Statistical Analysis Plan

Official Title of Study: A Phase I, Open-Label Study of GSK3174998 Administered Alone and in Combination with Anticancer Agents including Pembrolizumab in Subjects with Selected Advanced Solid Tumors

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Abbreviations

ADA	Antidrug antibody
AE	Adverse event(s)
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC(0-t)	Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration)
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
β-hCG	Beta-human chorionic gonadotropin
BUN	Blood urea nitrogen
CL	Systemic clearance of parent drug
CrCl	Calculated creatinine clearance
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CPMS	Clinical Pharmacology Modelling and Simulation
CR	Complete response
CRM	Continual reassessment method
CRP	C-reactive protein
CSR	Clinical Study Report
CT	Computed tomography
CV	Cardiovascular
DCR	Disease Control Rate
dL	Deciliter
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram(s)
ECOG	Eastern Cooperative Oncology Group
EOI	End of infusion
EOPI	End of pembrolizumab infusion
eCRF	Electronic case report form
FACTS	Fixed and Adaptive Clinical Trial Simulator
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose-positron-emission tomography
FTIH	First time in human
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
h	Hour(s)
HRT	Hormone replacement therapy
IB	Investigator's Brochure

ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
irAE	Immune-related adverse event(s)
irRECIST	Immune-related RECIST
IV	Intravenous
Kd	Equilibrium dissociation constant
kg	Kilogram(s)
L	Liter
LDH	Lactate dehydrogenase
LFT	Liver function Tests
µg	Microgram
MAD	Maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
min	Minute(s)
mL	Milliliter(s)
mmHg	Millimeters of mercury
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
MSI CRC	Colorectal carcinoma displaying microsatellite instability
MTD	Maximum tolerated dose
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NOAEL	No observed adverse effect level
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PGx	Pharmacogenetics
PI	Principal investigator
PK	Pharmacokinetic(s)
PR	Partial response
PS	Performance status
Q3W	Every 3 weeks
QTc	Corrected QT interval duration
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event(s)

SD	Stable disease
SFU	Survival follow-up
SRM	Study Reference Manual
STS	Soft tissue sarcoma
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WBC	White blood cells
WNL	Within normal limits

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1. INTRODUCTION

This reporting and analysis plan (RAP) details all planned analyses required for a Clinical Study Report of study 201212. This is a first time in human (FTIH), open-label, non-randomized, multicenter study designed to evaluate the safety, tolerability, PK, pharmacodynamics, and preliminary clinical activity of GSK3174998 administered intravenously to subjects with selected advanced or recurrent solid tumors.

For further information on the study design, see Protocol Amendment 04 dated 04-FEB-2020 (2014N225045_04).

The RAP was written by staff of ICON Clinical Research. The execution of the RAP, with exception to CRM-based analyses in FACTS, will be undertaken by staff of ICON Clinical Research.

All decisions regarding final analysis, as defined in this RAP document, have been made prior to Database Freeze of the study data.

2. SUMMARY OF KEY PROTOCOL INFORMATION

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

Objectives	Endpoints
Part 1: GSK3174998 Monotherapy	
Primary	
• To evaluate the safety and tolerability and identify the MTD[a] or the MAD of GSK3174998 administered intravenously to subjects with selected advanced or recurrent solid tumors.	• AEs, SAEs, DLT, withdrawals due to AEs, dose reductions or delays, and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters).
Secondary	
• To evaluate the antitumor activity of GSK3174998 in subjects with selected advanced or recurrent solid tumors. • To characterize the PK of GSK3174998 monotherapy. • To determine the immunogenicity of GSK3174998.	• ORR and DCR (CR+ PR+ SD ≥12 weeks) [b] • GSK3174998 concentrations in plasma and PK parameters including Cmax, AUC(0-τ), and Cmin. • Number and percentage of subjects who develop detectable ADA.
Exploratory	
• To explore the relationship between antitumor activity, PK parameters, pharmacodynamic activity and other patient characteristics. • To explore onset and durability of response • To evaluate the pharmacodynamic activity of GSK3174998 in the peripheral blood and to explore the utility of these measures to enrich for clinical efficacy and development of a diagnostic test.	• Evaluation of antitumor activity (CR, PR, SD, PD), tumor kinetic parameters, PK parameters, pharmacodynamic activity, and other patient characteristics. • TTR and DOR • Assessment of lymphocyte OX40 receptor membrane expression and occupancy by GSK3174998. Measures of immune function in blood (e.g. phenotype, quantity, and activation state of T cells in the periphery, TCR diversity, expression of circulating soluble factors such as cytokines and stress-related proteins). Changes in genomic DNA, gene expression (RNA and protein), (e.g. using cfDNA, exosomes or circulating tumor cells [CTCs]) and mutational load.

Objectives	Endpoints
Part 1: GSK3174998 Monotherapy	
Exploratory	

• To evaluate the pharmacodynamic activity of GSK3174998 in the tumor microenvironment and to explore the utility of these measures to enrich for clinical efficacy and development of a diagnostic test.
 	
• Pharmacogenetics (PGx): To evaluate the association of genetic variations in the host DNA and response to therapy or disease characterization.
	• Assessment of tumor biopsies via IHC for the numbers of tumor-infiltrating lymphocytes and other immune cells expressing key phenotypic markers. Changes in gene expression (RNA and protein), TCR diversity or mutational load (genomic DNA).
	
	• Germline genetic evaluations may be conducted for:
	  • Medicine response, including GSK3174998 or any concomitant medicines.
	  • Disease susceptibility, severity, and progression and related conditions.

Hypothesis	
For the primary objective, no formal statistical hypothesis will be tested; analysis will be descriptive and exploratory	

a. In the final determination of the MTD, all available safety and tolerability data will be considered
b. Unless otherwise specified, all response endpoints will be assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and by irRECIST (immune-related RECIST); irRECIST will be used to determine treatment decisions.

RNA = Ribonucleic acid; DNA = Deoxyribonucleic acid

Objectives	Endpoints
PART 2: Combination GSK3174998 plus pembrolizumab	
Primary	
• To evaluate the safety and tolerability and identify the MTD[a] or the MAD of GSK3174998 administered intravenously in combination with IV pembrolizumab to subjects with selected advanced or recurrent solid tumors.	• AEs, SAEs, DLTs, withdrawals due to AEs, dose reductions or delays, and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters).
Secondary	
• To evaluate the antitumor activity of GSK3174998 in combination with pembrolizumab in subjects with selected advanced or recurrent solid tumors.	• ORR and DCR (CR+PR+SD ≥12 weeks)[b]
• To characterize the PK of GSK3174998 and pembrolizumab when administered in combination.	• Plasma GSK3174998 and serum pembrolizumab concentrations and PK parameters including Cmax, AUC(0-τ), and Cmin.
• To determine the immunogenicity of GSK3174998 and pembrolizumab when administered in combination.	• Number and percentage of subjects who develop detectable ADA.
Exploratory	
• To explore the relationship between antitumor activity, PK parameters, pharmacodynamic activity and other patient characteristics.	• Evaluation of antitumor activity (CR, PR, SD, PD), tumor kinetic parameters, PK parameters, pharmacodynamic activity, and other patient characteristics.
• To explore onset and durability of response	• TTR and DOR
• To evaluate the pharmacodynamic activity of GSK3174998 in combination with pembrolizumab in the peripheral blood and to explore the utility of these measures to enrich for clinical efficacy and development of a diagnostic test.	• Assessment of lymphocyte OX40 receptor membrane expression and occupancy by GSK3174998. Measures of immune function in blood (e.g. phenotype, quantity, and activation state of T cells in the periphery, TCR diversity, expression of circulating soluble factors such as cytokines and stress related proteins). Changes in genomic DNA, gene expression (RNA and protein), (e.g. using cfDNA, exosomes or CTCs) and mutational load.

Objectives	Endpoints
PART 2: Combination GSK3174998 plus pembrolizumab	
Exploratory	
• To evaluate the pharmacodynamic activity of GSK3174998 in combination with pembrolizumab in the tumor microenvironment and to explore the utility of these measures to enrich for clinical efficacy and development of a diagnostic test. • PGx: To evaluate the association of genetic variations in the host DNA and response to therapy or disease characterization.	• Assessment of tumor biopsies via IHC for the numbers of tumor-infiltrating lymphocytes and other immune cells expressing key phenotypic markers. Changes in gene expression (RNA and protein), TCR diversity or mutational load (genomic DNA). • Germline genetic evaluations may be conducted for: • Medicine response, including GSK3174998 and pembrolizumab or any concomitant medicines. • Disease susceptibility, severity, and progression and related conditions.
Hypothesis	
For the primary objective, no formal statistical hypothesis will be tested; analysis will be descriptive and exploratory	

a. In the final determination of the MTD, all available safety and tolerability data will be considered
b. Unless otherwise specified, all response endpoints will be assessed by RECIST v1.1 and by irRECIST; irRECIST will be used to determine treatment decisions.

RNA = Ribonucleic acid; DNA = Deoxyribonucleic acid

3. STATISTICAL HYPOTHESES

3.1. Part 1: Monotherapy Dose Escalation (GSK3174998)

With respect to the primary objectives and endpoints, no specific statistical hypotheses are being tested. The primary focus will be on determining the recommended dose for further exploration, the safety profile, and antitumor activity of GSK3174998.

3.2. Part 2: Combination Dose Escalation (GSK3174998 + Pembrolizumab)

No formal statistical hypotheses are being tested. Analysis of the data obtained from this study will be focused on comparison between dose cohorts and only descriptive methods will be used in analysis of the data obtained from this study.

3.3. Part 2: Combination Dose Expansion (GSK3174998 + Pembrolizumab)

The expansion cohorts of GSK3174998 + pembrolizumab are designed to evaluate preliminary clinical activity.

There are multiple dose expansion cohorts being planned for STS, melanoma and other cancers types in the dose-expansion phase. For each cohort the objective is to test the null hypothesis that the overall response rate for the combination of GSK3174998 + pembrolizumab is equal to the historical response rate of monotherapy pembrolizumab.

The observed monotherapy pembrolizumab overall response rate was approximately 18% for STS. The observed monotherapy pembrolizumab overall response rate was assumed to be approximately 10% for melanoma in the pretreated population.

The sample size is chosen based on an improvement of 20% in the overall response rate on the combination therapy over the null hypothesis, with power of at least 80% and no more than a 10% type 1 error rate. In the population previously treated with pembrolizumab, the goal would be to observe a response rate of 30% after treatment with the combination of GSK3174998 and pembrolizumab.

Therefore, the hypotheses for both PD-(L)1 naïve and PD-(L)1 pretreated cohorts are shown as below:

For PD-(L)1 naïve dose expansion cohorts (e.g., STS), the null hypothesis for ORR is:
H0: p=18%

and the *alternative hypothesis* is:
HA: p=38%

For PD-(L)1 pretreated dose expansion cohorts (e.g., melanoma), the null hypothesis for ORR is:
H0: p=10%

and the *alternative hypothesis* is:
HA: p=30%

4. STUDY DESIGN

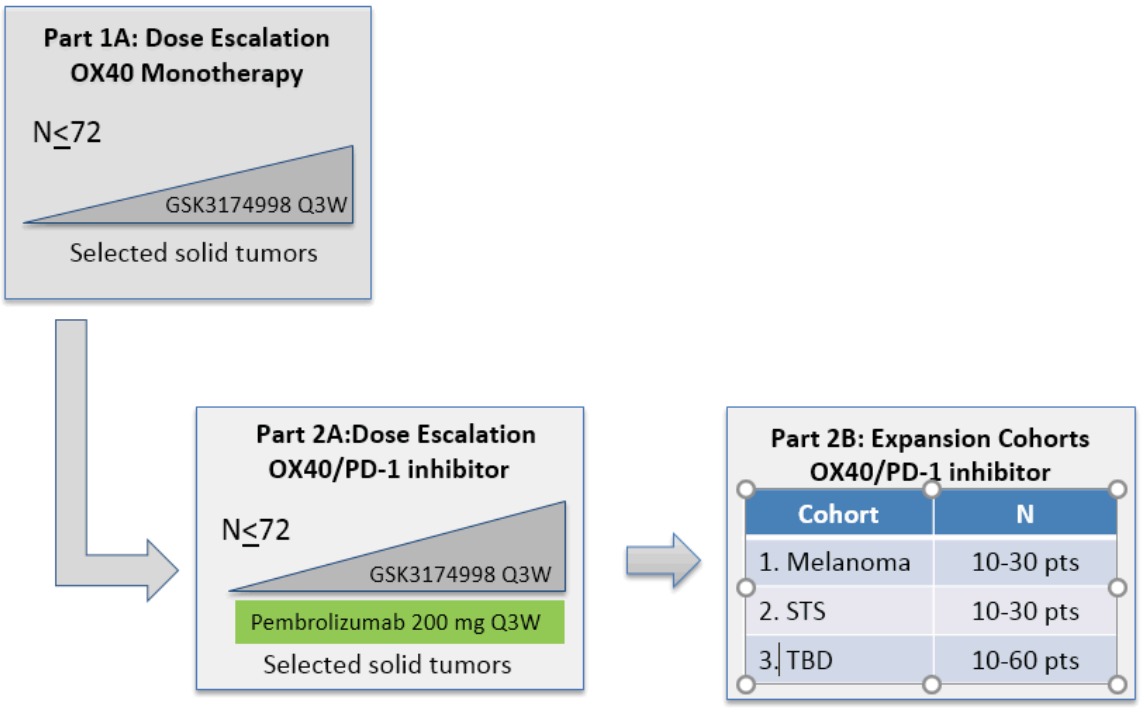
This is a first time in human (FTIH), open-label, non-randomized, multicenter study designed to evaluate the safety, tolerability, PK, pharmacodynamics, and preliminary clinical activity of GSK3174998 administered intravenously to subjects with selected advanced or recurrent solid tumors.

The study will be conducted in two parts (see Figure 1). Part 1 will evaluate GSK3174998 monotherapy, while Part 2 will evaluate GSK3174998 in combination with pembrolizumab. As shown in Figure 1, GSK3174998 will first be evaluated as monotherapy in escalating doses. Once a dose of GSK3174998 has been identified that is both tolerable and demonstrates pharmacodynamic activity, enrollment of Part 2 may begin. In Part 2, escalating doses of GSK3174998 will first be evaluated with fixed doses of pembrolizumab. Part 1A and 2A will also include a Pharmacodynamic Cohort, which requires mandatory fresh pre- and on-treatment biopsies and an additional disease assessment at week 6. Part 2 will also include expansion cohorts for specified tumor types.

The study will enroll up to approximately 264 subjects with tumor types that may include NSCLC, SCCHN, RCC, melanoma, bladder cancer, STS, TNBC, and MSI CRC. In the dose-escalation phase of the study, subjects with any of the aforementioned tumor types may be included; whereas in the cohort expansion phase of the study, each expansion cohort will enroll subjects with one specific tumor type selected from the aforementioned list. A subject's disease status and determination of disease progression at postbaseline visits will be evaluated by the local investigators' assessments of radiology by RECIST v1.1 and irRECIST; a decision to discontinue treatment due to disease progression will be based upon irRECIST and the primary endpoint analysis will use irRECIST. Scans will be collected centrally and stored to allow for the option of central radiologic audit or review.

A Steering Committee will be established to review safety, PK, and other clinical data during the course of the study, to provide objective interpretation of study results, and guidance for key decisions. The remit of the Steering Committee will include guidance for the transition of the study from dose-escalation to cohort expansion and from Part 1 to Part 2, the selection of specific tumor types to include in the expansion cohorts, and the selection of the recommended Phase 2 dose (RP2D); the study team will also seek endorsement from GSK Medical Governance for the transition of the study from one part to another. In the final determination of the MTD and RP2D, all available safety and tolerability data will be considered. Pending a review of emerging data from this study and under the guidance of the Steering Committee, the protocol may be subsequently amended to include investigation of additional anticancer agent combinations with GSK3174998. The remit, membership, roles and responsibilities of the Steering Committee are described in a Steering Committee Charter. Key decisions of the Steering Committee will be documented and reported to all participating principal investigators (PIs) and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs). The schedule of time and events can be found in the study protocol Section 7.1. Details regarding dose escalations can be found at the study protocol Section 4.1.1.

Figure 1 Study Design



5. PLANNED ANALYSES

In line with ICH E9 [European Agency for the Evaluation of Medicinal Products, 1998], membership of the analysis populations will be determined using the definitions in Section 7 of this RAP.

5.1. Interim Analyses

No formal interim analyses will be performed using the data generated from dose escalation cohorts. Preliminary safety and available PK/PD data will be performed and reviewed by study team (to include at minimum, the GSK medical monitor and investigator) after completion of each dose cohort. This review will support the decision on the dose level in the next dose cohort. Dose escalation decisions making will be based on the rules as described in protocol Section 4.1.1 and protocol Section 9.3. The Steering Committee will guide the transition of the study from dose escalation to cohort expansion for both monotherapy and combination therapies.

For dose expansion cohorts, continuous assessment of efficacy and safety was planned to be performed after first interim analysis based upon a minimum of 10 subjects in at least one of the disease-specific cohorts with available unconfirmed overall response data for at least 12 weeks. However, after implementation of protocol Amendment 4, no further subjects were enrolled in the study; therefore, no futility analyses were performed.

5.2. Analyses for Dose Escalation Cohorts and Expansion Phases

In the dose escalation cohorts, the dose will be escalated based on all available data, including biomarker, PK data, and the safety profile of prior cohorts. In addition, the recommended dose from a Continuous Reassessment Method (N-CRM) analysis [Neuenschwander, 2008] will be calculated. The N-CRM is a type of Bayesian adaptive dose-escalation scheme. The method is fully adaptive and makes use of all the DLT information available at the time of each dose assignment. The Fixed and Adaptive Clinical Trial Simulator (FACTS) will be used to conduct the N-CRM analysis. The DLT information on all subjects enrolled in the trial are used to update the estimated dose-toxicity relationship and provide supportive information in addition to the 3+3 design in the next escalation/de-escalation decision.

There is no futility analysis for dose expansion cohorts as specified in Section 5.1.

5.3. Final Analyses

The final analysis of the study will be performed when the study is completed or terminated. Upon Protocol Amendment 4 implementation, ongoing subjects will be considered withdrawn due to study closure and will be followed for up to 3 months after the last dose. Only when a subject dies is he/she considered to have completed the study; consequently, "death" is not listed as a reason for withdrawal from the study. Furthermore, disease progression, discontinuation of study treatment, and AEs, are not by themselves reasons for withdrawal from the study. If a subject dies a copy of the death certificate should be available for review, if possible, and the cause of death should be evaluated and documented.

The end of the study is defined as the last subject's last visit.

6. SAMPLE SIZE CONSIDERATIONS

6.1. Sample Size Assumptions

The sample size for each part of the trial was chosen to adequately characterize the safety, clinical activity, PK, and pharmacodynamic marker data according to the objectives of each part of the study.

The study will enroll up to approximately 264 subjects with tumor types that may include NSCLC, SCCHN, RCC, melanoma, STS, bladder cancer, TNBC, and MSI CRC.

Up to 72 subjects will be enrolled in each of the two dose escalation parts of the study (Parts 1A and 2A); up to 30 subjects will be enrolled in each of dose expansion cohorts. The sample size of each expansion cohort at a given dose level will be minimum of 10 subjects and maximum of 30 subjects based on the overall response assessments. More details of sample size calculation are described in protocol Section 9.2.

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7. ANALYSIS POPULATIONS

7.1. All Treated Population

The **All Treated Population** is defined as all subjects who receive at least one dose of GSK3174998. Safety and anticancer activity will be evaluated based on this analysis population.

7.2. PK Population

The **PK Population** will consist of all subjects from the All Treated Population for whom a PK sample is obtained and analyzed.

7.3. Analysis Datasets

Analysis datasets will be created according to CDISC/ADaM standards, and data will be listed and summarized according to GSK Integrated Data Standards Library (IDSL) reporting standards. Formatting for dates, times, and decimal places will follow GSK standards except where specified.

8. TREATMENT COMPARISONS

There are no treatment comparisons in the study.

8.1. Data Display Treatment and Other Subgroup Descriptors

For Part 1 (i.e., Part 1A), Monotherapy: Investigated doses of GSK3174998 will be displayed in summary tables and listings.

For Part 2A, Combination Dose Escalation: Some AE and exposure tables and listings will be displayed for GSK3174998 and pembrolizumab separately, all other tables and listings will display by dose levels of both GSK3174998 plus pembrolizumab.

For Part 2B, Combination Dose Expansion: Data will be displayed by each cohort type at the recommended phase 2 dose; for combination therapy expansions, selected AE and exposure display requirements as noted in Part 2A will also apply.

9. GENERAL CONSIDERATIONS FOR DATA ANALYSES

SAS 9.3 or higher version will be used to perform all data analyses, generate tables, figures, and listings. The exception would be CRM analyses, which are specified to take place in FACTS.

All data within scheduled visits up to the time of study completion/withdrawal from study will be included in the analysis summaries, regardless of duration of treatment. Unscheduled visits will be considered for most extreme result reporting (e.g. worst grade post-baseline) and included in data listings.

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Actual treatment derivation is specified in Section 10.2.10. Planned treatment is collected on dosing regimen eCRF page.

Efficacy analysis will be based on planned treatment.

For Part 1 and Part 2A, Safety and PK analysis will be based on actual treatment the subjects received and displayed by dose level. Efficacy analysis will be based on planned treatment and displayed by dose level.

For Part 2B, tables and figures will be displayed by cohort type. The subject will be summarized in the cohort type though the actual dose level may be different from the planned dose level. A footnote will be added in the Safety and PK table or figure to explain the discrepancy.

Unless otherwise noted, Safety and PK listings will be based on the actual treatment and efficacy listings will be based on the planned treatment.

In addition, for PK and receptor occupancy analysis, if a subject received different doses of treatment, the subject will be excluded from the analysis.

Deviations from the analyses in the RAP will be identified in the CSR.

Unless otherwise noted, the denominator for the percentage is the number of subjects in the analysis population used for the summary.

9.1. Other Strata and Covariates

In all efficacy analyses, there are no formal plans for any stratification. There are no formal plans for investigating any covariates.

9.2. Examination of Subgroups

There are no formal plans for examining subgroups.

9.3. Multiple Comparisons and Multiplicity

There is no adjustment for multiplicity in all primary and secondary analyses.

10. DATA HANDLING CONVENTIONS

10.1. Premature Withdrawal and Missing Data

For endpoints which determine the percentage of responders, subjects with unknown/not evaluable or missing best overall response will be assumed to be non-responders, and will be included in the denominator when calculating the percentages.

In the event that the study is terminated, all available data will be listed and a review carried out by the study team to assess which statistical analyses are still considered appropriate.

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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 subject listing displays. Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.

Subjects with the designation of treatment relationship for AEs and SAEs missing will have the worst case assumed to impute the relationship: if relationship to study treatment is missing it will be assumed to be "Yes". There will be no other imputation for missing data other than what is described in Section 10.2 for partial dates.

10.2. Derived and Transformed Data

The following sections provide a general description of the derived and transformed variables used to describe and analyze the data. Separate analysis dataset specifications provide full details on all data derivations and transformations including descriptions of core standard algorithms and standard oncology algorithms. The analysis dataset specifications will clearly communicate the content and source of the datasets supporting the statistical analyses.

10.2.1. Reference dates

Unless otherwise stated, the safety reference (start) date will be the start of treatment of GSK3174998. This will also be the efficacy reference date for this study. The reference date for baseline characteristics (e.g. age) will be the date of screening.

10.2.2. Study Day for Safety Measures

If the date of interest occurs on or after the safety reference date then the safety study day will be calculated as (date of interest - safety reference date) + 1. There is no safety study day 0.

10.2.3. Study Day for Efficacy

If the date of interest occurs on or after the efficacy reference date then efficacy study day will be calculated as (date of interest - efficacy reference date) + 1. If the date of interest occurs prior to the efficacy reference date then efficacy study day will be calculated as (date of interest – efficacy reference date). There is no efficacy study day 0.

10.2.4. Duration and Elapsed Time

Durations (e.g., the duration of an AE, duration of exposure, etc.) are calculated as the stop date minus the start date plus one.

For elapsed time (e.g., the time since initial diagnosis):

- If the reference date is on or after the event date, then the elapsed time is the reference date minus the event date + 1.
- If the reference date is before the event date then the elapsed time is the reference date minus the event date.

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When reporting time to event (TTE) durations 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 AEs, 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)))

The algorithms above for age and duration 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.

10.2.5. Imputation of Partial Dates

Imputed partial dates will not be used to derive study day, duration (e.g., duration of AEs), or elapsed time variables.

Imputed dates will not be displayed in listings. However, where necessary, display macros may impute dates as temporary variables for the purpose of sorting data in listings only. In addition, partial dates may be imputed for determining treatment-emergent AEs.

The partial date imputation will follow ADaM conventions. The ADaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the dataset that indicates the level of imputation.

The flag variable can contain the values: blank, 'D', 'M', 'Y'.

blank: indicates that no imputation was done

D='Day': indicates that the day portion of the date is imputed

M='Month': indicates that the month and day portions of the date are imputed

Y='Year': indicates that the entire date (year, month, and day) is imputed

Example of Date Variables:

XYZD_ - character date variable

XYZDT - numeric date variable

XYZDTFL - flag variable

Details on imputing partial dates for specific datasets are outlined below.

Adverse Events (AE):

Imputations in the adverse events dataset are used for determining treatment-emergent AEs and for sorting in data listings.

Dataset	Date	Missing Element	Rule
Adverse Events (AE)	Start Date	day, month, and year	• No Imputation for completely missing dates
		day, month	• If study treatment start date is missing (i.e. subject 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.
		day	• If study treatment start date is missing (i.e. subject 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.
	End Date		• No imputation for partial end dates will be performed

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Surgery:

Imputed dates will not be displayed in listings. However, where necessary, display macros may impute dates as temporary variables for the purpose of sorting data in listings only.

Dataset	Missing Element	Rule
Surgical Procedures	day, month, and year	• No Imputation for completely missing dates
	day, month	• If partial date contains a year only set to January 1st.
	day	• If partial date contains a month and year set to the 1st of the month

Concomitant Medication and Blood and Blood Supportive Care Products:

Imputed dates will not be displayed in listings. However, where necessary, display macros may impute dates as temporary variables for the purpose of sorting data in listings only.

Dataset	Date	Missing Element	Rule
Concomitant Medication Blood and Blood Supportive Care Products	Start Date	day, month, and year	No Imputation for completely missing dates
		day, month	• If study treatment start date is missing (i.e. subject 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. Else set start date = January 1.
		day	• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = 1st of month.

Dataset	Date	Missing Element	Rule
Concomitant Medication Blood and Blood Supportive Care Products	End Date	day, month, and year	• No Imputation for completely missing dates
		day, month	• If partial end date contains year only, set end date = earliest of December 31 or date of last contact.
		day	• If partial end date contains month and year, set end date = earliest of last day of the month or date of last contact

Start Date of New Anticancer Therapy:

Start dates for follow-up anticancer therapy, radiotherapy (where applicable), and surgical procedures (where applicable) will be temporarily imputed in order to define duration of response. Dates will only be imputed when a month and year are available but the day is missing. The imputed date(s) will not be stored on the anticancer therapy, radiotherapy, or surgical procedure datasets. The following rules will be used to impute the date when partial start dates are present on anticancer therapy radiotherapy, and/or surgical procedures dataset[s]:

Dataset	Date	Missing Element	Rule
Anticancer Therapy Where applicable: Radiotherapy Surgical Procedures	Start Date	day, month, and year	• No Imputation for completely missing dates
		day, month	• No imputation for missing day and month (note the eCRF should only allow for missing day)
		day	• If partial date falls in the same year and month as the last dose of study treatment, then assign to earlier of (date of last dose of study treatment+1, last day of month). • If partial date falls in the same year and month as the subject's last assessment and the subject's last assessment is PD, then assign to earlier of (date of PD+1, last day of month). • If both rules above apply, then assign to latest of the 2 dates

Dataset	Date	Missing Element	Rule
			• Otherwise, impute missing day to the first of the month.
	End Date		• No imputation for partial end dates will be performed

The date of new anticancer therapy is derived as the earliest date of new anticancer therapy (e.g., chemotherapy), radiotherapy (where applicable), or cancer related surgical procedure (where applicable) and will include imputed dates. If the date of new anticancer therapy is an imputed date, then the date of new anticancer therapy flag variable is assigned the value of 'D' to indicate that the day portion of the date is imputed (following ADaM convention).

As multiple dates are used to derive the date of new anticancer therapy ensure that the date of new anticancer therapy flag is only set to 'D' if the derived date is imputed. For example if the date of new radiotherapy is imputed but the date of new anticancer therapy is prior to date of new radiotherapy and the new anticancer therapy date is not a partial date then the flag should be set to missing as the date used for the new anticancer therapy is not an imputed date.

10.2.6. Imputation of Missing Exposure End Dates

Missing exposure end date will not be imputed.

10.2.7. Baseline Definition

Baseline will be defined as the most recent, non-missing value prior to or on the first study treatment dose date (this can be either GSK 3174998 or pembrolizumab). For laboratory data, baseline will be defined as the most recent, non-missing value from a central laboratory prior to or on the first study treatment dose date. If there are no central labs collected for a subject and lab test prior to or on the first dose of study treatment, the most recent, non-missing value from a local laboratory prior to or on the first dose of study treatment will be defined as the baseline value.

If the latest pre-dose value is collected on the day of treatment, the time of treatment will be used to identify the baseline value. If the pre-dose time point value is identified as baseline, and the data is recorded in triplicate the average will be used.

For subjects who did not receive study treatment during the study, baseline will be defined as the latest, non-missing collected value.

10.2.8. Change from baseline

Change from baseline will be presented for safety data as described in Section 13.

Change from baseline is calculated as:

- For records occurring after baseline: (visit value) – baseline value.

Percent change from baseline is calculated as:

- For records occurring after baseline: (change from baseline / baseline value) * 100

Unless otherwise stated, if either the baseline or visit value is missing, the change from baseline and/or percent change from baseline is set to missing as well.

10.2.9. Multiple Assessments

All data will be reported according to the nominal visit date for which it was reported (that is, no visit windows will be applied during dataset creation). Unscheduled data will only be included in the display sections that report worst-case. For summaries that collapse data across multiple planned time intervals, the worst-case data at each collapsed interval will be selected.

If multiple assessments on different days are reported for the same scheduled assessment, then the latest assessment for that scheduled assessment will be analyzed.

If multiple assessments are reported on the same date for the same scheduled planned time, then the worst-case result will be analyzed, with the exception of laboratory data reported from both central and local laboratories.

Furthermore, as quantitative ECG values will be measured in triplicate: 3 assessments are collected for each scheduled planned time, the first 3 measures will be used to compute the mean values for ECG intervals at each scheduled planned time.

For vital signs, three readings of blood pressure (BP) and pulse rate will be taken and the first reading will be discarded. The second and third readings will be averaged and recorded on eCRF to give the measurement reported at each time point.

Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in listings.

10.2.10. Actual Treatment

The actual treatment of a subject will be derived from exposure data. The first dose the subject received is used as actual treatment.

10.2.11. Extended Loss to Follow-up or Extended Time without an Adequate Assessment

If [two] or more scheduled disease assessments are missed and are then followed by an assessment of PD or death, PFS will be censored at the last adequate assessment prior to PD or death. As scheduled disease assessment is every 12 weeks, a window of 175 days (24 weeks + 7 day window) will be used to determine whether there was an extended time without adequate assessment. That is, if the time difference between PD/death and

last adequate assessment is more than 175 days, then PFS will be censored at the last adequate assessment prior to PD/death.

10.2.12. Date Associated with Response

For each disease assessment after baseline, a date will be associated with the response based on collective group of disease assessments made within the protocol visit window. For complete response (CR) and partial response (PR), this will be assigned to the latest date within the disease assessments. For stable disease (SD), Non-CR/Non-PD or Not Evaluable, this will be assigned to the earliest date within the disease assessments. For progressive disease (PD), assign to the earliest assessment date associated with the progression. Dates associated with irRECIST response values will be handled similarly.

10.3. Values of Potential Clinical Importance

10.3.1. Laboratory Parameters

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). The laboratory reference ranges will be provided on the listings of laboratory data. Clinical laboratory test results outside of the reference range will be flagged in the listings.

Laboratory grades will be reported, where applicable, using the Common Terminology Criteria for Adverse Events (CTCAE v4.0).

10.3.2. ECG Parameters

The following criteria will be used to flag electrocardiogram (ECG) values that are values of potential clinical importance:

To identify QTc (Fridericia's) values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign grades (see adverse event 'Electrocardiogram QT corrected interval prolonged'). Note that there is a slight inconsistency between NCI-CTCAE v4.0 and ICH E14 (Absolute QTc interval prolongation). It was decided to align with NCI-CTCAE v4.0 for the oncology standard categories.

ECG Parameter	Potential Clinical Importance (PCI) Range	Unit
Absolute QTcF interval	>450 to <481 (Grade 1) ≥481 to <501 (Grade 2) ≥501 (Grade 3)	msec
Increase from baseline QTcF	Increase of ≥31 to ≤60 Increase of >60	msec

The following criteria will be used to flag some ECG values that are values of potential clinical importance:

ECG Parameter	Potential Clinical Importance (PCI) Range	Unit
PR interval	<110 (L) and >220 (H)	msec
QRS interval	<75 (L) and >110 (H)	msec

Averages (rounded to the integer) are the basis of analyses when time point data is collected in triplicate.

10.3.3. Vital Signs

To identify heart rate values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Sinus bradycardia', 'Sinus tachycardia', 'Supraventricular tachycardia', and 'Ventricular tachycardia'.

The following criteria will be used to flag vital sign values (based on the averaged value) that are values of potential clinical importance:

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Decrease from baseline Heart Rate	Decrease to <60	bpm
Increase from baseline Heart Rate	Increase to >100	bpm

To identify blood pressure values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Hypertension'.

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Increase from baseline Systolic Blood Pressure	Increase to ≥120 to <140 (Grade 1) Increase to ≥140 to <160 (Grade 2) Increase to ≥160 (Grade 3)	mmHg
Increase from baseline Diastolic Blood Pressure	Increase to ≥80 to <90 (Grade 1) Increase to ≥90 to <100 (Grade 2) Increase to ≥100 (Grade 3)	mmHg

Systolic blood pressure below 120 and diastolic blood pressure below 80 are considered as normal range and will receive Grade 0 designations.

To identify temperature values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Hypothermia' and 'Fever'.

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Increase from baseline temperature	Increase to ≥38	Degrees C
Decrease from baseline temperature	Decrease to ≤35	Degrees C

Additionally, temperature and heart rate will be further categorized for reporting based on the following:

- Heart rate (beats/min): <60, 60-100, and >100; and
- Temperature (°C): ≤35, 35<-38, ≥38.

11. STUDY POPULATION

Unless otherwise stated, all tables and listings in this section will be based on the All Treated Population, and all summaries and data listings will use treatment labels as specified in Section 7.

11.1. Disposition of Subjects

A summary of the number of subjects in each of the analysis populations described in Section 7 will be provided. In addition, the number of subjects enrolled by center will be summarized by treatment group using the All Treated Population. A listing of subjects excluded from analysis populations will also be provided.

A summary of subject status and reason for study withdrawal will be provided. This display will show the number and percentage of subjects who withdrew from the study, including primary reasons for study withdrawal; the number and percentage of subjects who died will also be presented . Reasons for study withdrawal will be presented in the order they are displayed in the eCRF. In addition, a summary table and listing identifying reasons for screening failures will be presented.

A summary of study treatment status will be provided. This display will show the number and percentage of subjects who have discontinued study treatment and a summary of the primary reasons for discontinuation of study treatment. Reasons for study treatment discontinuation will be presented in the order they are displayed in the eCRF. A listing of study treatment discontinuation will be generated. The listing will include last dose date, and reasons for study treatment discontinuation as well as study part and phase of discontinuation.

11.2. Protocol Deviations

All protocol deviations will be summarized and listed and will include inclusion/exclusion deviations as well as other deviations.

A separate listing of inclusion/exclusion deviations will also be provided.

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11.3. Demographic and Baseline Characteristics

The demographic characteristics (e.g., age, race, ethnicity, sex, baseline height, and baseline body weight) will be summarized and listed. Age, height and weight will be summarized using the mean, standard deviation, minimum, median, and maximum. In addition, age will also be categorized and summarized by 18-64, 65-74, and >74. The count and percentage will be computed for sex and ethnicity. Planned treatment, if different from actual treatment, will be listed in demographic characteristics listing. In addition, for the re-enrolled subjects from Part 1 to Part 2, the information will be indicated in Part 2 demographic characteristics listing.

Race and racial combinations will be summarized and listed. Family history, history of tobacco use and alcohol intake at screening will be listed.

Disease history and characteristics: primary tumor type, histology, histologic grade, HPV status, time since initial diagnosis in months, stage at initial diagnosis, and time from last occurrence will be summarized. Indicators (yes/no) for the following, collected at screening, will also be summarized: measurable disease, non-target lesions, and progression on previous therapy. Medical conditions present at screening will be listed and will be summarized by past and current. Disease history and characteristics, as well as these medical conditions, will be presented in data listings.

Prior anticancer therapy will be coded using GSK Drug coding dictionary and will be classified by type (chemotherapy, immunotherapy, hormonal therapy, biologic therapy, small molecule targeted therapy, and vaccine, etc.). Some prior anticancer therapy may not have type available and will be summarized under “Missing” type. Prior anticancer therapy will be summarized by type of therapy. A subcategory immunotherapy - prior anti PD1/PD-L1 will be included in the summary table as well. A summary of the number of prior anticancer therapy regimens by type will also be produced. Prior anticancer therapy will be listed.

Prior anticancer radiotherapy will be listed. Prior cancer and non-cancer related surgeries will be summarized and listed.

11.4. Concomitant Medications

Concomitant medications will be coded using GSK Drug coding dictionary and listed. 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.

Blood products or blood supportive care products will be listed.

11.5. Subsequent Anticancer Therapies

Follow-up anticancer therapy will be coded using GSK Drug coding dictionary. A listing of follow-up anticancer therapy will show the relationship between preferred term and verbatim text; therapies will be classified by type (chemotherapy, immunotherapy, hormonal therapy, and biologic therapy, etc.).

On treatment and follow-up anticancer radiotherapy will be listed.

On treatment and follow-up cancer and non-cancer related surgeries, together with prior cancer and non-cancer related surgeries will be summarized and listed.

12. EFFICACY ANALYSES

12.1. 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. If the overall response reviewed by investigator is non-radiologic PD per RECIST v1.1 at a time point, the tumor response at that time point will be derived based on the assessments of target lesion, non-target lesion, and new lesion at that time point, using the below logic:

Target Lesion Response Assessment per RECIST v1.1	Non-target Lesion Assessment per RECIST v1.1	New Lesion Assessment per RECIST v1.1	Derived Overall Response per RECIST v1.1
No target lesion at baseline	CR	No	CR
No target lesion at baseline	NON-CR/NON-PD	No	NON-CR/NON-PD
No target lesion at baseline	NE	No	NE
No target lesion at baseline	PD	No	PD
No target lesion at baseline	PD	Yes	PD
No target lesion at baseline	Any	Yes	PD
CR	CR	No	CR
CR	NON-CR/NON-PD	No	PR
PR	NON-CR/NON-PD	No	PR
PR	NE	No	PR
SD	NON-CR/NON-PD	No	SD
SD	NE	No	SD
SD	No non-target lesion at baseline	No	SD
NE	NON-CR/NON-PD	No	NE
NE	No non-target lesion at baseline	No	NE
PD	any	any	PD
any	PD	any	PD
any	any	Yes	PD

ORR, DCR, DOR and TTR will be reported by both RECIST v1.1 and irRECIST.

12.2. Summary Measure

The evaluation of anticancer activity will be evaluated based on the All Treated Population as defined in Section 7 unless otherwise specified. Since this is a Phase I study, anticancer activity will be evaluated based on clinical evidence and response criteria. If data warrant, the response data will be summarized by dose level or expansion cohort type.

Lesion assessment method and timing, evaluation of disease, disease progression and response criteria will be conducted according to RECIST (version 1.1) [Eisenhauer, 2009] and irRECIST as outlined in Appendix 5 of the protocol. irRECIST will be used to determine treatment decisions and will be used for the primary analysis of anticancer activity.

12.2.1. Best Overall Response (BOR)

Best response will be summarized. A swimmer plot of study duration and best response will be produced by cohort.

12.2.1.1. Confirmed Best Overall Response (BOR)

The confirmed best overall response is the best confirmed response recorded from the start of treatment until disease progression or start of new anti-cancer therapy, whichever earlier, and will be determined programmatically based on investigator assessment at each time point. Note that if the investigator assessment is non-radiologic PD by RECIST v1.1 at a time point, the overall response will be derived based on the logic specified in Section 12.1. The derived overall response at that time point will be used to derive BOR.

If there are two assessments separated by not evaluable (NE) assessment(s) the best response shall be assessed applying the algorithm below, collapsing data by ignoring NE assessments.

12.2.1.1.1. Confirmed Best Overall Response per RECIST (version 1.1) Criteria and irRECIST Criteria

- To be assigned a status of SD/irSD, follow-up disease assessment must have met the SD/irSD criteria at least once after the first dose at a minimum interval of 77 days.
- If the minimum of 77 days for SD/irSD is not met, the best overall response will depend on the subsequent assessments. For example, if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement the best response will be PD. Alternatively, subjects lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.
- To be assigned a status of PR/irPR or CR/irCR, 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, irCR/irPR that do not meet the requirements of confirmed CR/PR, irCR/irPR are still eligible to be considered SD/irSD if it has met the SD/irSD criteria.

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12.2.1.1.2. Confirmed Best Overall Response per irRECIST Criteria

Besides the principles specified in Section 12.2.1.1.1, the below principle needs to be considered when deriving the confirmed BOR per irRECIST.

- To be assigned a status of confirmed irPD, a confirmatory disease assessment should be performed at the next disease assessment no less than 4 weeks (28 days) after the criteria for irPD are first met.
- irPD will not override a subsequent best overall response of irSD, irPR, or irCR, meaning that irPR or irSD can be assigned (timepoint response or BOR) even if new lesions have not regressed, or if unequivocal progression (non-target lesions) remains unchanged, providing that the criteria for confirmation of irPD are not met.

Confirmed and confirmed BOR per irRECIST (irBOR) takes into account the requirement for confirmation of irCR, irPR, and irPD. If irBOR is irPD and is confirmed consecutively, irBOR will be termed as 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 confirmed and unconfirmed 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 N/A (not applicable) and the unconfirmed irBOR will be termed as irUPD.

Examples of Scenarios of Assignments of Confirmed/Unconfirmed Best Overall Response Using irRECIST (assuming the adjacent timepoints are 28 days apart at least):

Case	Timepoint Response 1	Timepoint Response 2	Timepoint Response 3	Timepoint Response 4	Timepoint Response 5	Timepoint Response 6	Confirmed BOR	Unconfirmed BOR
1	irSD [1]	irPR	irPR	irCR	irCR	irPD	irCR	irCR
2	irPR	irSD [1]	irPR				irSD	irPR
3	irSD [2]	NE					NE	NE
4	irSD [2]	irCR	irCR	irPD			irCR	irCR
5	irSD	irSD	irSD	irPR			irSD	irPR
6	irPR	irPR	irPD	irPD			irPR	irPR
7	irPD	irPD [4]					irCPD	irCPD
8	irPD [3]	irPD [4]					N/A	irUPD
9	irPD	irSD [1]	irPD				irSD	irSD
10	irPD [4]						N/A	irUPD
11	irSD [2]	irPD [4]					N/A	irUPD
12	NE	irPD [4]					N/A	irUPD
13	irPD	NE	NE	NE	NE	NE	N/A	irUPD

Assume any two adjacent assessments are at least 28 days apart
[1] Assessment at least 77 days after the first dose
[2] Assessment less than 77 days after the first dose
[3] This assessment and next assessment is < 28 days
[4] Last assessment before the subject died/discontinued from study

12.2.1.2. Unconfirmed Best Overall Response

The unconfirmed best overall response is the best overall response cross visits and will be determined programmatically based on investigator assessment at each time point. Note that if the investigator assessment is non-radiologic PD by RECIST v1.1 at a time point, the overall response will be derived based on the logic specified in Section 12.1. The derived overall response at that time point will be used to derive BOR.

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If there are two assessments separated by not evaluable (NE) assessment(s), the best response shall be assessed applying the algorithm below, collapsing data by ignoring NE assessments.

12.2.1.2.1. Unconfirmed Best Overall Response per RECIST V1.1 and irRECIST Criteria

- To be assigned a status of SD/irSD, follow-up disease assessment must have met the SD/irSD criteria at least once after the first dose at a minimum interval of 77 days.
- If the minimum of 77 days for SD/irSD is not met, the best overall response will depend on the subsequent assessments. For example, if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement the best response will be PD. Alternatively, subjects lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

12.2.1.2.2. Unconfirmed Best Overall Response per irRECIST

Besides the principles specified in Section 12.2.1.2.1, irCPD and irUPD will be derived following the same principles described in Section 12.2.1.1.2.

12.2.2. Objective Response Rate (ORR) and Disease Control Rate (DCR)

ORR and 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 subjects achieving a (confirmed) CR/PR as BOR, as assessed by the investigator per RECIST 1.1 criteria (Note that if the investigator assessment is non-radiologic PD by RECIST v1.1 at a time point, the overall response will be derived based on the logic specified in Section 12.1).
- DCR is defined as the percentage of subjects achieving a (confirmed) CR/PR, or SD as BOR, as assessed by the investigator per RECIST 1.1 criteria (Note that if the investigator assessment is non-radiologic PD by RECIST v1.1 at a time point, the overall response will be derived based on the logic specified in Section 12.1). 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 at a minimum of 77 days.
- DCR with SD durability is defined as the percentage of subjects achieving a (confirmed) CR/PR, or SD≥161 days. A status of SD≥161 days will be assigned if the follow-up disease assessment has met the SD criteria at least once after the date of first dose at a minimum of 161 days.

Confirmation of responses is required for the final analysis.

ORR and DCR will be reported by both RECIST v1.1 and irRECIST. An adequate assessment is defined as an assessment where the Investigator determined response is irCR, irPR, or irSD.

12.2.3. Time to response (TTR)

Time to response (TTR) is defined as the time from the first dose of study treatment to the date of the first documented irCR or irPR. Only the subset of subjects who show a

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confirmed irCR or irPR from All Treated Population will be included in this analysis. TTR per RECIST v1.1 criteria is defined similarly.

Time to response will be listed.

12.2.4. Duration of response (DOR)

12.2.4.1. DOR per irRECIST

DOR will be derived and listed for subjects with a confirmed irCR or irPR. It is defined as the interval of time in months from the date of the first documented evidence of a confirmed response (irCR or irPR) to the date of first documented evidence of a confirmed disease progression according to radiological response from investigator assessment per irRECIST, or date of last adequate assessment of response, or the date of death due to any cause. An adequate assessment is defined as an assessment where the Investigator determined response is irCR, irPR, or irSD.

A summary of the assignments for progression and censoring dates for DOR per irRECIST is specified in the following table.

Assignments for Progression and Censoring Dates for DOR Analysis per irRECIST:

Situation	Date of Event (Progression/Death) or Censoring	Outcome Event (Progression/Death) Or Censored
No (or inadequate) baseline tumor assessments and the subject has not died (if the subject has died follow the rules for death indicted at the bottom of the table)	Start Date of Treatment	Censored
No post-baseline assessments and the subject has not died (if the subject has died follow the rules for death indicted at the bottom of the table)	Start Date of Treatment	Censored
Progression documented and confirmed at the next disease assessment and no less than 4 weeks apart	Date of first assessment of irPD which is confirmed consecutively	Event
Unconfirmed irPD followed by NE or another PK less than 4 weeks apart, or not further assessment,	Date corresponding irPD	Event

Situation	Date of Event (Progression/Death) or Censoring	Outcome Event (Progression/Death) Or Censored
and subject dies or discontinues from the study		
No progression (or death) or initiation of new anti-cancer therapy	Date of last 'adequate' assessment of response[1]	Censored
Received subsequent anti-cancer therapy prior to the date of documented events	Date of last 'adequate' assessment of respnose[1,2] (*prior to starting initiation of therapy*)	Censored
Death before first irPD assessment (or Death at baseline or prior to any adequate assessments)	Date of death	Event
Death or progression after more than one missed visit	Date of last 'adequate' assessment of response[2] *(prior to missed assessments), refer to Section 10.2.11*	Censored

1. An adequate assessment is defined as an assessment where the Investigator determined response is irCR, irPR, or irSD.
2. If irPD and New anti-cancer therapy occur on the same day assume the progression was documented first e.g., outcome is progression and the date is the date of the assessment of progression). If anti-cancer therapy is started prior to any adequate assessments, censoring date should be the start date of treatment.

12.2.4.2. DOR per RECIST

DOR will be derived and listed for subjects 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 confirmed response (CR or PR) to the date of first documented evidence of a confirmed disease progression according to radiological response from investigator assessment per RECIST, or date of last adequate assessment of response, or the date of death due to any cause. An adequate assessment is defined as an assessment where the Investigator determined response is CR, PR, or SD.

A summary of the assignments for progression and censoring dates for DOR per RECIST is specified in the following table.

Assignments for Progression and Censoring Dates for DOR Analysis per RECIST:

Situation	Date of Event (Progression/Death) or Censoring	Outcome Event (Progression/Death) Or Censored
No (or inadequate) baseline tumor assessments and the subject has not died (if the subject has died follow the rules for death indicted at the bottom of the table)	Start Date of Treatment	Censored
No post-baseline assessments and the subject has not died (if the subject has died follow the rules for death indicted at the bottom of the table)	Start Date of Treatment	Censored
Progression documented between scheduled visits	Date of assessment of progression[1]	Event
No progression (or death) or initiation of new anti-cancer therapy	Date of last 'adequate' assessment of response[2]	Censored
Received subsequent anti-cancer therapy prior to the date of documented events	Date of last 'adequate' assessment of respnose[2,3] (*prior to starting initiation of therapy*)	Censored
Death before first PD assessment (or Death at baseline or prior to any adequate assessments)	Date of death	Event
Death or progression after more than one missed visit	Date of last 'adequate' assessment of response[2] *(prior to missed assessments), refer to Section 10.2.11*	Censored

3. The earliest of (i) Date of radiological assessment showing new lesion (if progression is based on new lesion); or (ii) Date of radiological assessment showing unequivocal progression in non target lesions, or (iii) Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)
4. An adequate assessment is defined as an assessment where the Investigator determined response is CR, PR, or SD.
5. If PD and New anti-cancer therapy occur on the same day assume the progression was documented first e.g., outcome is progression and the date is the date of the assessment of progression). If anti-cancer therapy is started prior to any adequate assessments, censoring date should be the start date of treatment.

13. SAFETY ANALYSES

Unless otherwise specified, all the safety analyses will be based on the All Treated Population as defined in Section 7 and summaries will include all events or assessments collected during the study. All the analyses will be performed by groups identified in Section 9.

13.1. Extent of Exposure

Extent of exposure to GSK3174998 and pembrolizumab will be summarized separately.

The number of subjects and duration of exposure to study treatment in weeks (from first day to last day of treatment + 1 days) will be summarized. Descriptive statistics including mean, median, standard deviation, minimum, and maximum will be calculated for time on study treatment. Moreover, time on study treatment will be categorized in different time period: <3 months, 3 months to 6 months, >6 months to 12 months and >12 months.

The number of infusions administered as study treatment will be summarised with mean, median, standard deviation, minimum, and maximum.

Infusion dose intensity (the cumulative doses, divided by the total number of infusions) will be summarized using mean, median, standard deviation, minimum, and maximum. The cumulative dose is the sum of the doses administered during each infusion for a subject.

The relative dose intensity (%) of GSK3174998 is the infusion dose intensity divided by the target dose.

The number of dose delays and reasons for dose delays will be summarized.

All infusion interruptions and dose delays will be listed separately.

13.2. Adverse Events

AEs will be coded to the preferred term (PT) level using the Medical Dictionary for Regulatory Affairs (MedDRA dictionary) and grouped by system organ class (SOC). AEs will be graded by the investigator according to the NCI-CTCAE v4.0.

An overview summary of on-treatment AEs, including counts and percentages of subjects with the below category will be produced:

- Any AEs
- Treatment-related AEs
- AEs of special interest (AESI)
- AEs leading to discontinuation of study treatment
- AEs leading to dose reduction
- AEs leading to dose interruption/delayed
- and AEs leading to study withdrawal
- SAEs

- Treatment-related SAEs
- Fatal SAEs
- Treatment-related fatal SAEs

On-treatment AEs (or treatment-emergent AEs) include those with onset dates on or after the first study treatment dose date (this can be either GSK 3174998 or pembrolizumab). Treatment-related AE and AEs leading to discontinuation of study treatment will further be summarized by the treatment to which causality was attributed for Part 2.

Events will be summarized by frequency and proportion of total subjects, by PT. Separate summaries will be given for:

- All AEs
- Treatment-related AEs (for Part 2, the summary will include AEs related to GSK3174998 or Pembrolizumab or both)
- AEs leading to discontinuation of study treatment (for Part 2, the summary will include AEs leading to discontinuation of GSK3174998 or Pembrolizumab or both)
- AEs leading to study withdrawal
- SAEs
- Treatment-related SAEs
- AEs recorded as dose-limiting toxicities
- AESI

The summary by PT will be sorted by descending incidence.

On-treatment AEs will be summarized by the maximum grade according to the NCI-CTCAE v4.0 and sorted by PT and by PT in descending order of total incidence. The summary will use the following algorithms for counting the subject:

- **Preferred term row**: Subjects experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.
- **Any event row**: Each subject with at least one adverse event will be counted only once at the maximum grade no matter how many events they have.

All AEs will be listed.

13.3. Adverse Events of Special Interest

Characteristics (e.g., number of occurrences, action taken, grade, etc.) of AESI (also referred to as immune-related adverse event, see Appendix 11 in protocol) will be summarized separately.

In addition, AESI will be listed separately.

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13.4. Deaths and Serious Adverse Events

In the event that a subject has withdrawn consent, no data after the withdrawal of consent date from this subject including death is supposed to appear in the database, which should be part of the data cleaning process. All deaths will be summarised based on the number and percentage of subjects. This summary will classify subjects and primary cause of death as collected on the eCRF. A supportive listing will be generated to provide subject-specific details on subjects who died.

Summaries related to SAEs are specified in Section 13.2.

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

- Fatal SAEs
- Non-Fatal SAEs.

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

AEs Leading to Discontinuation of Study Treatment will be summarized separately in descending order of total incidence by PT only and separate supportive listings will be generated with subject level details for those subjects:

- AEs leading to discontinuation of study treatment
- AEs leading to withdrawal from the study

13.6. 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 female subjects or female partners of male subjects become pregnant while on the study, the information will be included in the narratives and no separate table or listing will be produced.

13.7. Clinical Laboratory Evaluations

The assessment of laboratory toxicities will examine the following laboratory tests:

Clinical Chemistry: Total bilirubin, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase, Total protein, Albumin, Sodium, Potassium, Calcium, Urea/Blood Urea Nitrogen (BUN), Creatinine, Creatinine Clearance, and Glucose.

Hematology: Hemoglobin (HGB), Hematocrit (HCT), Platelet count, Red Blood Cell (RBC) count, White Blood Cell (WBC) count, Neutrophils (Absolute), Lymphocytes (Absolute), Monocytes (Absolute), Eosinophils (Absolute), Basophils (Absolute),

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Neutrophils (%), Lymphocytes (%), Monocytes (%), Eosinophils (%) and Basophils (%); RBC indices (MCV and MCH).

Thyroid Function Test: Thyroid-stimulating hormone (TSH) and free thyroxine (T4 and T3) test.

Urinalysis: pH, Microscopic examination, Specific gravity, Ketones, Protein, and Glucose, Blood.

Hepatitis Screening: Hepatitis B (HBsAg) and Hepatitis C (Hep C antibody).

Pregnancy Screening: Serum β–hCG pregnancy test (as needed for women of child bearing potential).

Laboratory grades will be reported using the NCI-CTCAE v4.0.

Summaries of lab data by maximum toxicity grade will be provided.

Summaries of worst case grade increase (including unscheduled assessments) from baseline grade will be provided for all the lab tests that are gradable by NCI-CTCAE v4.0. These summaries will display the number and percentage of subjects with a maximum post-baseline grade increasing from their baseline grade. Any increase in grade from baseline will be summarized along with any increase to a maximum grade of 3 and any increase to a maximum grade of 4. Missing baseline grade will be assumed as grade 0. In addition, the summary will include grade increase from baseline by scheduled visits. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Separate summary tables for hematology and clinical chemistry laboratory tests will be produced.

A supporting listing of abnormal urinalysis data will be provided.

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

13.7.1. Analyses of Liver Function Tests

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

A plot of maximum total bilirubin versus maximum ALT will be generated. A trellis display of LFT shifts from baseline to maximum values will be provided. A matrix display of LFT results will also be produced.

13.8. Other Safety Measures

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

13.8.1. Vital Signs

Values of vital signs will be listed. The categories defined in Section 10.3.3 will be flagged in listings.

13.8.2. Performance Status

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

A supporting listing will also be provided.

13.8.3. ECG

For numerical values measured in triplicate, averages at each visit will be the basis of analysis summaries.

The QTc values based on Fridericia formula (QTcF) will be rounded to the integer and the values will be categorized into the ranges identified in Section 10.3.2.

The changes in QTc values will be categorized into the clinical concern ranges which are specific to changes in QTc: 31-60 and >60 msec. Similarly, categories identified for PR interval and QRS interval will also be reported.

Listings of abnormal ECG findings and a listing of ECG values will be provided with PCS records flagged.

14. HEALTH OUTCOMES ANALYSES

No health outcomes analyses were planned for the study.

15. PHARMACOKINETIC ANALYSES

Statistical analysis of GSK3174998 and pembrolizumab pharmacokinetic parameters will be performed by, or under the direct auspices of, Oncology Quantitative Sciences (Statistician), GSK or Merck.

15.1. Drug Concentration Measures

PK analysis of GSK3174998 and pembrolizumab drug concentration-time data will be conducted by non-compartmental methods under the direction of CPMS, Quantitative Sciences, GSK or Merck.

Drug concentration-time data will be listed for each subject and summarized by descriptive statistics at each time point by cohort.

15.2. Deriving and Summarizing Pharmacokinetic Parameters

For the calculation of individual pharmacokinetic profiles, if one or more non-quantifiable (NQ) values occur in a profile before the first measurable concentration, they will be assigned a value of zero concentration. For linear plots, zero concentration value(s) before the first measurable concentration will be included in the plot. For log-linear plots, zero concentration value(s) before the first measurable concentration will be assigned a missing value.

If a single NQ value occurs between measurable concentrations in a profile, the NQ should generally be omitted (set to missing) in the derivation of pharmacokinetic parameters, statistical analysis, and the individual subject plots. If two or more NQ values occur in succession between measurable concentrations, the profile will be deemed to have terminated at the last measurable concentration prior to these NQs.

For the purpose of individual subject plots, these NQs will be set to 0, and the subsequent measurable concentrations will be retained. For the derivation of pharmacokinetic parameters, these NQs and any subsequent measurable concentrations will be omitted (set to missing).

NQs which occur after the last measurable concentration will be omitted (set to missing) in the derivation of pharmacokinetic parameters and from the individual subject plots. In some circumstances, there may be a pharmacokinetic rationale for fluctuation resulting in non-measurable concentrations in the middle of the concentration-time profile (e.g., entero-hepatic recycling, erratic absorption from transdermal/inhaled formulations). In these cases, the NQ values could be set to missing or to some other values (e.g., ½ LLQ) and subsequent valid concentrations may be retained. A reference line indicating LLQ will be included in plots.

For the calculation of mean or median pharmacokinetic profiles, when estimating the mean or median value for the concentration at a given time point (i.e., descriptive mean or median curve), the following guidelines should be considered:

All NQ values will be set to zero except when an individual NQ falls between two quantifiable values, in which case it will be omitted from the calculation of mean or median profiles. Measurable concentrations which follow more than one consecutive mid-profile NQ will be omitted (set to missing).

The mean/median value at a time-point where one or more samples have NQ values will be reported (in tabular or graphical fashion) even if the mean/median value is below the

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LLQ of the assay. For linear plots, zero concentration value(s) will be included in the plot. For log-linear plots, zero concentration value(s) will be assigned a missing value. Zero mean or median values will be included in summary tables. PK concentration values will be summarized.

The pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices. All calculations of non-compartmental parameters will be based on actual sampling times. The following PK parameters will be determined if data permit:

- Cmax
- Cτ
- area under the plasma concentration-time curve AUC(0-τ) (repeat dosing)
- apparent terminal phase elimination rate constant (λz)
- apparent terminal phase half-life (t½)
- systemic clearance of parent drug (CL)
- steady-state volume of distribution (Vss)

All derived PK parameters will be listed. For each of these parameters, the following summary statistics will be calculated for each dose level: median, minimum, maximum, arithmetic mean, 95% confidence interval for the arithmetic mean, standard deviation, coefficient of variation (CV = sqrt (exp (SD2) - 1) * 100 [NOTE: SD = SD of log transformed data]), geometric mean, 95% confidence interval for the geometric mean and standard deviation of logarithmically transformed data. 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.

15.3. Statistical Analyses

There's no statistical analysis planned on PK data.

15.4. 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.

16. PHARMACODYNAMIC AND BIOMARKERS ANALYSES

16.1. Pharmacodynamic and Biomarker Analyses

Receptor occupancy data will be summarized and plotted.

Other biomarker data may be reported separately from the main clinical study report, generated by GSK biomarker team if applicable. All endpoints of interest from all

comparisons will be descriptively and/or graphically summarized as appropriate to the data.

16.2. Immunogenicity Analyses

Serum samples will be collected and tested for the presence of antibodies that bind to GSK3174998 and pembrolizumab. Serum samples for testing anti-GSK3174998 and anti-pembrolizumab antibodies will be collected as described in the Time and Events schedule (protocol Section 7.1). 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.

The timing and number of planned immunogenicity samples may be altered during the course of the study, based on newly-available data to ensure appropriate safety monitoring. In the event of a hypersensitivity reaction that is either 1) clinically-significant in the opinion of the investigator, or 2) leads to the subject withdrawing from the study, blood samples should be taken from the subject for immunogenicity testing at the time of the event and again 30 days, 12 weeks, and 24 weeks after. For subjects who prematurely withdraw from the study, immunogenicity testing will occur at withdrawal and at follow-up 30 days, 12 weeks, and 24 weeks after the last dose.

Serum will be tested for the presence of anti-GSK3174998 antibodies using the currently approved analytical methodology using a tiered testing schema: screening, confirmation and titration steps. The presence of treatment emergent ADA will be determined using a GSK3174998 bridging style ADA assay with a bio-analytically determined cut-point determined during assay validation. Samples taken after dosing with GSK3174998 that have a value at or above the cut-point will be considered treatment-emergent ADA-positive. These ADA positive samples will be further evaluated in a confirmatory assay, and confirmed positive samples will be further characterized by assessment of titer. Number and percentage of subjects with confirmed positive immunogenicity at each visit will be summarized. Denominator for the percentage is number of subjects with non-missing Screening, Confirming or Titer results at each visit. Results of anti-GSK3174998 antibody testing will be listed.

16.3. Translational Research Analyses

The results of translational research investigations may be reported in the main clinical study report (CSR). All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

17. PHARMACOGENETIC DATA ANALYSES

Further details on PGx analyses discussed in the protocol Appendix 7 may be identified/addressed in a separate PGx RAP, if applicable.

18. REFERENCES

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