for participants in non-randomized cohorts or at the date of randomization for participants in randomized cohorts. Participants without any adequate post-baseline tumor assessments will be censored at the date of first dose for participants in non-randomized cohorts or at the date of randomization for participants in randomized cohorts.

A summary of the assignments for progression and censoring dates for PFS per RECIST v1.1 criteria are specified in the following Table 8.

Table 8 Assignments for Progression and Censoring Dates for PFS Analysis per RECIST v1.1

Scenario	Date of Event (Progression/Death) or Censoring	Outcome Event (Progression/Death) Or Censored
No adequate[1] baseline tumor assessments and the participant has not died	First dose or randomization[2]	Censored
No adequate[1] post-baseline assessments and the participant has not died	First dose or randomization[2]	Censored
Progression documented between scheduled visits	Date of assessment of progression	Event
With post-baseline assessment but no progression (or death)	Date of last adequate assessment of response[1]	Censored
No adequate post-baseline assessment before start of new anticancer therapy	First dose or randomization[2]	Censored
With adequate[1] post-baseline assessment and new anticancer therapy started (prior to documented disease progression or death)[3]	Date of last adequate assessment of response[1] (on or prior to starting anticancer therapy)	Censored
With adequate[1] post-baseline assessment and crossover started (prior to documented disease progression or death)[3]	Date of last adequate assessment of response[1] (on or prior to starting crossover)	Censored
Death before first scheduled assessment	Date of death	Event
Death between adequate assessment visits	Date of death	Event
Death or progression after two or more missed scheduled assessment	Date of first dose or randomization (if there is no adequate post-baseline assessments) or date of last adequate assessment of response (prior to missed assessments): If the time difference between PD/death and last adequate disease assessment/start date is more than the duration of extended time without adequate assessment, PFS will be censored at the last adequate	Censored

Scenario	Date of Event (Progression/Death) or Censoring	Outcome Event (Progression/Death) Or Censored
	disease assessment prior to PD/death/start date	

1. An adequate assessment is defined as an assessment where the Investigator determined response is CR, PR, or SD.
2. The date of first dose of GSK3359609 or the randomization date.
3. If PD and New anticancer therapy/crossover occur on the same day assume the progression was documented first. The outcome is progression (event) and the event date is the date of the assessment of progression. If anticancer therapy/crossover is started prior to any adequate assessments, censoring date should be the date of first dose or randomization.

The non-parametric Kaplan-Meier method will be used to estimate the survival curves for PFS within the All Treated population for each cohort, as specified in Section 5.1.3. Kaplan-Meier plots of the PFS survival curves will be presented. Kaplan-Meier estimates for the median PFS, the first and third quartiles and the survival estimates at 6 months will be presented, along with 95% CIs. CIs for quartiles will be estimated using Brookmeyer-Crowley method [Brookmeyer, 1982] and based on the loglog transformation.

8.3.2.3. Overall Survival (OS)

OS is defined as the interval between the date of first assigned study therapy/randomization and date of death due to any cause. The length of this interval is calculated as the date of death minus date of first assigned study therapy/randomization plus 1 day.

In the absence of confirmation of death or if the death date is partial, survival time will be censored at the last date the participant is known to be alive. Only participant contacts recorded in the eCRF can be used for the calculation of last date of contact. The date of censorship will be the latest from either the follow-up record or the last assessment. Participants lacking data beyond the day of first dose/randomization will have their survival time censored at the date of first dose/randomization. When calculating overall survival, all deaths following crossover or re-treatment will be included.

The non-parametric Kaplan-Meier method will be used to estimate the survival curves for OS within the All Treated population for each cohort, as specified in Section 5.1.3. Kaplan-Meier plots of the OS survival curves will be presented. Kaplan-Meier estimates for the median overall survival, the first and third quartiles and the survival estimates at 6 months will be presented, along with 95% CIs. CIs for quartiles will be estimated using Brookmeyer-Crowley method [Brookmeyer, 1982] and based on the loglog transformation.

8.3.2.4. Duration of response (DOR) per RECIST v1.1

Duration of response (DOR) per RECIST v1.1 will be summarized for participants with a confirmed CR or PR. It is defined as the interval of time in months from the date of the first documented evidence of a response (confirmed CR or PR) to the date of first documented evidence of disease progression according to radiological response from

investigator assessment per RECIST v1.1, or date of last adequate assessment of response or the date of death due to any cause (whichever occurs earlier). Censoring rules will follow those of the PFS analysis per RECIST v1.1 where they apply.

The non-parametric Kaplan-Meier method will be used to estimate the survival curves for DOR within the All Treated population for each cohort where data permits. Kaplan-Meier plots of the DOR survival curves will be presented. Kaplan-Meier estimates for the median DOR, the first and third quartiles, along with 95% CIs. CIs for quartiles will be estimated using Brookmeyer-Crowley method [Brookmeyer, 1982] and the loglog transformation. Only the subset of participants who show a response of CR or PR from All Treated population will be included in these analyses.

8.3.2.5. Time to response (TTR) per RECIST v1.1

Time to overall response (TTR) will be summarized at the final analysis for the All Treated Population with a confirmed CR or PR and is defined as the time from date of first dose of study treatment/randomization to the date of first documented confirmed (≥4 weeks) CR or PR. Although only confirmed CR and PR will be included, the first date of the (at least) two occurrences of the response will be used.

The non-parametric Kaplan-Meier method will be used to estimate the survival curves for TTR within the All Treated population for each cohort where data permits. Kaplan-Meier plots of the TTR survival curves will be presented. Kaplan-Meier estimates for the median TTR, the first and third quartiles, along with 95% CIs. CIs for quartiles will be estimated using Brookmeyer-Crowley method [Brookmeyer, 1982] and the loglog transformation. Only the subset of participants who show a confirmed CR or PR from All Treated population will be included in this analysis.

8.3.2.6. Change of Tumor Measurement

Best percentage change from baseline will be the minimum percentage change from baseline across visits on or prior to the first documented PD or crossover/new anticancer therapy.

(1) If PD occurred, all disease assessments until the PD date will be considered.

(2) If PD is unavailable, all disease assessments before crossover/new anticancer therapy, will be considered

Waterfall plots will display the best percentage change in tumor measurement (the minimum value) for both irRECIST and RECIST v1.1 with the respective unconfirmed BOR included in the display.

8.3.3. Population of Interest

The efficacy analyses will be based on the All Treated population for the final analyses.

Table 9 Population of interest for Efficacy Endpoints

Endpoints	IA / IPM	SAC
PFS/OS	All Treated Population	All Treated Population
TTR/DOR	All Evaluable Population	All Treated Population
ORR/DCR	All Evaluable Population	All Treated Population

8.3.4. Statistical Analyses / Methods

Planned displays will be based on GSK Data Standards and statistical principles.

8.3.4.1. Statistical Methodology Specification

PFS and OS will be summarized and plotted using the Kaplan-Meier method if the data warrant.

Statistical Analyses
Endpoint(s)
• PFS • OS • DOR • TTR
Method of Analysis
• Kaplan-Meier (if data warrant) for PFS, OS, TTR and DOR

9. OTHER STATISTICAL ANALYSES

9.1. Pharmacodynamic and Biomarker Analyses

The pharmacodynamic and biomarker analysis for this study will be defined separately in an independent analysis plan. All details of endpoints, populations, analyses and display of results will be provided.

9.2. Pharmacokinetic/Pharmacodynamic Analyses

CCI

[redacted]

9.3. Pharmacogenetic Analyses

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

9.4. Immunogenicity Analyses

Serum samples will be collected and tested for the presence of antibodies that bind to GSK3359609 and pembrolizumab, or GSK3359609 and GSK3174998, refer to Section 10.7.5 in the protocol. These samples may also be tested for presence of antibodies that bind to Chinese Hamster Ovary (CHO) host cell proteins such as phospholipase B- like 2 (PLBL2).

The actual date and time of each blood sample collection will be recorded. Details of blood sample collection (including volume to be collected), processing, storage, and shipping procedures are provided in the SRM. Binding assays will primarily be used.

Participants who have been treated will be initially assessed for anti-drug antibodies (ADA) with a screening assay at each planned visit. Where there is a positive screening assay result, a confirmatory assay will be performed. Positive confirmatory results will be accompanied by a titer value indicating the level of ADA detected. The results from the screening and confirmatory assay will be listed alongside the titer value. The incidence rates of positive immunogenicity via confirmatory assay will also be summarized, and ADA data may potentially be pooled with ADA data from the Phase I (204691) or other trials.

CCI

[redacted]

CCI

9.6. Patient Reported Outcomes

CCI

10. REFERENCES

Brookmeyer, R. and Crowley, J. A confidence interval for the median survival time. Biometrics. 1982; 38:29-41. doi:10.2307/2530286

Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the Treatment of Non‐Small-Cell Lung Cancer. N Engl J Med. 2015; 372:2018-2028.

Nishino M, Giobbie-Hurder A, Gargano M, et al. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res. 2013; 19:3936-3943.

Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. Clin Cancer Res 2009;15(23): 7412-20.

11. APPENDICES

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

11.1.1. Exclusions from Per Protocol Population

Not applicable.

11.2. Appendix 2: Schedule of Activities

11.2.1. Protocol Defined Schedule of Events

See Protocol Section 8.

11.3. Appendix 3: Assessment Windows

11.3.1. Definitions of Assessment Windows for Analyses

Duration of SD for both RECIST v1.1 and irRECIST is calculated when SD is the unconfirmed best overall response. A one-week visit window was considered in the duration of SD, i.e., a minimum of 8 weeks for iSD (irSD≥9 weeks) and 17 weeks for SD≥18 weeks. This is a result of post-baseline assessments, a window of ±7 days is permitted to allow for flexible scheduling.

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

11.4.1. Study Phases

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
Post-Treatment	Date > Study Treatment Stop Date + 30

11.4.1.1. 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

NOTES:

- Please refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

11.4.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date is on or after treatment start date or missing & on or before treatment stop date. ○ Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 30. ○ AE Start Date is missing

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.
- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

11.5. Appendix 5: Data Display Standards & Handling Conventions

11.5.1. Reporting Process

CCI

11.5.2. 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
• Unscheduled visits will not be included in summary tables and/or figures except for worst post – baseline analysis. • All unscheduled visits will be included in listings.
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.

11.5.3. 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 (CPMS) 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 (v 4.0)
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(v 4.0) 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 as data permits: Cmax, tmax, Ctau, AUC(0-t), AUC(0-τ), AUC(0-∞), λz, t½, CL
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to GUI_51487(v 4.0)
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to Reporting Effort specific Mockup specifications.

11.6. Appendix 6: Derived and Transformed Data

11.6.1. 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. • 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
• Calculated as the number of days from First Dose Date/Randomization Date: 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 Data ≥ First Dose Date/Randomization Date → Study Day = Ref Date – (First Dose Date/Randomization Date) + 1 • For participants in non-randomized cohorts, First Dose Date will be used in study day for both safety and efficacy. • For participants in randomized cohorts, First Dose Date will be used in study day for safety and Randomization Date will be used in study day for efficacy.
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 CR) is assigned to the latest date of disease assessments within a particular visit; for other response categories (SD [or Non-CR/Non-PD], NE, PD), the date of response is assigned to the earliest date of disease assessments within a particular visit.
Date of New Anticancer Therapy/Crossover
• Derived as the earliest date of new anticancer therapy, radiotherapy, cancer-related surgical procedure, or the first dosing date of the combination therapy after crossover. • Missing or partial dates will be imputed for derivation of date of new anticancer therapy following rules specified in Section 11.7.2.
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): o If the reference date is on or after the event date, then the elapsed time is the reference date minus the event date + 1 o 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.

11.6.2. Study Population

Extent of Exposure

- Number of weeks 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 actual dose administered during each infusion)
- The infusion dose intensity is the cumulative dose divided by the number of 3 weeks periods (cycles) across the entire treatment period:

  Dose intensity = Cumulative Dose/((last infusion date – first infusion date + 21)/21)

Refer to Section 6.5 for further details.

11.6.3. Efficacy

Efficacy Endpoints

Overall Response Rate (ORR) (irRECIST and RECIST v1.1)

- ORR per RECIST v1.1 is defined as the percentage of participants with a best overall response of CR or PR from the start of treatment until disease progression or death due to any cause or the start of new anticancer therapy/crossover.
- ORR per irRECIST is defined as the percentage of participants with a best overall response of irCR or irPR from the start of treatment until confirmed disease progression or death due to any cause or the start of new anticancer therapy/crossover.
- This will be based on overall responses from the Investigator assessment.
- The overall response observed for the participant will be used to derive best overall response. Refer to Section 8.3.2.1 for details

Disease Control Rate (DCR) (irRECIST and RECIST v1.1)

- DCR per RECIST v1.1 is defined as the percentage of participants with a best overall response of CR or PR at any time plus SD meeting the minimum time criteria from the start of treatment until disease progression or death due to any cause or the start of new anticancer therapy/crossover
- DCR per irRECIST is defined as the percentage of participants with a best overall response of irCR or irPR at any time plus irSD meeting the minimum time criteria from the start of treatment until confirmed

Efficacy Endpoints
disease progression or death due to any cause or the start of new anticancer therapy/crossover Refer to Section 8.3.2.1 for details
Progression Free Survival (PFS) (RECIST v1.1)
• Progression-Free survival (PFS) per RECIST v1.1 is defined as the interval of time from randomization date (or first dose date if not randomized); to the earlier date of first assessment of disease progression, or death due to any cause. Disease progression will be based on the assessments by the Investigator. Refer to Section 8.3.2.2 for details
Overall Survival (OS)
• OS is defined as the interval of time (in weeks) between from randomization date (or first dose date if not randomized) and the date of death due to any cause. Refer to Section 8.3.2.3 for details
Duration of Response (DOR) (RECIST v1.1)
• DOR per RECIST v1.1 is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause among participants who achieve a response (confirmed CR or PR) Refer to Section 8.3.2.4 for details
Time to Response (TTR) (RECIST v1.1)
• TTR per RECIST v1.1 is defined for participants with a confirmed CR or PR, as the time from first dose to the first documented evidence of CR or PR Refer to Section 8.3.2.5 for details

11.6.4. 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

ECG Parameters
Corrected QT Intervals
• When not entered directly in the eCRF, corrected QT intervals using Fredericia's (QTcF) formula will be calculated, in msec, using QT and the RR interval: $QTcF = \frac{QT}{3\sqrt{\frac{RR}{1000}}}$

11.6.5. Pharmacokinetic

PK Parameters
Cmax
• Maximum observed concentration, determined directly from the concentration-time data.
Tmax
• Time to reach Cmax, determined directly from the concentration-time data.
Ctau
• Concentration at the end of dosing interval.
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-τ)
• Area under the concentration-time curve over the dosing interval.
AUC(0-∞)
• Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time.
λz
• Apparent terminal phase elimination rate constant.
T½
• Apparent terminal phase half-life will be calculated as: $t_{½} = \ln 2 / \lambda z$

NOTES:

- Additional parameters may be included as required.

11.6.6. Population Pharmacokinetic (PopPK)

Parameters
CL
Systemic clearance of parent drug.
Vc
Apparent volume of distribution of parent drug.

11.6.7. Pharmacodynamic and Biomarker

The pharmacodynamic and biomarker endpoints for this study will be defined separately in an independent analysis plan.

11.7. Appendix 7: Reporting Standards for Missing Data

11.7.1. Premature Withdrawals

Element	Reporting Detail
General	• For Part 1A and Part 2A combination with pembrolizumab, the dose escalation phases of the study, participants will be considered as completing the study if they complete screening assessments, receive at least one dose of study treatment, 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 1A, 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 to achieve the three-participant required minimum. • For Part 2A combinations with chemotherapy, participants will be considered as completing the study if they complete the screening assessments, receive at least one dose of study treatment, are observed during the 28 day DLT observation period, and complete the treatment discontinuation visit and the safety follow-up visit or have died while receiving study treatment or during the post-study treatment safety follow-up period. • For Part 1B and 2B, the expansion phases of the study, 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 will be considered as completing the study. • 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. • Withdrawal visits will be summarized as withdrawal visits.

11.7.2. 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.

Element	Reporting Detail
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.

11.7.2.1. 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 addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.
Birth Date	• 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.
Adverse Events	• 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:

Missing start day	• 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.
Missing start day and month	• 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.
Missing stop day	Last day of the month will be used.
Missing stop day and month	No Imputation
Completely missing start/end date	No imputation

Concomitant Medications/Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
Missing start day	• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = 1st of month.

Element	Reporting Detail	
		• Else if study treatment start date is not missing: ○ 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. ○ Else set start date = 1st of month.
	Missing start day and month	• 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: ○ 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.
	Missing end day	A '28/29/30/31' will be used for the day (dependent on the month and year)
	Missing end day and month	A '31' will be used for the day and 'Dec' will be used for the month.
	Completely missing start/end date	No imputation
Prior Anticancer Therapy/Radiotherapy/Surgical Procedures	• 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.	
New Anticancer Therapy/ Radiotherapy/ Surgical Procedures/Crossover for Efficacy Evaluation (e.g., response rate, time to event)	Start dates for follow-up anti-cancer therapy, radiotherapy (where applicable), and surgical procedures (where applicable) will be imputed in order to define event and censoring rules for progression-free survival, response rate, or duration of response (i.e. start date for new anti-cancer therapy). Dates will only be imputed when a month and year are available, but the day is missing. 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 dataset[s]: • Completely missing start dates will remain missing, with no imputation applied; • Partial start dates will be imputed using the following convention: • If both month and day are missing, no imputation will be applied; • If only day is missing: ○ If the month of partial date is the same as the month of last dosing date, minimum of (last dosing date + 1, last day of the month) will be used for the day; ○ If the month of partial date is the same as the month of last disease assessment and the last disease assessment is PD, minimum of (last date of disease assessment + 1, last day of the month) will be used for the day; ○ If both conditions above are met, the later date will be used for the day; ○ Otherwise, a '01' will be used for the day;	

Element	Reporting Detail
	• Completely or partial missing end dates will remain missing, with no imputation applied;
Exposure End Dates	• If treatment end date is missing for a cycle, treatment start date for the cycle will be used. • If there is more than one study treatment, imputation of missing treatment end date will be applied to all applicable treatments following rules below and treatment end date is the latest treatment end date across all study treatments. • Only treatment cycles prior to crossover or re-treatment (if applicable) will be considered for exposure end date.

11.8. Appendix 8: Values of Potential Clinical Importance

11.8.1. Laboratory Values

To identify laboratory values of potential clinical importance (PCI), National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.0) will be used to assign grades to the relevant laboratory parameters and results categorized as Grade 1 and above will be considered as a PCI.

For laboratory data which are not listed in the NCI CTCAE (v4.0 and v4.03), a summary of values outside the normal range will be provided.

11.8.2. ECG

ECG Parameter	Units		Clinical Concern Range	
			Lower	Upper
		Absolute		
Absolute QTcF Interval	msec	Grade 1	≥ 450	< 481
		Grade 2	≥ 481	< 501
		Grade 3	≥ 501	
		Change from Baseline		
Increase from Baseline QTcF	msec		> 30	≤ 60
	msec		> 60	

11.8.3. Vital Signs

Vital Sign Parameter (Absolute)	Units		Clinical Concern Range	
			Lower	Upper
Systolic Blood Pressure	mmHg	Grade 1	≥120	<140
	mmHg	Grade 2	≥140	<160
	mmHg	Grade 3	≥160	
Diastolic Blood Pressure	mmHg	Grade 1	≥ 80	< 90
	mmHg	Grade 2	≥ 90	< 100
	mmHg	Grade 3	≥ 100	
Pulse Rate	bpm	L/H	< 60	> 100
Temperature	Degrees C	L/H	≤ 35	≥ 38

11.9. Appendix 9: Population Pharmacokinetic (PopPK) Analyses

11.9.1. Population Pharmacokinetic (PopPK) Dataset Specification

The PopPK dataset specification will be developed according to current CPMS SOPs and best practices to capture relevant information for analyses.

11.9.2. Population Pharmacokinetic (PopPK) Methodology

Population PK analysis may be performed in the following sequence of steps:

2. Base structural model development
    - Plasma concentration-time data may be analysed with nonlinear mixed effects modelling using appropriate validated software to develop a base population PK model
    - Based on the preliminary analysis, drug concentration data of GSK3359609 may be analysed using a two-compartment IV infusion model parameterized using either clearances and distribution volumes or using macro rate constants (A, B, ALPHA and BETA), depending on parameters to be estimated
    - Inter-individual or between-participant variability (IIV or BSV) may be initially modelled using an exponential random effects model. Random effects for clearances and volumes or A and B and BETA may be incorporated, depending on model parameterization used. If the goodness-of-fit plots reveal potential biases in the random effects model, alternative random effects models may be considered
    - A proportional error model may initially be used to describe the residual variability. If the goodness-of-fit plots reveal potential biases in the residual variability model, other residual error models will be considered as appropriate
3. Covariate analysis
    - Covariate analysis may be performed to explore measurable sources of PK variability. Different approaches may be evaluated for covariate model building including a step-wise process consisting of a forward and a backward selection procedure and/or a full-model approach. Some of the prospectively identified covariates are listed below:
        - Continuous covariates such as age, albumin, measures of body size (e.g., body weight, body mass index,);

- Categorical covariates such as gender, race, ethnicity, tumor type, disease status, prior treatment status

4. Model refinement
    - Model refinement steps may be performed, including, where appropriate, exploration of model improvement through reparameterization or the estimation of off-diagonal random effects, interpretation of magnitude of the variability, interpretation of standard errors of the fixed and random effects parameters, and simplification of covariate models.
5. Model evaluation
    - Non-parametric bootstrapping may be performed to test model robustness.
    - The model performance may be evaluated by performing predictive check
    - Individual *post hoc* estimated PK parameters may be summarized descriptively
    - Individual participant PK parameters and exposure measures for Cycle 1 may be estimated and documented for the purposes of any subsequent exposure-response (PK/PD) analyses

Any population PK analyses not described *a priori* but undertaken based on emerging data will be described in detail in the report.

11.10. Appendix 10: Pharmacokinetic / Pharmacodynamic Analyses

11.10.1. Pharmacokinetic / Pharmacodynamic Dataset Specification

The PK/PD dataset specification(s) will be developed according to current CPMS SOPs and best practices to capture relevant information for analyses.

11.10.2. Pharmacokinetic / Pharmacodynamic Methodology

The primary goal of PK/PD analyses is to characterize the exposure-response relationships for GSK3359609. The exposure-response analyses may focus on SAEs (≥Grade 3) as well as efficacy endpoints and may also include an investigation to assess the impact of different exposure estimates. Where appropriate, drug plasma concentration (or pharmacokinetic parameter) data and pharmacodynamic data may be combined and analysed with nonlinear mixed effects modelling using suitable software. The influence of participant demographics and baseline characteristics, including disease activity, in this population may also be investigated. All participants included in the pharmacokinetic analysis set with at least one follow-up scan will be included in exposure-efficacy assessments.

11.10.2.1. Exposure Metrics for Exposure – Response

Exposure measures may be derived from observed peak or trough concentrations or using the individual *post hoc* estimates obtained from the population PK analysis. Example exposure measures are as follows: peak concentration (Cmax) after first dose, trough concentration (Cmin), or model-derived $AUC_{0\text{-}t}$, where t represents the planned cycle time in days

11.10.2.2. Exposure – Response Assessments for Clinical Endpoints

Exposure – Adverse Events

Data permitting and as deemed relevant, presence or absence of adverse events may be described using a conventional logistic regression model for ≥ Grade 3 AE. Severity of AE may also be analyzed using an ordered logistic regression model assuming Grades 0 (no toxicity), 1, 2 and 3, with exposure subdivided into quartiles/quintiles.

Time-to-event analysis may also be applied to assess exposure-safety relationships. In this case, non-parametric Kaplan-Meier method may be used to estimate survival curves, with Kaplan-Meier plots of SAE event-free survival presented by binned exposure estimates (e.g. quartiles of exposure). The Kaplan-Meier estimates for the median SAE event-free survival may be presented, along with 95% CIs. The treatment difference in survival may then be assessed by the stratified log-rank test. A hazard ratio and its 95% confidence interval from a Cox model may also be reported separately.

Exposure – Efficacy

CCI

Exposure – Clinical Response Relationship

Data permitting and as deemed relevant, ORR per RECIST v1.1, defined as the proportion of the participants in the analysis population who have a CR or PR based upon investigator assessment may be summarized by binned exposure estimates. Presence or absence of clinical response may be described using a conventional logistic regression model. Time-to-response may be explored using Kaplan-Meier survival curves. Best clinical response may also be analyzed using an ordered logistic regression, with response categorized from 0 (progressive disease) to 3 (complete response). Exposure will be treated as a categorical variable, subdivided into quartiles and quintiles.

Exposure-Progression Free Survival Relationship

Data permitting and as deemed relevant, PFS may be explored using Kaplan Meier plots with exposure subdivided into quartiles and quintiles, and occurrence of progression may also be described using a conventional logistic regression model.

Exposure-Longitudinal Tumor Size Modeling

Data permitting and as deemed relevant, tumor size will be recorded as the sum of longest dimensions (SLD) of target lesions, using RECIST version 1.1. If data permits, tumor size modeling may be pursued to quantify exposure-response relationships for efficacy. Longitudinal tumor kinetics may be described via a nonlinear mixed-effects framework. Exposure may be assessed as a covariate on tumor growth/ shrinkage parameters. Other prognostic covariates may be explored to normalize for potential imbalances in exposure.

11.11. Appendix 11: Abbreviations & Trade Marks

11.11.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
ADA	Anti-drug antibodies
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
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
BMI	Body mass index
BOR	Best Overall Response
BSV	Between-subject variability
BP	Blood pressure
BUN	Blood Urea Nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CL	Clearance
Cmax	Maximum observed concentration
CPMS	Clinical Pharmacology Modelling & Simulation
CPS	Combined Positive Score
CR	Complete Response
CSR	Clinical Study Report
Ctau	Concentration at the end of dosing interval
DCR	Disease Control Rate
DE	Dose Expansion
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of Response
DP	Decimal Places
dMMR	Deficient Mismatch Repair
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
CCI	[redacted]
GSK	GlaxoSmithKline
HNSCC	Head and Neck Squamous Cell Cancer

Abbreviation	Description
HPV	Human Papillomavirus
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
IA	Interim Analysis
ICOS	anti-Inducible T cell Co-Stimulator
IDSL	Integrated Data Standards Library
IHC	Immunohistochemistry
IIV	Inter-individual variability
INR	International Normalized Ratio
irAE	Immune-related Adverse Event
irBOR	Immune-related Best Overall Response
irCR	Immune-related Complete Response
irSD	Immune-related Stable Disease
irPD	Immune-related Progressive Disease
irPR	Immune-related Partial Response
irRECIST	Immune-related RECIST
kg	Kilogram(s)
LFT	Liver Function Test
LVEF	Left Ventricular Ejection Fraction
MAD	Maximum Administered Dose
MSI-H	Microsatellite Instability-high
MTD	Maximum Tolerated Dose
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
mmHg	Millimeters of Mercury
msec	Milliseconds
MUGA	Multigated Acquisition Scan
NA	Not Applicable
NCI-CTCAE	National Cancer Institute - Common Toxicity Criteria for Adverse Events
NE	Not Evaluable
NSCLC	Non-small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-L1	Programmed Death
PFS	Progression-free Survival
PGx	Pharmacogenetics
PK	Pharmacokinetics
PR	Partial Response
PRO	Patient Reported Outcome
CCI	[redacted]
PS	Performance Status
PT	Preferred Term
Q3W	Every 3 Weeks
Q6W	Every 6 Weeks
QTc	Corrected QT interval duration, corrected
QTcF	Frederica's QT Interval Corrected for Heart Rate
QoL	Quality of Life
RAP	Reporting and Analysis Plan

Abbreviation	Description
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumors
REML	Restricted Maximum Likelihood
RNA	Ribonucleic acid
ROS1	c-ros oncogene 1
RP2D	Recommended Phase 2 Dose
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event(s)
SAS	Statistical Analysis Software
SD	Stable Disease
SLD	Sum of longest dimensions
STD	Standard Deviation
SDTM	Study Data Tabulation Model
t½	Terminal half-life
tmax	Time of maximum observed concentration
TTR	Time to Response
ULN	Upper Limit of Normal
WBC	White Blood Cells

11.11.2. Trademarks

Trademarks of the GlaxoSmithKline group of companies
None

Trademarks not owned by the GlaxoSmithKline group of companies
NONMEM
SAS
WinNonlin

11.12. Appendix 12: List of Data Displays

The list of data displays for each of the individual rolling CSRs compiled throughout the study will be provided within each individual reporting effort alongside other supporting documents such as a list of TLFs and mock shells within the relevant reporting effort (\arwork\gsk3359609\mid204691).