Statistical Analysis Plan

Study ID: 204653

Official Title of Study: An open-label, dose escalation study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of GSK3326595 in participants with solid tumors and non-Hodgkin's lymphoma

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Title	:	Reporting and Analysis Plan for a Phase I, Open-label, Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of GSK3326595 in Subjects with Solid Tumors and Non-Hodgkin's Lymphoma
Compound Number	:	GSK3326595
Effective Date	:	08 December 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 204653.
- This RAP is intended to describe the interim analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

RAP Author(s):

Approver	Date	Approval Method
PPD Senior Biostatistician II, ICON PLC	02/12/2022	Email
PPD Principal Statistician, GSK	05/12/2022	Email

RAP Team Review Confirmations:

Approver	Date	Approval Method
PPD Principal Programmer, Clinical Statistics	02/09/2022	Email
PPD Oncology Clinical Development	01/09/2022	Email
PPD Safety and Medical Governance Lead	31/08/2022	Email
PPD Clinical Pharmacology	28/11/2022	Email
PPD Scientific Writer	01/09/2022	Email

Clinical Statistics and Clinical Programming Line Approvals:

Approver	Date	Approval Method
PPD Statistics Leader		Pharma TMF e-signature
PPD		Pharma TMF e-signature

TABLE OF CONTENTS

PAGE

1. INTRODUCTION

This reporting and analysis plan (RAP) details all planned analyses required for a Clinical Study Report of study 204653.

The RAP was written by staff of ICON Clinical Research. The execution of primary and secondary analyses of the RAP, with exception to mTPI analysis and Part 2 Bayesian hierarchical design analysis, will be undertaken by staff of ICON Clinical Research. Additional interim and ad hoc analyses are also described within this document.

In addition, pharmacodynamic/ biomarker analysis and translational research analysis maybe identified and addressed in a separate RAP, if applicable. Exploratory analyses may be conducted at a later time.

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

1.1. Revision Chronology:

Version	Date	Revision Description
1.0	8 Sep 2022	Original
1.1	12 Sep 2022	• Section 4.1: Removed stray bullet in Table 7. • Section 6.3: Corrected reference in to Section 4.2 (not 4.1). • Section 7.2.6: Updated description of TTR endpoint in Section 7.2.6 from time-to-event to continuous variable • Section 15.12.12: Updated example shell for Listing 55 to “custom per GSK”.
1.2	21 Sep 2022	• Section 7.2.4: Added the survival estimates to be presented and the method for calculating 95% CI, as it differs from the estimates in Section 7.1.3. • Section 7.27: Added the estimates presented and method for calculating 95% CI.
1.3	30 Sep 2022	• Figure 4.5 should be linear not log-transformed parameters. • Added Section 3.1.3 to account for interim analysis that used evaluable population on Part 1 subjects. • Added evaluable population definition for Part 1 subjects for interim analysis.
1.4	18 Oct 2022	• Added hyperlinks within the text. • Added “number of infusions” to Section 8.1.1.1. • Added “calcium corrected” to list of chemistry measures in Section 8.4.1. • Updated titles for Table 3.21, Table 3.65, Table 4.5, Figures 4.6, Listing 14, Listing 79, Listing 82, and programming notes for Table 4.5 Table 4.7 and Figure 4.1 Figure 4.4 in Section 15.12. • Added more text to Section 8.4.6, and hepatobiliary injury definition. • Removed Figure 4.5 per GSK. • Added number category definitions for SBP and DBP in Section 15.8.3.
1.5	10 Nov 2022	• Corrected template references for Table 3.48 and Table 3.50 in Section 15.12. • Corrected subgroup for Listing 29 which should be ACC only.
1.6	18 Nov 2022	• Update Listing 77 and 78 titles to match previous delivery.

		• Update vital signs and ECG category descriptions in Section 15.8 to be more consistent with NCI-CTCAE grade definitions. • Add 2 more PK summaries and 2 more PK listings for Pembrolizumab PK concentration and immunogenicity. Add log-linear figures 4.2 and 4.3 per GSK request (R. Parasrampuria). • Update notes for Listing 80 and 81, as only Part 1 had samples collected.

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 protocol amendment 8 (dated: 20/APR/2022).

Section 2.2 replicates what is in protocol amendment 8 (dated 20 April 2022).

In general, the plan will be to report all the primary and secondary outcomes, and none of the exploratory outcomes (including pharmacodynamics and genetics outcomes). The following is the exception to this plan:

- Additional secondary analyses, for Part 1 are investigator-assessed percent change from baseline, and maximum percent reduction from baseline in sum of diameters, and progression-free survival (PFS), defined as time from first dose until radiographic progression per standard criteria, or death due to any cause, whichever is earlier.
- All Part 2 ACC cohorts will be included in the overall survival analysis.
- Time to response listings will be included with duration of response analyses for ACC TN cohort.
- All NHL P53 cohorts are being compared as part of secondary analyses, not exploratory analyses.
- PK analyses are considered secondary.
- Progression free survival (PFS) rate at six months after starting GSK3326595 will be conducted as a secondary analysis for all Part 2 cohorts not including GBM (for which this is the primary analysis).
- Progression free survival (PFS) rate at six months after starting GSK3326595 will be estimated using Kaplan-Meier plots (only) as a secondary analysis for Part 1 and Part 3 cohorts.

White blood cells will be included with laboratory assessments summarized. (Section 8.4.2)

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

The following tables represents the study objectives and endpoints as described in the protocol. Footnotes indicate changes to the SAP from the protocol which are also listed in Section 2.1.

2.2.1. Part 1 Dose Escalation

Objectives	Estimands / Endpoints
Primary	Primary
• To determine the safety, tolerability, and maximally tolerated dose (MTD) of orally administered GSK3326595 in subjects with solid tumors	• Adverse events (AEs), serious adverse events (SAEs), dose limiting toxicities (DLTs), withdrawals due to AEs, dose interruptions and reductions, and changes in safety assessments (e.g., clinical laboratory parameters, vital signs, physical examinations, and organ-specific parameters)
Secondary	Secondary
• To determine the recommended Phase 2 dose (RP2D) of orally-administered GSK3326595	• Safety profile (AEs, SAEs, DLTs), clinical response, and pharmacodynamic (PD) data [1]
• To describe the pharmacokinetics of GSK3326595 after single- and repeat-dose administration	• GSK3326595 PK parameters in plasma following single (Day 1) and repeat-dose administration of GSK3326595
• To determine clinical activity of GSK3326595	• Overall response rate (ORR; CR + PR), based on Response Evaluation Criteria in Solid Tumors (RECIST 1.1 criteria) [2]
• To evaluate the preliminary effects of fed versus fasted administration on the pharmacokinetics of GSK3326595	• GSK3326595 PK parameters in plasma following single-dose administration of GSK3326595 in a fed or fasted state
• To evaluate the relative bioavailability of GSK3326595 tablets as compared to capsules	• GSK3326595 PK parameters in plasma following single-dose administration of GSK3326595 in tablet or capsule formulation
Exploratory	Exploratory
CCI [redacted]	

Objectives	Estimands / Endpoints
CCI [redacted]	

2.2.2. Part 2: Dose Expansion

Objectives	Estimands / Endpoints
Primary	Primary
• To determine clinical activity of GSK3326595 in disease-specific expansion cohorts	• Solid tumor cohorts (non-GBM): Overall response rate (ORR, defined as % of subjects achieving a best response of CR and PR) based on RECIST 1.1 criteria; • GBM cohort: Six-month progression free survival (PFS) rate, defined as the percentage of subjects free from radiographic progression per Response Assessment in Neuro-Oncology (RANO) criteria, or death due to any cause, for six months after starting GSK3326595. • Non-Hodgkin's lymphoma cohort(s): ORR (% of subjects achieving CR and PR) based on Lugano criteria

Objectives	Estimands / Endpoints
Secondary	Secondary
• To further describe the clinical activity of GSK3326595	• PFS, defined as time from first dose until radiographic progression per standard criteria, or death due to any cause, whichever is earlier. • GBM cohort: Overall response rate (CR + PR) based on RANO Working Group criteria. • ACC tablet cohort: duration of response (DOR), defined as time from first evidence of response (CR or PR per RECIST 1.1) to earlier date of disease progression or death due to any cause, as determined by investigator assessments.[1] • ACC tablet cohort: Overall survival (OS), defined as time from first dose until death from any cause in ACC subjects who are systemic-treatment naïve [2]
• To evaluate the safety and tolerability of GSK3326595 in subjects treated at the RP2D	• AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., clinical laboratory parameters, vital signs, physical examinations, and organ-specific parameters)
Exploratory Objectives	Exploratory Endpoints
CCI [redacted]	

Objectives	Estimands / Endpoints
CCI [redacted]	

2.2.3. Part 3: Combination with Pembrolizumab

Objectives	Estimands / Endpoints
Primary	Primary
• To determine the safety and tolerability of orally-administered GSK3326595, administered in combination with pembrolizumab, in subjects with solid tumors	• AEs, SAEs, withdrawals due to AEs, dose interruptions and reductions, and changes in safety assessments (e.g., clinical laboratory parameters, vital signs, physical examinations, and organ-specific parameters)
Secondary	Secondary[1]
• To determine the RP2D of orally-administered GSK3326595, when administered in combination with pembrolizumab	• Safety profile (AEs, SAEs), clinical response, PK, and pharmacodynamic (PD) data

Objectives	Estimands / Endpoints
• To describe the clinical activity of GSK3326595 in combination with pembrolizumab in subjects with solid tumors	• Overall response rate (% of subjects achieving CR and PR) based on iRECIST 1.1 criteria
• To describe the pharmacokinetics of GSK3326595 after single and repeat dose administration of GSK3326595, when administered in combination with pembrolizumab	• GSK3326595 PK parameters in plasma following single- (Day 1) and repeat-dose administration
Exploratory Objectives	Exploratory Endpoints

CCI

[redacted]

2.3. Study Design

This is an open-label, repeat-dose, multicenter, three-part study to establish the MTD/RP2D (based on the profile of safety and tolerability) and preliminary clinical efficacy of orally-administered GSK3326595, administered as a single agent in subjects with solid tumors and non-Hodgkin's lymphoma, or administered in combination with pembrolizumab in subjects with select solid tumors.

The schedule for study assessments can be found in Protocol Section 8.

2.3.1. Part 1: Dose Escalation

The primary objective of Part 1 is to identify the MTD of GSK3326595 when administered orally in subjects with solid tumors. Dosing will start at 12.5 mg once daily and escalate until the MTD is reached. In Part 1, any subject who prematurely discontinues therapy during the DLT observation period for reasons other than a DLT will be replaced by additional subject(s) assigned to the same dose level. At or about the MTD, additional subjects will be enrolled in an exploratory expansion cohort to obtain additional PK, PD, and samples for analysis of GSK3326595 and its metabolites. Subjects will also be enrolled at or about the RP2D into a food effect and relative bioavailability sub-study to evaluate the effects of food and GSK3326595 formulation on GSK3326595 pharmacokinetics.

It is estimated that up to 66 subjects will be enrolled into the dose escalation cohort of the study, including approximately 42 subjects to identify the MTD, approximately 12 subjects in the PK/PD/metabolite/biomarker expansion cohort(s), and approximately 12 subjects in the food effect and relative bioavailability sub-study. The study population will be adults, with histologically- or cytologically-confirmed solid malignancies.

Part 1: Dose Escalation Decisions and Determination of MTD

Dose escalation will be conducted in two stages: dose exploration and MTD confirmation. Details are described in Protocol Section 4.2. Section 2.2, Section 4.2.3, and Section 4.2.4.

Projected daily dose levels of GSK3326595 are 12.5 mg, 25 mg, 50 mg, 100 mg, 200 mg, 400 mg, 600 mg, 800 mg, and 1200 mg. BID dosing may divide this total daily dose into two equal doses, administered twice daily. Additional doses (either lower than 12.5 mg, higher than 1200 mg, or intermediate doses between those listed above) and schedules may be explored based on emerging safety, PK, and PD data

The dose-escalation decision and rationale for each cohort will be discussed with investigators during teleconference(s) and documented in writing with copies maintained at each study site and in the master study files at GlaxoSmithKline (GSK).

The dose escalation portion of Part 1 is expected to be completed when approximately 42 subjects enrolled in the dose escalation and dose confirmation stages have completed the DLT evaluation period. The RP2D will be the MTD or a lower dose that provides adequate PK exposure and biologic activity with superior tolerability. The identification

of MTD may not be necessary if a clear RP2D emerges without reaching the MTD. The final determination of RP2D will be based on the mTPI suggested dose level, or the biologically active dose (e.g., clinical response), the safety profile, and available PK and PD data generated from all subjects in Part 1. If necessary, alternate schedules can be explored to determine additional biologically active doses even after a RP2D is defined. Subjects may be enrolled at previously completed dose levels for the purpose of obtaining additional safety, PK, PD, metabolite, or biomarker data. Paired fresh biopsies (pre- and post-dose) may be required in these subjects based on the need to obtain tumor PD data. In addition, a reduced PK schedule may be used in subjects enrolled to obtain additional PK/PD data

Part 1: PK/PD, Metabolite, and Biomarker Expansion Cohort(s)

Any dose level at or near the MTD/RP2D in Part 1 may be expanded up to 12 subjects in order to collect additional data on safety and pharmacokinetics (PK). More than one dose level may be selected for expansion (e.g., to establish a dose-response curve for PD or other biomarkers), based on emerging data. Clinical samples from this/these cohort(s) will also be collected for analysis of pharmacodynamics (PD), metabolite profiling, and biomarkers. Subjects may be enrolled into this cohort even after MTD/RP2D has been identified and Part 2 of the study has been initiated.

Refer to Protocol Section 8.1, Time and Events Table (Table 10), which highlights the additional sampling requirements for this cohort.

Food Effect and Relative Bioavailability Sub-Study

Part 1 will include a sub-study that will be an open-label, randomized, single dose, three period, cross over study to investigate the effect of a high-fat, high-calorie meal on the bioavailability of GSK3326595, and compare two formulations of GSK3326595 (capsule versus tablet). The dose of GSK3326595 will be 300 mg once a day (QD). GSK3326595 dosing will be separated by at least 48 hours between each period. Up to 12 subjects in the United States may be enrolled in the sub-study. A subject requiring dose reduction or discontinuation from study before completion of the sub-study will be replaced by a new subject. Depending on the data from the initial 12 subjects, up to an additional 12 patients may be enrolled in this sub-study.

Subjects enrolled in the sub-study will be assigned to one of two sequences, as described in Table 1; equal numbers will be assigned to each sequence.

Table 1 Food Effect and Relative Bioavailability Sub-Study

Sample Size	Sequence	Period 1 (D1)	Period 2 (D4)	Period 3 (D8)
6	1	Fasted / tablet	Fed / tablet	Fasted / capsule
6	2	Fed / tablet	Fasted / tablet	Fasted / capsule

Fasted: Subjects should take nothing by mouth apart from water and other medications for at least 8 hours before drug administration and should continue fasting until at least 4 hours after administration of the morning dose. Subjects should be administered the drug product as a capsule or tablet (as indicated) with 200 mL (8 fluid ounces) of water. Water

can be allowed, as desired, except for one hour before and after drug administration. All subjects will receive standardized meals at approximately 4- and 9- hours post dose. Additional details of the meals will be provided in the SRM.

Fed: Following an overnight fast (at least 8 hours), subjects should start the recommended high fat, high calorie breakfast 30 minutes prior to administration of the GSK3326595. Study subjects should eat this meal in 30 minutes or less; however, GSK3326595 should be administered 30 minutes after start of the meal. The GSK3326595 should be administered as a tablet with 200 mL (8 fluid ounces) of water. No food should be allowed for at least 2 hours post-dose. Water can be allowed, as desired, except for one hour before and after drug administration. All subjects will receive standardized meals at approximately 4- and 9- hours post dose. Further details of the meals will be provided in the SRM.

Any subject who experiences vomiting within 3 hours of dosing will be removed from the statistical analysis of PK comparability between tablet/capsule and tablet (fasted)/tablet (fed), and additional subjects will be enrolled to ensure 12 subjects complete all three periods.

The Day 4 (Period 2) visit may be performed on Day 4 or Day 5. The Day 8 (Period 3) visit (capsule administered in a fasting state) may be performed ± 1 day. Continuous daily dosing with GSK3326595 will only commence once the subject has completed the Period 3 visit, irrespective of whether that visit occurs ± 1 day.

If the GSK3326595 tablet bioavailability is comparable to that of the GSK3326595 capsules, all new and ongoing subjects may be switched from capsules to tablets for the remainder of the study, once they have been notified by the Sponsor.

Note that per GSK communication, 3Nov2021, tablet and capsule cohorts within the same disease/dosage groups will be combined.

2.3.2. Part 2: Disease-Specific Expansion Cohort(s)

Once the RP2D has been determined, subjects will be enrolled in disease-specific expansion cohorts at the RP2D in order to better characterize the clinical activity and safety profile of GSK3326595. Expansion cohorts will enroll subjects with TNBC, mTCC, recurrent GBM, NHL (all subtypes recruited to Protocol Amendments 1-4 and indolent subtypes of NHL recruited to Protocol Amendment 5 onwards, which will be analyzed based on TP53 status: p53 mutant and p53 wild-type), ACC (which will be separated into two separate cohorts: one dosed with GSK3326595 capsules, and a second dosed with GSK3326595 tablets [this tablet cohort will enroll subjects who have not received any systemic therapy for their locally advanced or metastatic ACC]), ER+BC, HPV-positive solid tumors of any histology, and p53 wild-type NSCLC of any histological subtype. CCI [redacted]

Subjects in Part 2 will start with a continuous daily dosing schedule unless safety, PK or PD data necessitate a different dosing schedule. The final dose and regimen for Part 2

will be decided upon completion of dose escalation in Part 1. Dose reduction and/or scheduled interruptions will be permitted based on tolerability and toxicity.

Plasma samples for PK evaluation will be collected, at reduced frequency compared to Part 1, in all subjects. Plasma samples and other clinical samples (e.g. lymph node or bone marrow biopsies) will be collected pre- and post- study drug treatment as defined in the Time and Events Table in protocol Section 8.1 for the PD evaluations. The timing of samples may be altered and/or extra samples may be obtained at additional time points to ensure thorough PK and PD monitoring. For example, the timing of PK and PD monitoring maybe moved earlier or later in the evaluation schedule based on emerging preclinical or clinical data that suggests a more optimal time frame to monitor biologic activity.

It is estimated that up to 316 subjects will be enrolled in the disease-specific expansion cohorts of the study. Cohorts will initially be limited to the following diseases in Table Table 2. However, additional tumor-specific cohort(s) may be added based upon emerging pre-clinical and clinical data from Part 1 or Part 2 of the study:

In Part 2, subjects will not be replaced if they prematurely discontinue therapy. Initially, the NHL cohorts enrolled subjects irrespective of histological subtype. However, in December 2019 it was noted that of the subjects enrolled with high-grade and other aggressive subtypes of diffuse large B-cell lymphoma (DLBCL), including double- and triple-hit lymphomas, there were zero objective responses out of 14 subjects dosed. Conversely, clinical benefit was observed in subjects with more indolent subtypes (including complete/partial responses in were observed in subjects with FL and tFL, and stable disease for several disease assessments was observed in subjects with MCL). Therefore, Protocol Amendment 5 limited further enrollment to this population to subjects with more indolent disease who may receive more benefit from treatment with GSK3326595 monotherapy.

Table 2 Part 2 Cohorts and Number of Subjects

Cohorts	Number of Subjects
Triple-negative breast cancer (TNBC)	Up to 32
Metastatic transitional cell carcinoma of the urinary system (mTCC)	Up to 40
Glioblastoma multiforme (GBM)	Up to 28
Non-Hodgkin's lymphoma all subtypes recruited to Protocol Amendments 1-4 and indolent subtypes of NHL recruited to Protocol Amendment 5 onwards, without mutations in the TP53 gene (p53 wild-type, NHL [-])	Up to 25
Non-Hodgkin's lymphoma all subtypes recruited to Protocol Amendments 1-4 and indolent subtypes of NHL recruited to Protocol Amendment 5 onwards, with mutations in the TP53 gene (p53 mutant, NHL [+])	Up to 25
Adenoid cystic carcinoma (ACC), dosed with GSK3326595 capsule formulation	Up to 38
Adenoid cystic carcinoma (ACC), dosed with GSK3326595 tablet formulation, in a population that is systemic therapy-naïve	Up to 50
Hormone receptor-positive adenocarcinoma of the breast (ER+BC)	Up to 35

Cohorts	Number of Subjects
Human papillomavirus (HPV) positive solid tumors of any histology	Up to 28
p53 wild-type non-small cell lung cancer (NSCLC) of any histological subtype	Up to 15

Subjects will start dosing on Day 1 with the dose and schedule selected as the RP2D in Part 1 of the study. At a 21 March 2018 investigator meeting, 400 mg once daily (QD) was selected as the RP2D, based on safety, tolerability, efficacy, PK, and PD. Dose reductions and scheduled interruptions are permitted for toxicity and tolerability as described in Table 3. At that meeting, it was also determined that if emerging data demonstrated that 400 mg QD proved intolerable for a majority of subjects, that the starting dose for all subjects enrolled from that time forward may be reduced (e.g., to Dose level [DL]-1). The final dose selection will take into account all available clinical data, as well as a PK/PD model to predict the optimal dose with minimal cytopenias.

All new subjects enrolled, following approval of Protocol Amendment 4 (food effect and relative bioavailability sub-study in Part 1, and all dose expansion cohorts in Part 2), will start on 300 mg QD (i.e., at Dose level-1 [DL-1] in Table 3). In all cohorts, dose reduction for toxicity will be permitted, as described in Table 3). .

Table 3 RP2D and Planned Dose Reduction

RP2D	400 mg QD
DL-1	300 mg QD
DL-2	200 mg QD
DL-3	200 mg QD, administered for 3 weeks, followed by a 1-week rest period

Note: These dose levels may be adjusted on a case-by-case basis after discussion with the GSK medical monitor.

2.3.3. Part 3: GSK3326595 + Pembrolizumab Combination Study

The primary objective of Part 3 is to evaluate the safety and tolerability of GSK3326595 when administered in combination with pembrolizumab in subjects with select solid tumors. Three cohorts will be evaluated. All subjects will receive pembrolizumab at the approved dose (200 mg IV every 3 weeks), in combination with GSK3326595 dosed orally at 100 mg QD, 200 mg QD, or 300 mg QD.

All available data from Part 3, including safety, tolerability, efficacy, PK, and PD will be used to select a dose of GSK3326595 to be administered with pembrolizumab in future studies. In order to collect PD data, pre- and on-study biopsies will be required for all subjects. Subjects will receive GSK3326595 at the assigned dose as monotherapy for 14 days, at which time the on-study biopsy will be collected. Subjects will then commence therapy with pembrolizumab administered every 3 weeks. Safety will be assessed continuously. Cohort(s) may be closed to further enrolment based on toxicity emerging at any time on study.

The study population will be adults, with locally advanced or metastatic NSCLC, melanoma, mTCC, or HNSCC that have failed to respond to treatment (e.g., SD, with subsequent documented progression as per iRECIST 1.1, or PD as best response) with prior PD-1 or PD-L1 directed therapy. Subjects who initially responded (e.g., iPR or iCR) to these therapies, then subsequently progressed, will **not** be eligible for participation in Part 3.

Overall, approximately 30 subjects will be enrolled in Part 3. These subjects will be divided evenly between three cohorts, each receiving a different dose of GSK3326595 in combination with a single dose of pembrolizumab. CCI [redacted]

2.4. Statistical Hypotheses

In Part 1, the primary endpoints of this study are safety and tolerability; the MTD and RP2D will also be determined. No formal statistical hypotheses will be tested. The primary focus will be on determining the recommended dose for further exploration, the safety profile, and the PK of GSK3326595 in subjects with advanced solid malignancies. Analyses will be descriptive and exploratory.

The primary goal of Part 2 is to evaluate disease-specific clinical activity in subjects with select solid tumors and NHL. The cohorts will be terminated for futility based on interim analysis described in Section 3.1

- For TNBC and ER+BC, efficacy is defined as a clinically meaningful response rate (defined as the percentage of subjects that have achieved a CR or PR) of 25% relative to a 10% historical control response rate.
- For mTCC, efficacy is defined as a clinically meaningful response rate (defined as the percentage of subjects that have achieved a CR or PR) of 30% relative to a 15% historical control response rate.
- For recurrent GBM, efficacy is defined as a clinically meaningful improvement in the rate of subjects who remain progression-free at six months (defined as a 35% six-month PFS rate relative to a 17% historical six-month PFS rate).
- For ACC and HPV-positive solid tumors, efficacy is defined as a clinically meaningful response rate (defined as the percentage of subjects that have achieved a CR or PR) of 30% relative to a 10% historical control response rate.
- For NHL (p53 wild-type, p53 mutant, and p53 unknown cohorts), efficacy is defined as a clinically meaningful response rate (defined as the percentage of subjects that have achieved a CR or PR) of 30% relative to a 10% historical control response rate.
- For NSCLC, efficacy is defined as a clinically meaningful response rate (defined as the percentage of subjects that have achieved a CR or PR) of 30% relative to a 10% historical control response rate. An interim futility analysis will be used to determine the scope of further development in this cohort.

The primary goal of Part 3 is to evaluate the safety and tolerability of GSK3326595 in

combination with pembrolizumab in solid tumors. No formal statistical hypotheses will be tested. CCI [redacted]

3. PLANNED ANALYSES

3.1. Interim Analyses

3.1.1. Interim Analysis for Part 2: Bayesian Predictive Adaptive Design for GBM Cohort

A Bayesian predictive adaptive design that allows the trial to be monitored more frequently at multiple stages [Lee, 2008] will employed for GBM cohort in Part 2 of the study. The criteria will be based on a historically unimportant six-month PFS rate of 17% versus a six-month PFS rate of interest of 35%. The six-month PFS rate is defined as the proportion of the subjects who are progression free and still alive at six months from the start of treatment. Bayesian statistics will be employed to calculate the posterior probability that the six-month PFS rate ≥35% and ≥17% at interim assuming a Beta prior for the Binomial distributed data. Predictive probability calculates the probability that the six-month PFS rate ≥35% or ≥17% given the responses have already been observed. A weak prior Beta (0.03, 0.07) is used, which is equivalent to the information present in 0.1 subject. The first interim analysis may be conducted when at least 10 evaluable subjects are available for GBM cohort at a given dose. The evaluable subjects for GBM cohort are defined as the GBM subjects who have had three post baseline disease assessments or have progressed or have died or have withdrawn from study treatment due to any reason. Futility interim analysis decision rules for the 10^{th} to 27^{th} evaluable subjects, specifying the number of subjects who have not progressed six months after receiving the first dose of GSK3326595 needed for continuing enrollment or stopping for futility when total sample size is up to 27 is presented in Table 4. These rules are intended as a guideline. Actual decisions will depend on the totality of the data.

Table 4 Decision Making Criteria for GBM Futility

Number of Evaluable Subjects	Number progression-free at 6 months to Stop Early for Futility	Probability of declaring futility when 6m PFS rate=0.17	Probability declaring futility when 6m PFS rate=0.35
10	0	0.1552	0.0135
11	0	0.0000	0.0000
12	0	0.0000	0.0000
13	1	0.1817	0.0199
14	1	0.0000	0.0000
15	1	0.0000	0.0000
16	1	0.0000	0.0000
17	2	0.1325	0.0144
18	2	0.0000	0.0000
19	2	0.0000	0.0000

Number of Evaluable Subjects	Number progression-free at 6 months to Stop Early for Futility	Probability of declaring futility when 6m PFS rate=0.17	Probability declaring futility when 6m PFS rate=0.35
20	2	0.0000	0.0000
21	3	0.1004	0.0108
22	3	0.0000	0.0000
23	4	0.1125	0.0194
24	4	0.0000	0.0000
25	4	0.0000	0.0000
26	5	0.0799	0.0174
27	6	0.0869	0.0390

The enrollment for GBM cohort may be stopped due to futility if the predictive probability that the 6 month PFS rate ≥17% (historical control) is small (e.g., less than a 2% chance for a total sample size of 28 subjects). Enrollment may also be stopped due to futility if the equivalent of all the evaluable subjects are progressed or off study treatment before 6 months from the first dose in the first 10 enrolled evaluable subjects in GBM cohort or less than 1 subject who is not progressed still on treatment at month 6 are observed in the first 13 evaluable subjects. For example, when there are 10 evaluable subjects available at the time of interim analysis with all subjects progressed before month 6, then the cohort may be stop for futility. Otherwise, the enrollment of the respective cohort will continue to the target sample size.

When the total sample size in a treatment arm is 28 and at least 8 subjects who are not progressed before 6 months from first dose and still on treatment at month 6 out of 28 subjects are observed, we can claim null hypothesis is rejected.

3.1.2. Interim Analysis for Part 2: Bayesian Hierarchical Modeling for mTCC, TNBC, and NHL Cohorts

To further investigate clinical activity across the pre-specified cohorts, an adaptive design utilizing a Bayesian hierarchical model will be employed for the mTCC, TNBC, p53 WT NHL and p53 mutant NHL cohorts in Part 2. [Berry, 2013; Escobar, 1995; Neal, 2000; Sethuraman, 1994] Multiple interim evaluations of the accumulating data to determine if one or more cohorts should discontinue enrollment early due to futility will be incorporated. Interim and final evaluations will be based on a hierarchical model that borrows information in a limited way from cohorts that demonstrate similar treatment effects based on the accumulated trial data. Traditional estimates based on independent analyses will also be provided. π_j is the true response rate for cohort *j,* where $j = 1,\ldots, 4$ and indexes the four cohorts. C_j is the historical control response rate for the jth cohort. The historical controls vary by cohort and are provided in Section 2.4. The study is powered to detect a high clinically meaningful response rate and is based on the cohort model assessment of whether there is sufficiently high probability that π_j exceeds C_j. The posterior probability that the ORR for a given cohort is greater than C_j will be computed according to the following comparison:

$$P(\pi_j > C_j \mid \text{current data}) \text{ for the j-th cohort}$$

If this posterior probability is sufficiently low within a given cohort, then this will provide insufficient evidence to suggest that the ORR is greater than its respective historical control. Conversely, if a sufficiently high posterior probability is observed, this will provide evidence that the ORR is greater than the historical control, and the dose will be declared efficacious in that cohort. Thresholds for decision making are defined in the protocol.

Full details regarding the hierarchical modeling framework are described in the protocol at Appendix 11.

3.1.3. Interim Analysis for Part 1 Cohorts and for ACC Cohort in Part 1 and Part 2

The purpose of this interim analysis is to summarize safety and efficacy endpoints within all Part 1 cohorts and the Part 1 and Part 2 ACC cohort for the purpose of publication. For Part 1 dosing cohorts, demographics, disease history, safety, treatment duration, percent change from baseline, best overall response, and PK will be summarized on the all-treated population. For ACC cohorts, best overall response, duration of follow-up, percent change from baseline, duration of treatment, and disease history will be summarized on the all-treated population, while progression-free survival will be summarized and plotted using the evaluable population.

3.1.4. Interim Analysis for Part 2: Simon's Two Stage Design for ACC Cohort

Simon's optimal two-stage design (Simon, 1989) will be used for both ACC cohorts (tablet and capsule formulation). For both cohorts, the null hypothesis that the true response rate is 10% will be tested against a one-sided alternative of 30%.

For the capsule cohort, in the first stage, 10 subjects will be accrued. If there are 1 or fewer responders in these 10 subjects, the cohort will be stopped early for futility. The maximum number of subjects to be enrolled for this cohort is 38. The null hypothesis will be rejected if 8 or more responders are observed in 38 patients. This design yields a type I error rate of 0.023 and power of 80.8% when the true response rate is 30%.

For the tablet cohort, in the first stage, 17 subjects will be accrued. If there are 2 or fewer responders in these 17 subjects, the cohort will be stopped early for futility. This rule is intended as a guideline, development decisions will depend on the totality of the data. The maximum number of subjects to be enrolled for this cohort is 50. The null hypothesis will be rejected if 10 or more responders are observed in 50 patients. This design yields a type I error of 0.02 and power of 89.9% when the true response rate is 30%.

3.1.5. Interim Analysis for Part 2: Bayesian Predictive Adaptive Design for ER+BC Cohort

The ER+BC cohort will employ the Bayesian design that allows the trial to be monitored frequently with the constraint of both Type I and Type II error rates. The evaluation is designed to exclude a 10% overall response rate (ORR) representing best available therapy in favour of a 25% ORR. A close to non-informative prior will be used. Let p

denote the response rate, the prior distribution used is p ~ Beta (0.025, 0.075). The cohort will be stopped early due to futility if the predictive probability of success is less than 8%. The success is defined as posterior probability of ORR > 10% at the end of the cohort is larger than 80%. The first interim analysis will be performed when at least 10 subjects become evaluable. The max sample size is 35 subjects, and the design will have type I error of 0.10 and power of 82%.

The decision rules, specifying the number of subjects with a clinical response needed for continuing enrolment or, stopping for futility, are displayed in Table 5. The methodology is based on the predictive probability of success if enrolment continues to maximum number of subjects (Lee, 2008). The interim analysis will be for futility only, i.e., the dose expansion cohort will not stop early for efficacy.

Table 5 Decision Making Criteria for ER+BC Futility

Number of Evaluable Subjects	≤ This Number of Confirmed Responses to Stop Early for Futility	Probability of continuing enrolling when ORR=0.1	Probability of continuing enrolling when ORR=0.25
10	0	0.6513	0.9437
11	0	0.6513	0.9437
12	0	0.6513	0.9437
13	0	0.6513	0.9437
14	1	0.3971	0.8843
15	1	0.3971	0.8843
16	1	0.3971	0.8843
17	1	0.3971	0.8843
18	1	0.3971	0.8843
19	1	0.3971	0.8843
20	1	0.3971	0.8843
21	1	0.3971	0.8843
22	2	0.2938	0.8674
23	2	0.2938	0.8674
24	2	0.2938	0.8674
25	2	0.2938	0.8674
26	2	0.2938	0.8674
27	3	0.2108	0.8511
28	3	0.2108	0.8511
29	3	0.2108	0.8511
30	3	0.2108	0.8511
31	3	0.2108	0.8511
32	4	0.1509	0.8369
33	4	0.1509	0.8369
34	4	0.1509	0.8369

3.1.6. Interim Analysis for Part 2: Bayesian Predictive Adaptive Design for HPV+ Cohort

The HPV+ cohort will employ the Bayesian design that allows the trial to be monitored frequently with the constraint of both Type I and Type II error rates. The evaluation is designed to exclude a 10% overall response rate (ORR) representing best available therapy in favour of a 30% ORR. A close to non-informative prior will be used. Let p denote the response rate, the prior distribution used is p ~ Beta (0.03, 0.07). The cohort will be stopped early due to futility if the predictive probability of success is less than 1%. The success is defined as posterior probability of ORR > 10% at the end of the cohort is larger than 87.6%. The first interim analysis will be performed when at least 10 subjects become evaluable. The max sample size is 28 subjects, and the design will have type I error of 0.05 and power of 87%.

The decision rules, specifying the number of subjects with a clinical response needed for continuing enrolment or, stopping for futility, are displayed in Table 6. The methodology is based on the predictive probability of success if enrolment continues to maximum number of subjects (Lee, 2008). The interim analysis will be for futility only, i.e., the dose expansion cohort will not stop early for efficacy.

Table 6 Decision Making Criteria for HPV+ Futility

Number of Evaluable Subjects	≤ This Number of Confirmed Responses to Stop Early for Futility	Probability of continuing enrolling when ORR=0.1	Probability of continuing enrolling when ORR=0.3
10	0	0.6513	0.9718
11	0	0.6513	0.9718
12	0	0.6513	0.9718
13	0	0.6513	0.9718
14	0	0.6513	0.9718
15	0	0.6513	0.9718
16	0	0.6513	0.9718
17	1	0.4660	0.9618
18	1	0.4660	0.9618
19	1	0.4660	0.9618
20	1	0.4660	0.9618
21	2	0.3107	0.9500
22	2	0.3107	0.9500
23	2	0.3107	0.9500
24	2	0.3107	0.9500
25	3	0.2019	0.9383
26	3	0.2019	0.9383
27	4	0.1129	0.9161

3.1.7. Interim Analysis for Part 2: Statistical Design for NSCLC Cohort

The Part 2 NSCLC cohort is intended to explore the clinical activity in the p53 wild-type NSCLC population. Simon's optimal two-stage design will be used as a basis for analysis of the NSCLC cohort. The null hypothesis that the true response rate is 10% will be tested against a one-sided alternative. ORR will be assessed for the 10 subjects that are confirmed with p53 wild-type.

In the first stage, 10 subjects will be accrued. If there are 1 or fewer responders in the first 10 subjects, the cohort will be stopped for futility. If 2 or more responses are observed, further expansion of the p53 wild-type NSCLC cohort may be triggered via protocol amendment or as a part of another study. If the cohort were to expand to 29 subjects, the null hypothesis would be rejected if 6 or more responders are observed. This design yields a type I error rate of 0.047 and power of 80.5% when the true response rate is 30%.

Note that at the time GSK made a decision to cease enrollment in the study, this cohort did not have 10 subjects. Therefore, the interim analysis was not conducted.

3.1.8. Food Effect and Relative Bioavailability Sub-study

This analysis is described in Section 9.2.2.2.

3.1.9. Interim Analysis for Part 2: Statistical Design for All Part 2 Cohorts

The purpose of this interim analysis is to summarize safety and efficacy endpoints within all Part 2 cohorts for purposes of publication. Efficacy endpoints for TNBC, mTCC, ER+BC, HPV+, ACC, and NSCLC cohorts will be investigator-assessed confirmed, best response based on RECIST 1.1 criteria. For NHL cohorts, investigator-assessed best response based on Lugano criteria will be reported. See Section 7.1for further details on criteria. For these groups, overall response rate (ORR) defined as the proportion of subjects with complete response (CR) or partial response (PR) with 95% confidence interval based on the Clopper-Pearson (1934) exact methods will be reported. In addition, frequency of best responses will also be reported by histology subtype for the NHL cohorts. For GBM, progression-free survival rate at 6 months will be reported, with a 95% confidence interval estimated using Greenwood's estimate of standard error.

Additional endpoints examined will be duration of treatment with best response for all cohorts. maximum percent reduction from baseline in sum of diameters as well as change from baseline for TNBC, mTCC, ER+BC, HPV+, ACC, and NSCLC cohorts, and maximum percent reduction from baseline in sum of areas for the GBM cohort.

In addition, safety parameters will be reported by dosage type (300 mg, 400 mg). Included will be a summary of adverse events, adverse events related to GSK3326595 by preferred term and by maximum grade, as well as adverse events leading to dose reduction, interruptions/delays, discontinuation and serious adverse events by preferred term, and summary of deaths.

CCI [redacted]

3.3. Final Analyses

The final analysis of the study will be performed after the completion of the following sequential steps: As per Protocol Amendment 8 implementation, final analysis will be performed following the data cut off (DCO). This will occur when all subjects have either died, discontinued treatment (including 30-day safety follow up), withdrawn consent, or have consented to continue with treatment as defined in Protocol Amendment 8.

All required database cleaning activities have been completed and final database release (DBR), source data lock (SDL) and database freeze (DBF) have been declared by Data Management.

Data from the three parts may be combined for some analyses at the end of the trial, as appropriate. All primary and secondary analyses will be conducted for the final analysis.

4. ANALYSIS POPULATIONS

4.1. List of Populations

Table 7 Analysis Populations

Population	Definition / Criteria	Analyses Evaluated
Screened	All participants who were screened for eligibility	Study Population
Enrolled	All participants who signed the ICF	Study Population
All Treated	Defined as all subjects who receive at least one dose of GSK3326595.	Safety Anti-cancer activity Efficacy (final analysis)
All Evaluable	For Part 1: Defined as subjects who have had any post-baseline response data, or who discontinued without any response data collected. For Part 2: Defined as subjects who have had two post baseline disease assessments, have progressed or died, or permanently discontinued from the study treatment for mTCC, TNBC, ER+BC, HPV+, NHL and NSCLC cohorts. It is defined as subjects who have had three post baseline disease assessments, have progressed or died, or permanently discontinued from the study treatment for ACC and GBM cohorts.	Interim Analysis

Population	Definition / Criteria	Analyses Evaluated
Pharmacokinetic (PK)	Consist of all subjects from the All Treated Population for whom a PK sample is obtained and analyzed. Note: PK samples that may be affected by protocol deviations will be reviewed by the study team to determine whether or not the sample will be excluded.	PK
Pharmacodynamic (PD)	Defined as subjects in the All Treated Subjects Population for whom paired and evaluable tumor biopsies (pre- and on- treatment time points) or plasma or urine were obtained and analyzed for biomarkers.	PD

Refer to Appendix 12: List of Data Displays which details the population used for each display. Note that for the interim analyses, the All Evaluable population will be used for efficacy analyses, and the All-Treated Population will be used for safety analyses. However, for the final analysis, the All Treated Population will be used for all displays.

4.2. 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.

Separately, important deviations which result in exclusion from analysis populations and events that result in exclusion from analysis populations will be summarized and listed, if there are any.

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

- Data will be reviewed prior to 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. This listing 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

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, response assessments for ORR), and included in data listings.

5.1.1. Treatment Display

The actual treatment of a subject will be derived from exposure data. The first dose the subject received will be used as actual treatment. Scheduled (planned) treatment is collected on dosing regimen eCRF page. Efficacy, safety and PK analysis will be based on the All Treated Population.

Per Protocol Amendment 7, if the GSK3326595 tablet bioavailability is comparable to that of the GSK3326595 capsules from Part 1 Food Effect and Relative Bioavailability Sub-study, all new and ongoing subjects may be switched from capsules to tablets for the remainder of the study, once they have been notified by the Sponsor. As of 3 Nov 2021, per GSK communication, tablet and capsule cohorts within the same disease/dosage groups will be combined.

The leading dose formulation (tablet or capsule) and the leading dose level are specified in treatment.

- For Part 1 dose escalation cohorts, all data will be pooled and descriptive analyses summarized and listed by investigated GSK3326595 dose under QD dose escalation cohort or BID dose escalation cohort. PK/PD expansion cohorts will be summarized together with dose escalation cohorts dose level. If applicable, Part 1 Food Effect Relative Bioavailability Sub-study data will also be included in Part 1 summary tables as a separate column. The treatment groups for Part 1 are:
  - Part 1 QD Dose GSK3326595 12.5 mg Capsule
  - Part 1 QD Dose GSK3326595 25 mg Capsule
  - Part 1 QD Dose GSK3326595 50 mg Capsule
  - Part 1 QD Dose GSK3326595 100 mg Capsule
  - Part 1 QD Dose GSK3326595 200 mg Capsule
  - Part 1 QD Dose GSK3326595 300 mg Capsule
  - Part 1 QD Dose GSK3326595 400 mg Capsule
  - Part 1 QD Dose GSK3326595 600 mg Capsule
  - Part 1 BID Dose GSK3326595 50 mg Capsule
  - Part 1 BID Dose GSK3326595 100 mg Capsule
  - Part 1 BID Dose GSK3326595 150 mg Capsule
  - Part 1 BID Dose GSK3326595 200 mg Capsule
  - Food Effect and Relative Bioavailability Sub-study 300mg QD (apply to table/figures)
  - Part 1 Food Effect 300mg Sequence 1 (Tablet Fasted - Tablet Fed - Capsule Fasted) (apply to listings)
  - Part 1 Food Effect 300mg Sequence 2 (Tablet Fed - Tablet Fasted - Capsule Fasted) (apply to listings)

- For Part 2 dose expansion cohorts, data will be summarized and listed by cohorts. The treatment groups for Part 2 are:
  - Part 2 TNBC 400mg QD Capsule Cohort

- Part 2 mTCC 400mg QD Capsule Cohort
- Part 2 GBM 400mg QD Capsule Cohort
- Part 2 ER+BC 400mg QD Capsule Cohort
- Part 2 HPV+ 400mg QD Capsule Cohort
- Part 2 ACC 400mg QD Capsule Cohort
- Part 2 ACC 300mg QD Tablet Cohort
- Part 2 NHL P53 Mutant 400 mg QD Capsule
- Part 2 NHL P53 Mutant 300 mg QD Capsule
- Part 2 NHL P53 Mutant 300 mg QD Tablet (if applicable)
- Part 2 NHL P53 Wild Type 400 mg QD Capsule
- Part 2 NHL P53 Wild Type 300 mg QD Capsule
- Part 2 NHL P53 Wild Type 300 mg QD Tablet (if applicable)
- Part 2 NHL P53 Unknown 400 mg QD Capsule
- Part 2 NHL P53 Unknown 300 mg QD Capsule
- Part 2 NHL P53 Unknown 300 mg QD Tablet (if applicable)
- Part 2 NSCLC 300 mg QD Capsule
- Part 2 NSCLC 300 mg QD Tablet (if applicable)
- Part 2 ACC TN 300mg Tablet Cohort

NB 1: NHL P53 status is based on central lab data. If the central lab data is missing then the status will be considered Unknown.

NB 2: As per GSK communication, as of *3Nov2021 tablet and capsule cohorts within the same disease/dosage groups will be combined*.

For Part 3 combination dose escalation, some AE and exposure tables and listings will be displayed for GSK3326595 and pembrolizumab separately. All others will be summarized and listed by dose levels of both GSK3326595 plus pembrolizumab. (e.g., GSK3326595 100mg + pembrolizumab).

Subjects enrolled in Part 1, may be included in a Part 2 disease-specific cohort analyses (tables and figures) if the subjects were treated at the Part 2 dose expansion and have the same disease type as required for the cohort. These subjects will be provided in a separate listing as well. Additional safety tables, may be provided for all subjects treated at the RP2D, regardless of the Part of the study to which they were enrolled.

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

5.1.2. PK Analysis: Handling of excluded data after NCA (Non-Compartmental Analysis) analysis

When Clinical Pharmacology perform the NCA analysis they may, in some circumstances, elect to exclude certain data points from the analysis. These data points should also be excluded from summary statistics. A separate analysis dataset ADPCWNL will be generated by adding a flag for those records to be excluded. PK listings and

individual PK figures will keep all the data, with listings indicated the records excluded from summary.

5.2. Baseline Definitions

Baseline will be defined as the most recent, non-missing value prior to or on the first study treatment dose date for GSK3326595, including those from unscheduled visits.

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 time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

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

5.3. Multicenter Studies

As it is anticipated that accrual will be spread thinly across centers and summaries of data by center would be unlikely to be informative, data from all participating centers will be pooled prior to analysis.

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

There are no formal plans for any stratification. There are no formal plans for investigating any covariates.

5.4.2. Examination of Subgroups

There are no formal plans for examining subgroups.

5.5. Multiple Comparisons and Multiplicity

There is no adjustment for multiplicity in primary or secondary analyses.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

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

Section	Component
15.3	Appendix 3: Assessment Windows

Section	Component
15.4	Appendix 4Study Phases
15.5	Appendix 5: Data Display Standards & Handling Conventions
15.6	Appendix 6: Derived and Transformed Data
15.7	Appendix 7Reporting Standards for Missing Data
15.8	Appendix 8Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be based on the All Treated population, unless otherwise specified.

Study population analyses including analyses of participant's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, exposure and treatment compliance, disease characteristics at initial diagnosis and at screening, prior and follow-up anti-cancer therapy, and substance use will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 12Only primary and secondary endpoints will be described in this analysis plan and necessarily conducted for the final clinical and statistical report.

6.2. Disposition of Subjects

A summary of the number of subjects in each of the analysis populations described in Section 4 will be provided. In addition, the number of subjects enrolled will be summarized by country and by center. In addition, a listing of subjects excluded from any analysis population will also be provided.

A summary and listing of screening status and reasons for screen failure will be provided using the Screened population.

A summary of subject status and reason for study withdrawal will be provided. This display will show the number and percentage of subjects who completed the study, are ongoing as of the analysis cutoff date, or withdrew from the study, including primary reasons for study withdrawal. Reasons for study withdrawal will be presented in the order they are displayed in the eCRF. A listing will also be provided.

A summary of study treatment status will be provided. This display will show the number and percentage of subjects who are ongoing or 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.

6.3. Protocol Deviations

Refer to Section 4.2 for the details.

6.4. Demographic and Baseline Characteristics

The demographic characteristics (e.g., age, race, ethnicity, sex, baseline height, and baseline body weight, BMI) 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. In a separate summary, age will be categorized as 12-17, 18-64, 65-84, >=85 using EudraCT standard. The count and percentage will be computed for sex and ethnicity. Race and racial combinations will be summarized and subject-level race detail will be listed.

6.5. Concomitant Medications and Medical Conditions

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

Note: To be considered concomitant, the medication must have been taken at some point during the on-therapy window. Please refer to Appendix 4for the details of concomitant medications classification.

Past and current medical conditions will be summarized in separate tables.

6.6. Anti-Cancer Therapy

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 “Other”. A summary for only those marked “Advanced or Metastatic” will also be produced. Prior anticancer therapy will also be listed.

The number and percentage of subjects that received chemotherapy, immunotherapy, hormonal therapy, biologic therapy, radioactive therapy, small molecule targeted therapy, as post study treatment anti-cancer therapy will be summarized. Time from study treatment discontinuation to the first post study treatment anti-cancer therapy will also be included in this summary table. Surgeries and radiotherapies will be added to this follow-up table. A listing of the type of follow-up anti-cancer therapy received (chemotherapy, immunotherapy, hormonal therapy, biologic therapy, radioactive therapy, small molecule targeted therapy) for each subject will be provided for ACC patients only.

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. Prior and on-treatment cancer and non-cancer related surgeries will be listed.

6.7. Disease Characteristics

Disease history and characteristics (time since initial diagnosis in months, stage at initial diagnosis, etc.) at screening will be listed. Separate summaries of disease characteristics at initial diagnosis and screening will be provided.

6.8. Treatment Compliance

Compliance will not be reported. However, summaries of study treatment exposure and dose modifications (e.g., duration of treatment in months, number of dose reductions, number of dose interruptions, number of dose escalations) will characterize exposure. These analyses are described in Section 8.1'Extent of Exposure'.

7. EFFICACY ANALYSES

All efficacy analyses will be based on the All Treated Population unless otherwise specified. Details of data displays are presented in Appendix 12: List of Data Displays.

Lesion assessment method and timing, evaluation of disease, disease progression and response criteria will be conducted according to RECIST 1.1 for subjects with solid tumors [Eisenhauer, 2009], standardized Response Assessment in Neuro-Oncology (RANO) [Wen, 2010] for subjects with GBM, and Lugano criteria for subjects with NHL [Cheson, 2007; Cheson, 2014]. In addition, Part 3 subjects will be assessed according to immune-based RECIST (iRECIST) [Seymour, 2017]. The timepoint overall response is accessed by the investigator and recorded on the eCRF.

The following table outlines the response criteria by cohorts or treatment group.

Table 8 Response Criteria by Cohort/Treatment Group

Cohort/Treatment Group	Response Criteria	Primary Assessments by
Part 1 and Part 2, Subjects with solid tumors	RECIST 1.1	Investigator
Part 2, GBM Cohort	RANO	Investigator
Part 2, NHL Cohort	Lugano	Investigator
Part 3 Subjects	iRECIST	Investigator

Abbreviation: RANO = Response Assessment for Neuro-Oncology; RECIST = Response Evaluation Criteria in Solid Tumors; GBM= Glioblastoma multiforme; NHL = Non-Hodgkin's lymphoma.

7.1. Primary Efficacy Analyses

7.1.1. Confirmed Overall Response Rate (ORR) based on RECIST 1.1 for Part 2 (non-GBM, non-NHL) cohorts

The primary endpoint for all Part 2 cohorts, except GBM, will be overall response rate (ORR). The timepoint overall response is assessed by the investigator and recorded on the eCRF. The ORR endpoint is defined as % of subjects achieving a best response of CR and PR recorded from the start of treatment until disease progression or start of new anti-cancer therapy, whichever is earlier.

Best response will be determined programmatically based on investigator assessment at each time point. 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. The first assessment may occur before the first planned assessment.

Confirmed responses, as outlined in RECIST 1.1 [Eisenhauer, 2009] will be summarized, as appropriate. Confirmation of response may be based on planned and/or unscheduled assessments.

The confirmed overall response rate (ORR) is defined as the ORR as per disease-specific criteria (more details in protocol Section 14.4). Subjects with unknown or missing response will be treated as non-responders, i.e., these subjects will be included in the denominator when calculating the percentage. The best overall response is a subject's best response over the time period referenced. In addition, with respect to best response:

- To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after the first dose for a minimum of 49 days.
- If the minimum time for SD is not met, best 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 or CR, a confirmatory disease assessment should be performed no less than 4 weeks (28 days) after the criteria for response are first met.

The ORR will be summarized with a 2-sided 95% exact confidence interval based on the Clopper-Pearson method. The observed confirmed ORR will be reported at the interim and final analysis and will be summarized by cohort.

7.1.2. Overall Response Rate (ORR) based on Lugano for Part 2 NHL Cohorts

Overall response confirmation is not needed for assessment according to Lugano criteria [Cheson, 2007; Cheson, 2014]. The NHL cohort will only have ORR summarized. Timepoint response will be the combined imaging response based on both anatomic and metabolic responses according to the following table:

Table 9 Overall Response Rate

Anatomic/Radiologic Response	Metabolic Response	Combined Imaging Response
CR	CMR, NE, missing	CR
PR	CMR	CR
CR	PMR	PR
CR	NMR, SMD	PR
PR	PMR	PR
PR	NMR, SMD	PR
SD	PMR	PR
PD	PMR	PD
SD	NMR, SMD	SD
CR, PR, SD or NE	PMD	PD

Anatomic/Radiologic Response	Metabolic Response	Combined Imaging Response
CR, PR, SD or NE	NE, missing	CR, PR, SD or NE (Anatomic Response)
PD	NMR, SMD	PD
PD	PMD	PD
PD	NE, missing	PD

CR = complete response; NE = not evaluable; PR = partial response; PD = unconfirmed progressive disease; SD = stable disease; SMD = No Metabolic Response.

7.1.3. Progression Free Survival (PFS) for Part 2 GBM cohort

Progression-free survival (PFS) is defined as the time (in months, interval in months is calculated by duration in days/30.4375) from date of first dose date of study drug until date of documented disease progression or death due to any cause, whichever comes first.

The PFS rate at 6 months for Part 2 GBM cohort will be estimated by the Kaplan-Meier method. These rates, estimate the proportion of patients who did not progress and were alive at month 6. The 95% confidence intervals for the PFS rate at month 6 will be estimated using Greenwood's estimate of the standard error (SE) and a log-log transformation of the progression-free survival function (Greenwood, 1926).

A summary of the assignments for progression and censoring dates for PFS is specified in the following table:

Table 10 Assignments for Progression and Censoring Dates for PFS Analysis

1. Situation	1. Date of Event (Progression/ Death) or Censoring	1. Outcome Event (Progression/ Death) or Censored
1. 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)	2. Start Date of Treatment	2. Censored
1. 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)	3. Start Date of Treatment	3. Censored
1. Progression documented between scheduled visits	4. Date of assessment of progression[1]	4. Event
1. No progression *(or death)* or initiation of new anti-cancer therapy	5. Date of last 'adequate' assessment of response[2]	5. Censored
1. Received subsequent anti-cancer therapy prior to the date of documented events	6. Date of last 'adequate' assessment of respnose[2,3] (*prior to initiation of* anti-cancer *therapy*)	6. Censored
1. Death before first PD assessment (or Death at baseline or prior to any adequate assessments)	7. Date of death	7. Event

1. Situation	1. Date of Event (Progression/ Death) or Censoring	1. Outcome Event (Progression/ Death) or Censored
1. Death or progression after more than one missed visit	8. Date of last 'adequate' assessment of response[2] *(prior to missed assessments)* 9. Refer to Section 15.7.2	8. Censored

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

7.2. Secondary Efficacy Analyses

7.2.1. Confirmed Overall Response Rate (ORR) based on RECIST 1.1 for Part 1 Cohorts

Best response will be estimated as described in Section 7.1.1and will be summarized by dose levels for Part 1.

7.2.2. Confirmed Overall Response Rate (ORR) based on RANO Criteria for Part 2 GBM Cohort

Best response will be estimated as described in Section 7.1.1 and will be summarized by dose levels for Part 1. The RANO criteria will be used to ascertain response (Wen, 2010). In comparison to RECIST 1.1 criteria, RANO criteria does not require a minimum of 49 days to assign as response stable disease (SD).

7.2.3. Confirmed Overall Response Rate (iORR) based on iRECIST for Part 3 Cohort

Overall response rate based on iRECIST (iORR) is defined as the percentage of participants with a best overall response (iBOR) of "immune" complete response iCR or immune partial response iPR (Seymour, 2017). "Immune" best overall response (iBOR) will be summarized by dose levels for Part 3. The derivation of iBOR per iRECIST will be as follows:

- Progressive disease is "confirmed (iCPD) in the new lesion category, if the next imaging assessment, done at 4–8 weeks after iUPD, confirms additional PD, i.e., new lesions or a further increase in new lesion size from iUPD (sum of measures increase in new lesion target ≥5 mm, any increase for new lesion non-target)"(Seymour, 2017).
- iSD, iPR, or iCR can still be assigned if one or more instances of iUPD occurred at a previous visit. However, iCR, iPR, and iSD cannot be assigned if iCPD occurred at a previous visit.

- To be assigned a status of iSD, follow-up disease assessment must have met the iSD criteria at least once after the first dose for a minimum of 49 days.

iBOR takes into account the requirement for confirmation of iCR, iPR, and iPD. If iBOR is iUPD and is confirmed consecutively, iBOR will be termed as iCPD. If iBOR is iUPD but not confirmed, there is no subsequent iSD, iPR, or iCR (e.g., NE or lost follow-up), the iBOR will be termed as iUPD. If iBOR is iUPD but not confirmed and the subject died or discontinued treatment or has initiated new anti-cancer therapy after this PD assessment, the iBOR will be termed as iCPD.

Examples of scenarios of assignments of confirmed/unconfirmed iBOR (assuming the adjacent timepoints are 28 days apart at least) are provided in the following table:

Table 11 Examples of iBOR Assignments

Case[a]	Time point Response 1	Time point Response 2	Time point Response 3	Time point Response 4	Time point Response 5	Confirmed iBoR	Unconfirmed iBoR
1	iCR	iCR	iCR,iPR, iUPD, or NE	iUPD	iCPD	iCR	iCR
2	iUPD	iPR, iSD, or NE	iCR	iCR	iCR, iPR, iSD, iUPD, iCPD, or NE	iCR	iCR
3	iUPD	iPR	iPR, iCR	iPR, iSD, iUPD, NE, or iCPD	iPR, iSD, iUPD, NE, or iCPD	iPR	iCR
4	iUPD	iSD or NE	iPR	iSD	iSD,iUPD, iCPD, or NE	iSD	iPR
5	iUPD	iSD	iSD, iUPD, or NE	iSD, iUPD, iCPD, or NE	iSD, iUPD, iCPD, or NE	iSD	iSD
6	iUPD	iCPD	Any	Any	Any	iCPD	iCPD
7	iUPD	iUPD (no iCPD)	iCPD	Any	Any	iCPD	iCPD
8	iUPD	NE	NE	NE	NE	iUPD	iUPD
9	iUPD[b]					iCPD	iCPD

BOR = best overall response; CPD = confirmed progressive disease; CR = complete response; iRECIST = immune Response Evaluation Criteria in Solid Tumors; NE = not evaluable; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; UPD = unconfirmed progressive disease. NOTE: "i" indicates immune responses assigned using the iRECIST evaluation criteria

a Assume any two adjacent assessments are at least 28 days apart

b Last assessment before the subject died/discontinued from treatment

7.2.4. Progression Free Survival (PFS) for Part 1, Part 2 (non-GBM), Part 3

Progression-free survival (PFS) will be estimated by cohorts for Part 2 as described in Section 7.1.3. RECIST 1.1 criteria will be used for non-NHL cohorts, and Lugano criteria for NHL cohorts. Estimates of 1st quartile survival, median survival, and 3rd quartile survival will be presented with 95% confidence intervals based on the Brookmeyer-Crowley method (Brookmeyer, 1982).D

7.2.5. Lesion Analysis – Parts 1, 2, and 3

Change/percent change from baseline based on the sum of target lesion diameters will be calculated by timepoint for all cohorts except NHL and GBM. Change/percent change from baseline based on the sum of target *lesion areas* will be calculated by timepoint for the *GBM cohort*. The following figures will be produced:

- Percent change from baseline in target lesions over time (spider plot) – all cohorts except NHL.
- Best change from baseline in target lesions (waterfall plot) – all cohorts except NHL.
- Treatment duration along with the overall response, the best change from baseline in target lesions, etc. (swimmer plot).

7.2.6. DOR and TTR for Part 2 ACC TN Cohort based on RECIST 1.1 Criteria

Duration of response (DOR) based on RECIST 1.1 for the Part 2 ACC TN cohort will be listed and summarized for subjects with a confirmed CR or PR and is defined as the time (in months) from first documented evidence of CR or PR until the first documented sign of disease progression or death, for the subset of subjects with a confirmed CR or PR. Censoring rules will follow those of the PFS analysis.

If there are a sufficient number of responders who subsequently progress or die due to PD, median DoR, first and third quartiles and 95% CI, will be estimated using the Brookmeyer-Crowley method (Brookmeyer, 1982).

Time to response (TTR) is defined as the time from date of first dose to date of first documented evidence of PR or CR among participants who achieve a response (i.e. PR or CR). A listing of TTR will be provided for the ACC TN cohort only.

7.2.7. Overall Survival (OS)

Overall survival (OS) is defined as the interval of time (in months) between the start date of treatment and the date of death due to any cause. This will be summarized for the Part 2 ACC TN cohort and all ACC subjects across Part 1 and Part 2.

For subjects who are alive, time of death will be censored at the date of last contact. The date of death should be taken from the *Record of Death* eCRF page. Death on study due to any cause will be included. Survival will be summarized using the Kaplan-Meier method. Estimates of 1st quartile survival, median survival, and 3rd quartile survival will be presented with 95% confidence intervals based on the Brookmeyer-Crowley method (Brookmeyer, 1982).

8. SAFETY ANALYSES

Safety analyses will be based on the All Treated Population, unless otherwise specified. Details of data displays are presented in Appendix 12: List of Data Displays.

8.1. Primary Safety Analyses

8.1.1. Safety Analyses – Part 1 and Part 3

8.1.1.1. Extent of Exposure

Extent of exposure to GSK3326595 and pembrolizumab (applies to Part 3 subjects only) will be summarized separately.

The duration of exposure to study treatment in month (from first day to last day of treatment) will be summarized. Descriptive statistics including mean, median, standard deviation, minimum, and maximum will be calculated for time on study treatment.

The subject's average daily dose, defined as the cumulative dose divided by the duration of exposure for each subject, will be summarized. Subject's average daily dose will only be calculated for GSK3326595. Number of infusions will be provided for pembrolizumab.

Dose reductions will be summarized by number of reductions and reasons for reductions, for GSK3326595 and/or pembrolizumab, where applicable. If there are no reductions, a summary will not be provided. Dose interruptions of GSK3326595 will be summarized by number of interruptions, reasons for the interruptions, and interruption duration (days). The mean, standard deviation, median, minimum value, and maximum value will be computed for the duration of interruptions as well as the number and percentage of the interruptions 1-5, 6-7, >7 days.

Dose delays of pembrolizumab will be summarized by number of delays, reasons for delay and duration of delay (days). The mean, standard deviation, median, minimum value, and maximum value will be computed for the duration of delay as well as the number and percentage of the delays 1-5, 6-7, >7 days.

Dose reductions and interruptions of GSK3326595will be listed separately.

8.1.1.2. Adverse Events

An overview summary of AEs, including counts and percentages of subjects with any AE, AEs related to study treatment, AEs leading to permanent discontinuation of study treatment, AEs leading to dose reductions, AEs leading to dose delays/interruptions, SAEs, SAEs related to study treatment, fatal SAEs, and fatal SAEs related to study treatment will be produced.

The relationship between MedDRA system organ class (SOC), preferred term (PT), and verbatim text will be listed.

Adverse events (AEs) will be graded according to the CTCAE, Version 4.03, [Basch, 2014]. Adverse events will be coded to the preferred term (PT) level using the Medical Dictionary for Regulatory Affairs (MedDRA dictionary).

A summary of number and percentage of subjects with any adverse events by maximum grade will be produced. AEs will be sorted by preferred term 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.

In addition, the frequency and percentage of AEs (all grades) will be summarized and displayed in two ways: 1) in descending order of total incidence by PT only and 2) in descending order of total incidence by SOC and PT. In the SOC row, the number of subjects with multiple events under the same system organ class will be counted once.

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 study treatment as "Yes". A 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' or missing. The summary table will be displayed in descending order of total incidence by PT and by maximum grade sorted by PT in descending order of total incidence.

For Part 3 treatment-related AE, the below 3 sets of tables will be generated by system organ class, preferred term, and maximum grade:

- AEs related to GSK3326595
- AEs related or pembrolizumab
- AEs related to GSK3326595 and pembrolizumab

All COVID-19 assessments and symptom assessments for subjects with COVID-19 adverse events will be summarized based on all recorded AEs. There will be no separate definition of "treatment-emergent" AEs.

All AEs will be listed. A listing of subject numbers for individual adverse events will be provided.

A listing of adverse events recorded as dose-limiting toxicities for Part 1 subjects will be provided. Additionally, a summary of the number of patients experiencing DLTs for Part 1 subjects will be provided.

8.1.1.3. 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 summarized based on the number and percentage of subjects. This summary will classify subjects by primary cause of death. A supportive listing will be generated to provide subject-specific profiles on subjects who died.

All SAEs will be tabulated based on the number and percentage of subjects who experienced the event. Separate summaries will also be provided for study treatment-related SAEs for both GSK3326595 and pembrolizumab where applicable. The frequency and percentage of SAEs will be summarized in descending order of total incidence by PT only.

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

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

8.1.1.4. Adverse Events Leading to Discontinuation of Study Treatment and Other Significant Adverse Events

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

- AEs Leading to Discontinuation of Study Treatment (note: Part 3 subjects will be summarized separately as follows: AEs leading to GSK3326595 discontinuation; AEs leading to pembrolizumab discontinuation. Supportive listings will only be for GSK3326595).
- AEs Leading to Dose Interruptions of GSK3326595.
- AEs Leadings to Dose Reductions of GSK3326595

8.1.1.5. Pregnancies

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. If female subjects or female partners of male subjects become pregnant while on the study, the information will be included in the narratives.

8.2. Secondary Safety Analyses

8.2.1. Safety Analyses – Part 2

Safety measures described in Section 8.1will comprise a secondary analysis for the Part 2 cohort and will be summarized and grouped by disease cohort.

8.2.2. Safety Analyses – Part 1 and Part 2

Safety tables will also be produced as a secondary analysis for all Part 1 and Part 2 patients combined as follows: 300 mg dose group (combining capsule and tablet cohorts), 400mg dose group, total RP2P dose group (combining those with 300 and 400 mg), and overall group (combining all Part 1 and Part 2 subjects of all dose levels). Food effect sub-study patients will be included with this summary.

8.3. Adverse Events of Special Interest Analyses

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event.

- Selected adverse events include anemia, neutropenia, thrombocytopenia (platelet count decrease and thrombocytopenia), and fatigue.

Summaries of the number and percentage of subjects with these events will be provided for each type of events separately. The summary of event characteristics will also be provided, including number of subjects with any event, number of events, number of subjects with any event that is serious, number of subjects with any event that is related to study treatment, the outcome of the event, maximum grade and the action taken for the event. The percentage will be calculated in two ways, one with number of subjects with event as the denominator and the other with total number of subjects as the denominator. The worst-case approach will be applied at subject level for the event outcome and maximum grade, i.e., a subject will only be counted once as the worst case from all the events experienced by the subject. For action taken to an event, subject will be counted once under each action, e.g., if a subject has an event leading to both study treatment discontinuation and dose reduction, the subject will be counted once under both actions.

The onset and duration of the first occurrence of the selected adverse events will be summarized. This will include the number of subjects experiencing the event, the time of onset of the first occurrence of the event in days from first dose of study treatment, as well as the duration of the event in days.

In addition, summaries of adverse events and serious adverse events by preferred term will be provided specifically for bone-related events and ocular events.

8.4. Clinical Laboratory Evaluations

Laboratory grades will be reported, where applicable, using the Common Terminology Criteria for Adverse Events (CTCAE v4.0), [Basch, 2014].

Summary of lab values and change from baseline by scheduled visits using mean, median, standard deviation, minimum and maximum will be provided.

Summaries of lab data by maximum toxicity grade will be provided for all the lab tests that are gradable by CTCAE v4.0.

Summaries of worst-case grade increase from baseline grade will be provided for all the lab tests that are gradable by 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. 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.

For lab 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. If a subject has a decrease to low and an increase to high during the same time interval, then the subject is counted in both the "Decrease to Low" categories and the "Increase to High" categories. In addition, the summary will include changes from baseline with respect to normal range by scheduled visits.

Separate summary tables for hematology, chemistry, urinalysis, troponin, and coagulation laboratory tests will be produced. A supporting listing of laboratory data for participants with any value outside the normal range will be provided. Troponin values outside the normal range, with value, normal range, abnormal/clinical importance flag will also be provided.

Detailed derivation of baseline assessment is specified in Section 5.2.

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 specified timepoint.

8.4.1. Chemistry

The laboratory assessment will include the following tests:

total protein, albumin, sodium, potassium, total calcium, calcium corrected, blood urea nitrogen (BUN), creatinine, creatinine clearance, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin (total), and direct bilirubin, amylase, lipase.

8.4.2. Hematology

The laboratory assessment will include the following tests:

Hemoglobin (HGB), hematocrit, platelet count, red blood cell (RBC) count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), reticulocytes (absolute), reticulocytes (%), white blood cell (WBC) count, neutrophils (absolute), lymphocytes (absolute), monocytes (absolute), eosinophils (absolute), basophils (absolute), neutrophils (%), lymphocytes (%), monocytes (%), eosinophils (%) and basophils (%).

8.4.3. Coagulation

The laboratory assessment will include the following tests:

Prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR). Both INR and PTT will be graded.

8.4.4. Urinalysis

The laboratory assessment will include the following tests:

pH, microscopic examination, specific gravity, ketones, protein, glucose, blood

8.4.5. Additional Tests

The laboratory assessments will include the following tests:

Serum: Troponin I, and troponin T. There will be a summary for local labs only.

8.4.6. Analysis of Liver Function Tests

A summary of Hepatobiliary Laboratory Abnormalities will be displayed. The general rules are:

- Categories are for subject counts and percentages, not events.
- To be counted in the denominator, the subject must have at least one post-baseline lab chemistry measurement for the specified lab tests (e.g. in the 'ALT ≥3xULN and BIL ≥2xULN' category, the denominator should include subjects who had both a post-baseline ALT value AND a post-baseline BIL value that was up to 28 days after ALT). This denominator is the most conservative for reporting percentages.
- Categories are not mutually exclusive. For example, a subject with ALT 20xULN will be included in each of the 3x, 5x, 8x, 10x, and 20x categories.
- If direct bilirubin is available, on the same day, the direct bilirubin as a portion of the total bilirubin must be ≥35% when total bilirubin is ≥2xULN. If all criteria for Hy's Law are satisfied except direct bilirubin exists and is <35% then the record will not be considered a Hy's Law event. If total bilirubin value is not provided within 28 days on or after ALT value, direct bilirubin cannot be used in place of total bilirubin in the Hy's law criteria.
- Hepatocellular injury is defined as ((ALT/ALT ULN)/ (ALP/ALP ULN)) ≥5 and ALT ≥3xULN. ALT and ALP values must occur on the same day. The denominator should include subjects who had both a post-baseline ALT and ALP on the same day. In addition, the denominator for Hepatocellular injury and BIL ≥2xULN should include subjects who had both a post-baseline ALT and ALP on the same day as well as BIL on or up to 28 days of that day.

8.5. 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.

8.5.1. Vital Signs

Change from baseline in vital signs will be summarized by scheduled visit using mean, median, standard deviation, minimum and maximum.

Summaries of increase in systolic blood pressure and diastolic blood pressure from the baseline with respect to the categories defined in Section 15.8.3will be performed. These summaries will display the number and percentage of subjects with any grade increase, increase to grade 2 and increase to grade 3 at each scheduled assessment time and in the worst-case post-baseline. Subjects with missing baseline value are to be assumed to have grade 0.

Summaries of changes in heart rate and temperature from the baseline value with respect to the categories defined in Section 15.8.3 will be performed. For heart rate and temperature, both an increase and decrease in value are of clinical concern. Subjects with missing baseline value are to be assumed to have normal baseline.

The determination of the worst-case post baseline takes into account both planned and unscheduled assessments. The percentages are based on the number of subjects in the treatment group with data for the vital sign parameter at the specified planned time.

A supporting listing will also be provided.

8.5.2. Performance Status

ECOG performance status [Oken, 1982] 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.

8.5.3. ECG

A summary of the number and percentage of subjects who had normal and abnormal (clinically significant and not clinically significant) ECG findings will be displayed by scheduled visits as well as for the worst-case post-baseline (including unscheduled assessments). When more than one ECG is performed during a 'Time Period' or when there are multiple values used to determine 'Worst Case Post-Baseline', the following rules will be used to determine the worst case finding based on the interpretation and the clinical significance:

- Count the subject as 'ABNORMAL' and 'CLINICALLY SIGNIFICANT', if any of the findings are 'ABNORMAL' and 'CLINICALLY SIGNIFICANT' during the time period/Post-Baseline.
- Else count the subject as 'ABNORMAL' and 'NOT CLINICALLY SIGNIFICANT', if any of the findings are 'ABNORMAL' and 'NOT CLINICALLY SIGNIFICANT' and none of the findings are 'ABNORMAL' and 'CLINICALLY SIGNIFICANT' during the time period/Post-Baseline.
- Else count the subject as 'NORMAL' if there is a finding of 'NORMAL' and none of the findings are 'ABNORMAL during the time period/Post-Baseline.
- Otherwise, do not count the subject during the time period/Post-Baseline, i.e. little n will reflect that the subject is not counted in the time period/Post-Baseline.

The QTc values based on Fridericia formula will be rounded to the integer and the values will be categorized into the ranges identified in Section 15.8.2. Summaries of grade

increase will be provided. These summaries will display the number and percentage of subjects with any grade increase, increase to grade 2 and increase to grade 3 at each scheduled assessment time and in the worst-case post-baseline (including unscheduled assessments). For grade increase summaries, missing baseline values will be assumed to be grade 0. For triplicate values, grades associated with the highest value will be reported.

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. A summary of change in QTc value will display the number and percentage of subjects with the worst-case post-baseline (including unscheduled assessments). For numerical values measured in triplicate, averages at each visit will be used for this analysis.

Listings of all ECG values will be provided.

8.5.4. LVEF

Absolute change from baseline in LVEF will be summarized at each scheduled assessment time and in the worst-case post-baseline. Only the post-baseline assessments that used the same method (ECHO or MUGA) as the baseline assessments will be used to derive the change from baseline. The change from baseline will be categorized as identified in Section 15.8.4.

8.5.5. Liver Events

For any liver events that occur during the study, the liver event information for Roussel Uclaf Causality Assessment Method (RUCAM) score will be summarized, including whether the subject was age 55 or over, whether the subject became pregnant, liver imaging normal or not, a biopsy was taken or not, whether there was fasting or significant dietary change, whether the subject took any unconventional medications, timing when the event occurs (while on treatment or after stopping treatment) and listings will be provided for time from first dose to start of liver event and time from last dose to start of liver event.

For subjects with multiple events, the first event will be used for the summary tables. All events with subject level details will be displayed in a supporting listing.

8.5.6. DEXA Bone Densitometry

A listing of DEXA bone densitometry data from local labs will be provided for all subjects. These will include scan region and assessment, site, planned time, date, study day, BMD in g/cm2, Z-scores, T-scores, and institution assessment. A summary of bone mineral density shifts from baseline relative to normal range will also be provided.

8.5.7. Ophthalmic Assessments

Listings of optical coherence tomography from local lab results with age/sex/race, date, study day, machine type, and left and right eye results in microns will be provided. In

addition, a listing of best corrected visual acuity (Snellen Acuity Equivalent) results will also be provided.

9. PHARMACOKINETIC ANALYSES

The pharmacokinetic (PK) analyses will be based on the Pharmacokinetic Population, unless otherwise specified.

Table 12 provides an overview of the planned analyses, with full details being presented in Appendix 12: List of Data Displays.

Table 12 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
Drug Concentration														
Plasma or Urine Pharmacokinetic Concentration				Y	Y	Y	Y							
Pharmacokinetic Parameters														
Plasma or Urine Pharmacokinetic Parameters				Y			Y							
Dose proportionality analysis														
Food effect study														
Relative Bio-availability study														

1. **NOTES :**

- T = Table, F = Figure, L = Listings, Y = Display generated
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modeling) 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 subject observed raw data.

9.1. Drug Concentration Measures

PK analysis of GSK3326595 and pembrolizumab (apply to Part 3 subjects only) drug concentration-time data will be conducted by non-compartmental methods under the direction of GSK CPMS.

Drug concentration-time data will be listed for each subject and summarized by descriptive statistics at each time point. Summary tables/figures will use planned relative time on x-axis; while individual figures will use actual time after dose on x-axis.

9.2. Pharmacokinetic Parameters

9.2.1. Deriving Pharmacokinetic Parameters

- Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 15.5.2 Reporting Process & Standards for Pharmacokinetic).

- The pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices [SOP_314000 and GUI_51487] and using Phoenix winnonlin.
- All calculations of non-compartmental parameters will be based on actual sampling times.
- Pharmacokinetic parameters described in Table 13 will be determined from the plasma concentration-time data, as data permits.

Table 13 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-∞)	Area under the concentration-time curve extrapolated to infinity will be calculated as: AUC = AUC(0-t) + C(t) / lambda_z
AUC(0-τ)	Area under the concentration-time curve from time zero to the predose of the next dose. For BID administration, AUC (0-12) will be computed
Cmax	Maximum observed plasma concentration, determined directly from the concentration-time data.
tmax	Time to reach Cmax, determined directly from the concentration-time data.
t½	Apparent terminal half-life will be calculated as: t½ = ln2 / lambda_z
CL/F	Oral clearance
TI	time invariance will be calculated as: • $TI = \frac{AUC(0-\tau),Day\ 15}{AUC(0-\infty),Day\ 1}$
AR	accumulation ratio will be calculated as: • $\mathrm{AR} = \frac{AUC(0-\tau),Day\ 15}{AUC(0-\tau),Day\ 1}$

1. **NOTES:**
- Additional parameters may be included as required.
- Lambda_z is the terminal phase rate constant.

GSK3326595 concentrations will be determined in urine samples to determine urinary recovery of unchanged drug and renal clearance.

Urinary Recovery: The urinary recovery of unchanged drug in a complete collection up to a fixed time point (Ae(0-x)), over a dosing interval (Ae(0- τ)), or up to the time of the last measurable urinary concentration when concentrations in subsequent collections are non-quantifiable (Ae(0-∞)), will be calculated as the sum of the products of concentration and urine volume over the appropriate collection intervals.

Urinary Excretion Rate: The urinary (renal) excretion rate of unchanged drug may be calculated based on urine collection over a specified time interval. In situations when

plasma drug concentrations are non-quantifiable, the estimation of elimination rate constant and elimination half-life of a drug can be made by analyzing urinary excretion rate data.

Renal Clearance: Renal clearance will be calculated from the ratio of the appropriate values for urinary recovery and area under the concentration-time curve e.g.,

$$CLr = \frac{Ae(0-x)}{AUC(0-x)}$$

9.2.2. Statistical Analysis of Pharmacokinetic Parameters

Plasma concentration-time data will be listed by dose, age group, and summarized using descriptive statistics (median, minimum, maximum, arithmetic mean, 95% confidence interval for the arithmetic mean, standard deviation, coefficient of variation (CV = √ (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) by planned relative assessment time. Mean and/ or median values will be plotted over time. For tmax the following summary statistics will be calculated for each dose level, median, maximum, minimum, arithmetic mean, 95% confidence interval, and standard deviation will be calculated.

Individual plasma pharmacokinetic parameters values as well as a descriptive summary (median, minimum, maximum, arithmetic mean, 95% confidence interval for the arithmetic mean, standard deviation, coefficient of variation (CV = √ (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) by dose cohort and age group will be reported. 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.

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

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

9.2.2.1. Dose-Proportionality Analysis for Part 1 Dose Escalation Subjects

Dose proportionality analysis will be done for QD doses and BID doses separately. A minimum of 3 values per dose must be available for a given parameter to estimate dose proportionality with the power model.

Dose proportionality of log-transformed parameters AUC(0-∞) (or if not available AUC(0-t)) and Cmax will be assessed using the power model for, as described below:

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

where y denotes the PK parameter being analysed and α depends on subject and error.

Dose proportionality implies that β=1 and will be assessed by estimating β along with its confidence interval. The exponent, β, in the power model will be estimated by regressing the $\log_e$-transformed parameter on $\log_e$-transformed dose:

$\ln(y) = \ln(\alpha) + \beta * \ln(\text{dose})$

The power model will be fitted by restricted maximum likelihood (REML), for every dose level (treatment) with minimum 3 values. Both the intercept and slope will be fitted as random effects. The following SAS code will be used:

```
proc mixed data = DSETIN;
      class subject;
      model LNVAR=LNdose / solution alpha=0.1 outp=pred ddfm=kr;
      random intercept / type=UN subject=subject;
      ods output solutionf=solutionf;
run;
```

Point estimates for the slopes of PK parameters with associated CIs will be presented.

If this model fails to converge, the model will be refitted with slope as a fixed effect.

If the log transformed models are not proportional and sufficient data are available, $\log_e$-transformed dose-normalised AUC(0-∞) (or if not available AUC(0-t)) and Cmax will be analysed using a suitable mixed effects model, fitting treatment as a fixed effect and subject as a random effect. Point estimates and corresponding 90% confidence intervals for the ratios of each dose level to the reference dose level 1 will be determined using code similar to that outlined above.

```
proc mixed data = DSETIN;
      class subject treatment;
      model LN(VAR/dose) = dose / ddfm=KR outp=pred_cmax;
      id dose usubjid;
      random usubjid;
      lsmeans dose;

      estimate "DL2 vs DL1" treatment 1 0 0 0 0 0 0 -1 /cl alpha=0.1 e;
      estimate "DL3 vs DL1" treatment 0 1 0 0 0 0 0 -1 /cl alpha=0.1 e;
      estimate "DL4 vs DL1" treatment 0 0 1 0 0 0 0 -1 /cl alpha=0.1 e;
      estimate "DL5 vs DL1" treatment 0 0 0 1 0 0 0 -1 /cl alpha=0.1 e;
      estimate "DL6 vs DL1" treatment 0 0 0 0 1 0 0 -1 /cl alpha=0.1 e;
      estimate "DL7 vs DL1" treatment 0 0 0 0 0 1 0 -1 /cl alpha=0.1 e;
      estimate "DL8 vs DL1" treatment 0 0 0 0 0 0 1 -1 /cl alpha=0.1 e;
      lsmeans treatment;
      ods output estimates=estimates lsmeans=lsmeans;
run;
```

The back-transformed estimate and 90% CI will be presented.

9.2.2.2. Food Effect and Relative Bioavailability Sub-Study

Estimates of LS mean, LS mean difference and 95% CI are based on log transformed AUC(0-INF) and Cmax using a mixed-effect model with fixed-effect terms of fed status (fed or fasted), sequence and period and subject within sequence as a random effect. The

point estimates and their associated 90% CIs were then backtransformed to provide point estimates of the geometric LS mean, and 90% CIs and ratios of fed (test) vs. fasted (reference).

Programming note: **Only use period 1 and period 2 data**

```
ods output LSMeans=lsmean;
ods output estimates=estg;
ods output CovParms=Covsparms;

 proc mixed data=pkparm1;
      class sequence period  treat subjid;
      model Lcmax=sequence period treat/ DDFM=SATTERTH;
      random subjid(sequence);
      lsmeans treat/pdiff cl alpha=0.1;
     estimate 'Tablet Fed vs Tablet Fasted' treat 1 -1 / cl alpha=0.1;
 run;
```

Where TREAT: FET = Tablet Fed; FFT = Tablet Fasted.

```
 * Anti-log transformation to obtain the Geometric Means;
 data glsmean;
      set lsmean;
      gmean=exp(estimate); *Geometric means;
 run;

 * Anti-log transformation to obtain the ratio of Geometric Means (point estimate) and its
90% confidence interval (lower and upper bounds);
 data diffs;
     set EST;
     gratio=exp(estimate); ** Ratio of geometric mean;
     glower=exp(lower); ** 90% CI lower bound;
     gupper=exp(upper); ** 90% CI upper bound;
 run;


**Calculate inter-subject CV and intra-subject CV;
DATA CV;
 set Covsparms;
 if covparm="subjid(sequence)" then intermse=estimate;
 else if covparm="Residual" then intramse=estimate;
 intercv = sqrt(exp(intermse) -1) *100;
 intracv = sqrt(exp(intramse) -1) *100;
run;
"
```

Non-parametric methods such as the Hodges and Lehmann estimator (Hodges, 1963) will be used to estimate the median differences between the fed treatments and the fasted state treatments for tmax and t½. An associated 90% CI for the median differences will be constructed. The analysis will exclude data for a given period if the subject did not receive the correct dose or formulation during that period or the protocol-defined diet was not adhered to.

Based on the US FDA guidance on food-effect bioavailability studies, the absence of a food-effect will be established if the 90% CI of the ratio for Cmax and AUC, based on log-transformed data, is within the 80 to 125% equivalence limit. Recommendation on the clinical significance of the effect of food will be based on the magnitude of the change and our understanding of the exposure-clinical response relationship.

For the evaluation of food effect, tmax at fed and fasted status will be presented by subject and dose cohort in tabular and graphical form.

Relative Bioavailability of Tablet

Pharmacokinetic (PK) parameters $AUC_{0-\infty}$ (or if not available AUC(0-t)) and Cmax will be log-transformed and analyzed using a mixed-effects model with formulation (tablet or capsule)sequence and period as fixed effects, and subject as a random effect. Point estimates and their associated 90% CIs will be constructed for the differences between between tablet and capsule. The point estimates and their associated 90% CIs will then be back transformed to provide point estimates and 90% CIs for the ratios of tablet (test) vs. capsule (reference) under fasted condition.

Code will be consistent with the above for food effect analysis. The analysis will exclude data for a given period if the subject did not receive the correct dose or formulation during that period.

10. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

Population pharmacokinetic analyses will 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 will be reported separately.

11. PHARMACODYNAMIC (AND/OR BIOMARKER) ANALYSES

Pharmacodynamic and biomarker analyses are not within the scope of this reporting and analysis plan. Any planned analyses will be described in a separate document.

12. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

Further exploratory pharmacokinetic/pharmacodynamic analyses are not within the scope of this SAP. Any planned analyses will be described in a separate document.

13. ADDITIONAL ANALYSES DUE TO THE COVID-19 PANDEMIC

A summary of the frequency and percent of subjects with Covid-19 case diagnosis will be provided, along with number of case diagnosis events, and subjects with multiple events. Also provided will be the following: the frequency and percent of subjects with worst case diagnosis of confirmed, probably, or suspected case diagnosis, as well as frequency and percent of those tested, and the results of the testing, based on number of tests performed.

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15. APPENDICES

15.1. Appendix 1: Exclusions from Per Protocol Population

A per-protocol population for this study is not defined and not planned.

15.2. Appendix 2: Schedule of Activities

Refer to protocol for schedule of events.

15.3. Appendix 3: Assessment Windows

15.3.1. Definitions of Assessment Windows for Analyses

Visit collected in the data will be used for the analysis and no visit window assigned for the study. Tumor response measurements from unscheduled visits will be included as well as most extreme result reporting (e.g. worst grade post-baseline).

15.4. Appendix 4: Study Phases

15.4.1. Study Phases for Treatment

Assessments and events will be classified according to the time of occurrence relative to first dose of study treatment.

Treatment Phase	Definition
Pre-therapy	Time prior to the subject's first dose of study treatment.
On-therapy	Time from first dose of study treatment to the last dose date of study treatment + 30 days.
Post-therapy	Time beyond the on-therapy period

15.4.2. Study Phases for Concomitant Medication and Blood and Blood Supportive Care Products

Concomitant medication and blood and blood supportive product start and end dates will be assigned to study time periods in relation to first dose of study treatment as defined below. The start date references time flag variables and end date reference time flag variables will be added to the concomitant medications and blood and blood supportive products datasets, respectively.

15.4.2.1. Start Date Relative to Treatment:

Treatment State	Definition
Before	Start Date < Study Treatment Start Date OR Study Treatment Start Date is missing (i.e., subject has not taken any study treatment) OR Start Date is missing and Stop Date < Study Treatment Start Date
During	Study Treatment Start Date <=Start Date < Study Treatment Stop Date + 30 days OR Study Treatment Stop Date is missing OR Start Date is missing and Stop Date >= Study Treatment Start Date
After	Start Date > Study Treatment Stop Date + 30 days

15.4.2.2. Stop Date Relative to Treatment:

Treatment State	Definition
Before	Stop Date < Study Treatment Start Date OR Study Treatment Start Date is missing (i.e., subject has not taken any study treatment)
During	Study Treatment Start Date <=Stop Date < Study Treatment Stop Date + 30 days OR Study Treatment Stop Date is missing OR End Date is missing and Start Date relative to treatment is not “After”
After	Start Date > Study Treatment Stop Date + 30 days OR End Date is missing and Start Date relative to treatment='AFTER'

15.4.2.3. Blood and Blood Supportive Care Products

Only on-therapy blood and blood supportive care products that start after the start of study treatment are included in the Blood Products and Blood Supportive Care Product summaries. Therefore, for summary tables, include blood and blood supportive care product records where start relative to treatment in ('DURING') and end relative to treatment in ('DURING','AFTER'). All data will be reported in listings.

15.4.2.4. Summary of Concomitant Medication

Concomitant medication start relative to treatment and end relative to treatment flags are used to select data to include in the concomitant medication summaries as follows:

- Summary of Concomitant Medications: This summary will contain medications including those with start date prior to study treatment start and continue (missing end date or end date after study treatment start date) on therapy. Note that any medications with start date and end date prior to study treatment start date will be excluded. In addition, any medication that was started during post-therapy will be excluded. Include concomitant medication records where start relative to treatment in ('BEFORE','DURING') and end relative to treatment in ('DURING','AFTER').

15.5. Appendix 5: Data Display Standards & Handling Conventions

15.5.1. Reporting Process

Software	
• The currently supported versions of SAS software 9.3 or higher version will be used.	
Reporting Area	
HARP Server	: [Insert Server]
HARP Area	: [Insert Area & Reporting Effort]
QC Spreadsheet	: [Insert Location]
Analysis Datasets	
• Analysis datasets will be created according to CDISC/ADaM standards. • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	
• RTF files will be generated for all analyses.	

15.5.2. Reporting Standards

General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: • 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
Formats
• All data will be reported according with the All Treated Population, according to the actual treatment the subject received unless otherwise stated. • 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. • 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.
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 Visits
• Unscheduled visits will not be included in summary tables except for most extreme result reporting (e.g. worst grade post-baseline), as well as tumor assessments.

• Unscheduled visits will not be included in figures except for tumor assessments. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
1. Continuous Data	1. Refer to IDSL Statistical Principle 6.06.1
1. Categorical Data	2. N, n, frequency, %

15.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to VQD-SOP-005939. Note: Concentration values will be imputed as per GUI_51487
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 for descriptive summary statistics/analysis and summarized graphical displays only.
NONMEM/Pop PK File	Not applicable.
NONMEM/PK/PD File	Not applicable.
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by Programmer	The following PK parameters will be derived by the Programmer : Cmax, Tmax, Ctrough, AUC0-t, AUC0-tau, AUCinf, t½, λz , TI, AR, C12 or C24, Ae(0-x) or Ae(0-∞), CLr
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	No.
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to GSK Data Standards and statistical principles

15.6. Appendix 6: Derived and Transformed Data

15.6.1. General

Multiple Measurements at One Time Point
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 most extreme result (e.g. worst grade post-baseline). 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. 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 qualitative ECG measures (Normal, Abnormal, Not Clinically Significant, Abnormal, Clinically Significant) and QTcF grade, the most clinically significant value (highest grade) will be summarized. Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of “Any visit post-baseline” row of related summary tables. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in listings.
Study Day
Reference Dates Unless otherwise stated, the safety reference (start) date will be the start of treatment of GSK3326595. 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. Study Day for Safety Measures/Efficacy If the date of interest occurs on or after the safety/efficacy reference date then the safety/efficacy study day will be calculated as (date of interest – safety/efficacy reference date) + 1. If the date of interest occurs before the safety/efficacy reference date then the safety study day will be calculated as (date of interest-safety/efficacy reference date). There is no safety/efficacy study day 0.
Duration of 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.

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 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)))

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.

15.6.2. Study Population

Demographics
Age
• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows: • Any subject with a missing day will have this imputed as day '15'. • Any subject with a missing date and month will have this imputed as '30th June'. • Birth date will be presented in listings as 'YYYY'.
Body Mass Index (BMI)
• Calculated as Weight (kg) / [Height (m)^2
Extent of Exposure
GSK3326595 • Number of days of exposure (duration on study treatment) to study drug will be calculated based on the formula: Duration of Exposure in Days = Treatment Stop Date – Treatment Start Date + 1 • Participants who were randomized but did not report a treatment start date will be categorised as having zero days of exposure. • The cumulative dose will be based on the formula: Cumulative Dose = Sum of (Number of Days x Total Daily Dose) If there are any treatment breaks during the study, exposure data will be adjusted accordingly.
• Pembrolizumab o Extent of exposure will be calculated based on treatment cycles derived based on cycle start dates in the exposure dataset o Duration on study treatment will be calculated based on the formula:

Duration on study treatment = Last Treatment Stop Date – First Treatment Start Date + [lag time, e.g., Duration of Cycle] Take into account of death date if a lag time>1, e.g., Duration of Cycle is used. • Participants who were randomized but did not report a treatment start date will be categorised as having zero days of exposure.
• Combination Treatments (Part 3) • Extent of exposure will be calculated for each treatment component • Duration of treatment will be calculated based on the formula: Duration on study treatment = Maximum of ([IV Treatment Stop Date + lag time], [Oral Treatment Stop Date]) – (Minimum of Treatment Start Date) + 1 Take into account of death date if a lag time>1, e.g., Duration of Cycle is used.
• Participants who were randomized but did not report a treatment start date will be categorized as having zero days of exposure
Actual Treatment
• Subject's actual treatment will be derived from [exposure data] [study treatment data provided by Clinical Operations]. If a subject's actual treatment is the same as assigned treatment, actual treatment is the assigned treatment; if a subject received treatment different from assigned treatment for the entire duration of treatment, actual treatment is different from assigned treatment.

15.6.3. Efficacy

Change from Baseline
Change from Baseline = Post-Baseline Visit Value – Baseline % Change from Baseline= 100 x (Post-Baseline Visit Value – Baseline) / Baseline Maximum Decrease from Baseline = maximum (Decrease from Baseline) prior to disease progression If either the Baseline or Post-Baseline Visit Value is missing, Change from Baseline and % Change from Baseline is set to missing
Date of Response
For post-baseline disease assessments, the date of response (PR or better) is assigned to the latest date of disease assessments; for other response categories ([MR,] SD [or Non-CR/Non-PD], NE, PD), the date of response is assigned to the earliest date of disease assessments. For the BOR, if BOR is SD, the latest date of SD is assigned to the date of BOR. If for other BOR responses, the earliest date of that response will be assigned as the date of BOR.
Date of New Anti-Cancer Therapy
Derived as the earliest date of new anti-cancer therapy, radiotherapy (where applicable) or cancer-related surgical procedure (where applicable) Missing or partial dates will be imputed for derivation of new anti-cancer therapy following rules specified in Section 15.7.3.3.

15.6.4. Safety

ECG Parameters
Corrected QT Intervals
• The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF; defined as [QT/($RR^{1/3}$)]).

15.6.5. Pharmacokinetic

See Section 9.2.1for descriptions of derived PK parameters.

15.6.6. Pharmacodynamic (and / or Biomarker)

Pharmacodynamic analyses are not within the scope of this analysis plan.

15.7. Appendix 7: Reporting Standards for Missing Data

15.7.1. Premature Withdrawals

Element	Reporting Detail
General	• A subject who is not treated with the RP2D will be considered to have completed the study if: o they complete screening assessments, at least 21 days of study treatment and the post-treatment follow-up visit, or o they discontinue study treatment for progression or reasons listed in Protocol Section 5.4 • A subject who is treated at RP2D will be considered to have completed the study if: o they discontinue study treatment for reasons listed in Protocol Section 5.4, or o they die while receiving study treatment, or o are receiving ongoing study treatment at the time of the Sponsor's decision to close the study. • The end of the study is defined as the completion of all cohorts as defined in Protocol Section 5.4, or termination of the study at any time by the Sponsor. • Subjects who have not died and are no longer being followed for survival are considered to have discontinued the study. The End of Study eCRF should only be completed when a subject is no longer being followed. The study may be considered completed for purposes of a final analysis when 70% of subjects enrolled in Part 2 or Part 3 (whichever is latest) have progressed or died. If available, subjects continuing on treatment at the time of final analysis may be offered the option to continue in a rollover trial.

15.7.2. 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 : o These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such. • Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument Subjects with the designation of treatment relationship for adverse events (AE)s and serious adverse events (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's described in Section 15.4.2. for partial dates and for missing exposure end dates.
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.
Responder Analysis	• For endpoints which determine the percentage of responders, subjects with unknown/not evaluable or missing best overall response will be assumed to be

Element	Reporting Detail
	non-responders, and will be included in the denominator when calculating the percentages.

15.7.3. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays. However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for 'slotting' data to study phases or for specific analysis purposes as outlined below. • 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. • With the exception of new anti-cancer therapy start date in the time to event analysis dataset and exposure end date in the exposure analysis dataset, imputed dates will not be stored on datasets.

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

15.7.3.1. Adverse Events (AE):

Imputations in the adverse events dataset are used for slotting events to the appropriate study time periods 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: 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. 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.

Dataset	Date	Missing Element	Rule
			Else set start date = 1st of month.
	End Date		No imputation for partial end dates will be performed

15.7.3.2. Concomitant Medication and Blood and Blood Supportive Care Products

Impute start and end dates for use in derivation of the reference variables concomitant medication start and end relative to treatment and blood and blood supportive care start and end relative to treatment, but do not permanently store the imputed start and end dates in the analysis datasets. The reference variables will be used to differentiate before, during and after for the concomitant medication or blood or blood supportive care start and end dates. The derived time in relation to treatment variables are not needed for reporting of these data.

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: 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. 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.

Dataset	Date	Missing Element	Rule
	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 (MSTONE.LCONTDT).

15.7.3.3. New Anti-Cancer Therapy/ Radiotherapy/Surgical Procedures for Efficacy Evaluation (e.g., response rate, time to event)

Start dates for follow-up anticancer therapy, radiotherapy (where applicable), and surgical procedures (where applicable) will be temporarily 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 anticancer therapy). 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
		day	• If partial date falls in the same year, same month as the last dose of study treatment, then assign to earlier of (date of last dose of study treatment + 1, last day of month). • If partial 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 last assessment + 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

15.7.3.4. 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 (using the earliest date of PD or death), PFS will be censored at the last adequate assessment prior to PD or death.

For NHL cohort, as the 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.

For other cohorts: as the scheduled disease assessment is every 8 weeks, a window of 119 days (16 weeks + 7 day window) will be used.

15.7.3.5. Treatment End Date

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.

In general, completely missing end dates are not imputed, with the following exceptions for imputation of missing treatment end date at interim analyses.

- For imputation of missing exposure end date at an interim analysis when subjects are still on treatment, the following conventions will be applied:
- If the missing end date is in the last exposure record, the earliest of: the date of the data cut-off, the date of withdrawal from the study, or the death date will be used
- If the missing end date is not in the last exposure record, treatment start date for the record will be used

15.7.3.6. Death Date

If death date is missing, the last contact date will be used.

15.8. Appendix 8: Values of Potential Clinical Importance

15.8.1. Laboratory Values

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern.

Laboratory grades will be reported, where applicable, using the Common Terminology Criteria for Adverse Events (CTCAE v4.0).[Basch, 2014]

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

15.8.2. ECG

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 v4.03 will be used to assign grades (see adverse event 'Electrocardiogram QT corrected interval prolonged'). Note that there is a slight inconsistency between CTCAE v4.03 and ICH E14 (Absolute QTc interval prolongation). It was decided to align with CTCAE for the oncology standard categories. Note that <=450 is considered to be Grade 0.

ECG Parameter	Potential Clinical Importance (PCI) Range	Unit
Absolute QTcF interval	>450 to <=480 (Grade 1) >480 to <=500 (Grade 2) >500 (Grade 3)	msec
Increase from baseline QTcF	Increase of 31 to 60 Increase of >60	msec

15.8.3. Vital Signs

To identify heart rate values of potential clinical importance, NCI-CTCAE v4.03 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 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 v4.03 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	≥120 to <140 (Grade 1) ≥140 to <160 (Grade 2) ≥160 (Grade 3)	mmHg
Increase from baseline Diastolic Blood Pressure	≥80 to <90 (Grade 1) ≥90 to <100 (Grade 2) ≥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 v4.03 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, vital signs will be further categorized for reporting based on the following:

- Heart rate (beats/min): <60, >=60 to =<100, and >100; and
- Temperature (°C): <=35, >35 to <38, ≥38.
- Systolic blood pressure:<90, >=90 to <120, >=120
- Diastolic blood pressure: <60, >=60 to <80, >=80

15.8.4. Left Ventricular Ejection Fraction

- The following criteria will be used to flag left ventricular ejection fraction (LVEF) values that are values of potential clinical importance:
- To identify LVEF values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Ejection fraction decreased'.

LVEF Parameter	Potential Clinical Importance (PCI) Range	Unit
Absolute change from baseline LVEF	No change or any increase Any decrease >0-<10 decrease 10-19 decrease ≥20 decrease ≥10 decrease and ≥ LLN ≥10 decrease and below LLN ≥20 decrease and ≥ LLN ≥20 decrease and below LLN	%

15.9. Appendix 9: Population Pharmacokinetic (PopPK) Analyses

Population-based PK analyses are not within the scope of this analysis plan.

15.10. Appendix 10: Pharmacokinetic / Pharmacodynamic Analysis

Pharmacokinetic/Pharmacodynamic analyses are not within the scope of this analysis plan.

15.11. Appendix 11: Abbreviations & Trade Marks

15.11.1. Abbreviations

Abbreviation	Description
ABCG2 (BCRP)	Breast cancer resistance protein
ACC	adenoid cystic carcinoma
ADA	Anti-drug antibodies
AE(s)	Adverse Event(s)
Aft	After
ALL	Acute lymphoblastic leukemia
ALT (SGPT)	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AR	Accumulation ratio
AST (SGOT)	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BC	Breast cancer
BCRP	Breast Cancer Resistance Protein
BID	Twice daily
BMD	Bone mineral density
Caco-2	Continuous cell of heterogeneous human epithelial colorectal adenocarcinoma cells
CBC	Complete blood count
CDK	cyclin-dependent kinase
cf-DNA	Circulating cell free DNA
CKD-Epi	Chronic Kidney Disease Epidemiology Collaborative
CL/F	Apparent clearance following oral dosing
Cmax	Maximum observed plasma concentration
CML	Chronic myeloid leukemia
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CPS	Combined Percentage Score
CR	Complete response
CRF	Case report form
CT	Computed tomography
CV	Cardiovascular
CV%	Coefficient of variance percent
D	Day
DART5	D. Melanogaster analog of mammalian prmt5
DCR	Disease control rate
DHEA	Dehydroepiandrosterone
DEXA	Dual-energy x-ray absorptiometry
DILI	Drug induced liver injury
DL-1	Dose Level 1

Abbreviation	Description
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of Response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern cooperative oncology group
eCRF	Electronic case report form
EGFR	Epithelial growth factor receptor
EIAC	Enzyme-inducing anticonvulsant
CCI [redacted]	
EOT	End of treatment
CCI [redacted]	
ER-	Estrogen receptor negative
ER+	Estrogen receptor positive
ER+BC	Hormone receptor-positive adenocarcinoma of the breast
CCI [redacted]	
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FFPE	Formalin fixed paraffin embedded
FL	Follicular lymphoma
FSH	Follicle stimulating hormone
FTIH	First time in human
GALT	Gut-associated lympoid tissue
GAR	Glycine and arginine residues
GBM	Glioblastoma multiforme
GCP	Good clinical practice
GDI	Growth-Death Index
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
GLP	Global laboratory practice
GSEA	Gene set enrichment analysis
GSK	GlaxoSmithKline
h	Hour/s
H3R8, H2AR3 and H4R3	Histone 3 Arginine 8, Histone 2A arginine 3 and Histone 4 arginine 3

Abbreviation	Description
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotrophin
HCV	Hepatitis C Virus
Hep C	Hepatitis C
Her2-	Human epidermal growth factor receptor 2 negative
HIV	Human immunodeficiency virus
HL	Hodgkin's lymphoma
HLA	Human leukocyte antigen
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HN	Head and neck carcinoma
HNSCC	squamous cell carcinoma of the head and neck
HNSTD	Highest non severely toxic dose
HPLC	High-performance liquid chromatography
HPMC	Hydroxypropyl methylcellulose
HPV	human papillomavirus
HRQoL	Health related quality of life
HRT	Hormone replacement therapy
IAG	Imaging acquisition guidelines
IB	Investigator's brochure
IC_{50}	Fifty percent inhibitory concentration
ICF	Informed consent form
ICR	Independent central review
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent ethics committee
IgG	Immunoglobulin G
IgG4	Immunoglobulin G 4
INDSRs	Investigational new drug safety reports
INR	International normalized ratio
IRB	Institutional review board
iRECIST	Immune-based RECIST
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
IVD	Invitro diagnostic device
KIM-1	Kidney injury molecule-1
KPS	Karnofsky Performance Status
LDH	Lactate dehydrogenase
LHRH	Luteinizing hormone releasing hormone
LLN	Lower limit of normal
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MABEL	Minimum anticipated biologically effective level

Abbreviation	Description
MCH	Mean corpuscular hemoglobin
MCL	Mantle cell lymphoma
MCV	Mean corpuscular volume
MDCK-II	Madine-Darby Canine Kidney-II cells
MedDRA	Medical Dictionary for Regulatory Activities
MEP50	Methylosome protein 50
mg	milligram
MM	Multiple myeloma
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MSDS	Material safety data sheet
mTCC	metastatic transitional cell carcinoma of the urinary system
MTD	Maximumally tolerated dose
mTPI	Modified Toxicity Probability Interval
n	Number
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NGAL	Neutrophil gelatinase-associated lipocalin
NHL	Non-Hodgkin's lymphoma
NOAEL	No-observed adverse effect level
NSCLC	Non small-cell lung cancer
NYHA	Newyork heart association
ORR	Overall response rate
OS	Overall survival
PAX	Paxgene
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PD-1	Programmed Cell Death Protein 1
PDCD4	Programmed cell death 4
PD-L1	Programmed Death-Ligand 1
PDX	Patient-derived tumor models
PEL	Primary effusion lymphoma
PET	Positron emission tomography
PET/CT	Positron emission tomography/Computed tomography
PFS	Progression free survival
PFSR	Progression free survival rate
CCI [redacted]	
P-gp	P-glycoprotein
PGx	Pharmacogenetic
PI	Prescribing Information
PI3K	Phosphoinositol-3 kinase
PK	Pharmacokinetic

Abbreviation	Description
PR	Partial response
PR-	Progesterone receptor negative
PR+	Progesterone receptor positive
PRMT	Protein arginine methyltransferases
PRO	Patient-reported outcomes
CCI [redacted]	
PT	Prothrombin time
PTT	Partial thromboplastin time
Q3W	Every 3 weeks
q4w	Every 4 weeks
q8w	Every 8 weeks
QD	Once a day
QLQ	Quality of life questionnaire
QT	QT interval duration
QTc	Corrected QT interval duration
QTcF	QT duration corrected for heart rate by Fridericia's formula
RANO	Response Assessment in Neuro-Oncology
RAP	Report and Analysis Plan
RBC	Red blood cells
RECIST	Response Evaluation Criteria in Solid Tumors
REML	Restricted maximum likelihood
RNA	Ribonucleic acid
RNAseq	RNA sequencing
RP2D	Recommended phase 2 dose
RR	Response rate
RT-PCR	Reverse transcription-polymerase chain reaction
SAE(s)	Serious Adverse Event(s)
SAS	Statistical analysis system
SCLC	Small-cell lung cancer
SCR	Screening
SD	Stable disease
CCI [redacted]	
SMD	No metabolic activity
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SPD	Sum of products of the diameters
SRM	Study reference manual
SRT	Safety review team
STD	Severely toxic dose
STD10	Severely toxic dose to 10% of the animals
t½	Half-life
TCL	T-cell lymphoma
tFL	Transformed follicular lymphoma

Abbreviation	Description
TGI	Tumor growth inhibition
TI	Time invariance
tmax	Time to Cmax
TNBC	Triple-negative breast cancer
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
UPM	Unit probability mass
VP	Vice president
Vss	Human volume of distribution
W1D1	Week 1 Day 1
W1D3	Week 1 Day 3
W3D1	Week 3 Day 1
WBC	White blood cell
WHO	World health organization
WT	Wild type

15.11.2. Trademarks

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15.12. Appendix 12: List of Data Displays

15.12.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.n	1.1 to 1.n
Efficacy	2.1 to 2.n	2.11 to 2.n
Safety	3.1 to 3.n	3.1 to 3.n
Pharmacokinetic	4.1 to 4.n	4.1 to 4.n
Population Pharmacokinetic (PopPK)	5.1 to 5.n	5.1 to 5.n
Pharmacodynamic and / or Biomarker	6.1 to 6.n	6.1 to 6.n
Pharmacokinetic / Pharmacodynamic	7.1 to 7.n	7.1 to 7.n
Section	Listings	
ICH Listings	1 to x	
Other Listings	y to z	

15.12.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 13: Example Mock Shells for Data Displays.

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

NOTES:

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

15.12.3. Deliverables

Delivery [Priority] [1]	Description
DS [X]	During Study
DE [X]	Dose Escalation
IA SAC [X]	Interim Analysis Statistical Analysis Complete
SAC [X]	Final Statistical Analysis Complete

NOTES:

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

15.12.4. Study Population Tables

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Subject Disposition					
1.1	All Treated	ES8	Summary of Subject Status and Subject Disposition for the Study Conclusion Record	ICH E3, FDAAA, EudraCT To use the following from ES1 shell : "Outcome of Adverse Events Which Led to Study Withdrawal" with "NON-FATAL" and "FATAL" options. Add overall column. Part 1 by dose level, Part 2 by cohort, Part 3 by dose	SAC
1.2	All Treated	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment (GSK3326595)	ICH E3 include footnote [1] and [2] from standard, but remove footnote [3] use same mock as created for ACC IA, Part 1 by dose level, Part 2 by cohort, Part 3 by dose	IA, SAC
1.3	All Treated	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment (Pembrolizumab)	ICH E3 include footnote [1] and [2] from standard, but remove footnote [3] use same mock as created for ACC IA, Part 3	IA, SAC
1.4	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	SAC
1.5	Enrolled	NS1	Summary of Number of Participants by Country and Site ID (Enrolled Population)	EudraCT/Clinical Operations, Part 1 by dose level, Part 2 by cohort, Part 3 by dose	SAC
Protocol Deviation					
1.7	All Treated	DV1	Summary of Important Protocol Deviations	ICH E3, Part 1 by dose level, Part 2 by cohort, Part 3 by dose	SAC
Analysis Populations					
1.8	Screened	SP1A	Summary of Study Populations	IDSL To include Enrolled, All Treated, PK, Evaluable (if diff from enrolled), PD, Part 1 by dose level, Part 2 by cohort, Part 3 by dose	IA, SAC
1.9	All Treated	SP2A	Summary of Exclusions from the Safety Population	IDSL Only if we have exclusions (i.e. food effect subjects?), Part 1 by dose level, Part 2 by cohort, Part 3 by dose	SAC
Demographic and Baseline Characteristics					
1.10	All Treated	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT, Part 1 by dose level, Part 2 by cohort, Part 3 by dose	IA, SAC
1.11	Enrolled	DM11	Summary of Age Ranges	EudraCT	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Disease Characteristics					
1.12	All Treated	DC1	Summary of Disease Characteristics at Initial Diagnosis	ICH E3 Make note of separate CRF page for NHL subjects, Part 1 by dose level, Part 2 by cohort, Part 3 by dose	IA, SAC
1.13	All Treated	DC2	Summary of Disease Characteristics at Screening	ICH E3 Make note of separate CRF page for NHL subjects, Part 1 by dose level, Part 2 by cohort, Part 3 by dose	IA, SAC
1.14	All Treated	MD1	Summary of Metastatic Disease at Screening	IDSL, Part 1 by dose level, Part 2 by cohort, Part 3 by dose	SAC
1.15	All Treated	LA1	Summary of Disease Burden at Baseline	ICH E3, Part 1 by dose level, Part 2 by cohort, Part 3 by dose	SAC
1.16	All Treated	MH1	Summary of Past Medical Conditions	ICH E3 , Part 1 by dose level, Part 2 by cohort, Part 3 by dose	SAC
1.17	All Treated	MH1	Summary of Current Medical Conditions	ICH E3, Part 1 by dose level, Part 2 by cohort, Part 3 by dose	SAC
Prior and Concomitant Medications and Prior and Follow-up Therapies					
1.21	All Treated	AC1	Summary of Prior Anti-Cancer Therapy	IDSL	SAC
1.23	All Treated	AC1	Summary of Prior Anti-Cancer Therapy (Advanced/Metastatic)	Include only therapies that have been marked “Advanced or Metastatic” as intent on eCRF, Part 1 by dose level, Part 2 by cohort, Part 3 by dose	SAC
1.24	All Treated	AC3	Summary of Number of Prior Anti-Cancer Therapies	IDSL, Part 1 by dose level, Part 2 by cohort, Part 3 by dose	SAC
1.26	All Treated	FAC1	Summary of Follow-Up Anti-Cancer Therapy, Radiotherapy, and Surgery	IDSL, Part 1 by dose level, Part 2 by cohort, Part 3 by dose	SAC
Follow-Up					
1.30	All Treated	FAC2	Summary of Duration of Follow-up	Part 1 by dose level, Part 2 by cohort, Part 3 by dose	SAC

15.12.5. Efficacy Tables

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Tumor Response					
2.1	All Treated	RE1a	Summary of Investigator Assessed Best Response with Confirmation (RECIST 1.1 Criteria)	By dose level for Part 1, by cohort for Part 2 (all but NHL/GBM) 95% CI is based on Clopper-Pearson exact CI	IA, SAC
2.2	All Treated	RE1a	Summary of Investigator Assessed Best Response with Confirmation (RANO Criteria)	Part 2 GBM cohort 95% CI is based on Clopper-Pearson exact CI	SAC
2.3	All Treated	RE1a	Summary of Investigator Assessed Best Response (Lugano Criteria)	Part 2 NHL cohort 95% CI is based on Clopper-Pearson exact CI	IA, SAC
2.4	All Treated	RE1a	Summary of Investigator Assessed Best Response with Confirmation (iRECIST Criteria)	Part 3 by dose level 95% CI is based on Clopper-Pearson exact CI	SAC
Time-to-Event					
2.5	All Treated	TTE6	Summary of Kaplan-Meier Estimates of Progression-Free Survival at 6 Months (RANO Criteria)	GBM cohort	IA, SAC
2.6	All Treated	TTE1	Summary of Progression-Free Survival Based on Investigator Assessments (RECIST 1.1 Criteria)	By cohort for Part 2 (excluding GBM, NHL)	SAC
2.7	All Treated	TTE1	Summary of Progression-Free Survival Based on Investigator Assessments (RANO Criteria)	GBM cohort	SAC
2.8	All Treated	TTE1	Summary of Progression-Free Survival Based on Investigator Assessments (Lugano Criteria)	NHL cohorts	SAC
2.9	All Treated	TTE1a	Summary of Duration of Response Based on Investigator Assessments (RECIST 1.1 Criteria)	Part 2 ACC TN cohort	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
2.10	All Treated	TTE1	Summary of Overall Survival	Part 2 ACC TN cohort and all ACC subjects across parts 1/2	SAC

15.12.6. Efficacy Figures

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Change in Sum of Diameters/Areas					
2.11	All Treated	RE8a	Investigator-Assessed Maximum Percent Reduction from Baseline in Sum of Diameters (RECIST 1.1 Criteria)	Part 1 one plot for QD, one for BID color/shade by dose level and indication within each	SAC
2.12	All Treated	RE8a	Investigator-Assessed Maximum Percent Reduction from Baseline in Sum of Diameters (RECIST 1.1 Criteria)	part 2 by cohort (excluding NHL , GBM)	IA, SAC
2.13	All Treated	RE8a	Investigator-Assessed Maximum Percent Reduction from Baseline in Sum of Areas (RANO Criteria)	Part 2 GBM cohort	SAC
2.14	All Treated	RE8a	Investigator-Assessed Maximum Percent Reduction from Baseline in Sum of Diameters (iRECIST Criteria)	Part 3	SAC
2.15	All Treated	custom	Spider Plot of Percent Change from Baseline in Sum of Diameters (Investigator Assessment Using RECIST 1.1 Criteria)	Part 1 one plot for QD, one for BID color/shade by dose level and indication within each	SAC
2.16	All Treated	custom	Spider Plot of Percent Change from Baseline in Sum of Diameters (Investigator Assessment Using RECIST 1.1 Criteria)	part 2 by cohort (excluding NHL, GBM)	IA, SAC

2.17	All Treated	custom	Spider Plot of Percent Change from Baseline in Sum of Areas (Investigator Assessment Using RANO Criteria)	Part 2 GBM cohort	SAC
2.18	All Treated	custom	Spider Plot of Percent Change from Baseline in Sum of Diameters (Investigator Assessment Using iRECIST Criteria)	Part 3	SAC
Time-to-Event					
2.19	All Treated	TTE10	Graph of Kaplan-Meier Survival Curves of Progression-Free Survival with 95% Confidence Bands (Investigator Assessment using RECIST 1.1 Criteria)	by dose level for part 1, by cohort for part 2 (excluding GBM/NHL)	SAC
2.20	All Treated	TTE10	Graph of Kaplan-Meier Survival Curves of Progression-Free Survival with 95% Confidence Bands (Investigator Assessment using RANO Criteria)	GBM cohort	SAC
2.21	All Treated	TTE10	Graph of Kaplan-Meier Survival Curves of Progression-Free Survival with 95% Confidence Bands (Investigator Assessment using Lugano Criteria)	NHL cohorts	SAC
2.22	All Treated	TTE10	Graph of Kaplan-Meier Survival Curves of Progression-Free Survival with 95% Confidence Bands (Investigator Assessment using iRECIST Criteria)	Part 3	SAC
2.23	All Treated	TTE10	Graph of Kaplan-Meier Survival Curves of Overall Survival with 95% Confidence Bands	Part 2 ACC TN cohort and All ACC subjects (across parts 1/2)	SAC

15.12.7. Safety Tables

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Adverse Events					
3.1	All Treated	AE13	Adverse Event Overview	Including subjects with any AE, AEs related to GSK3326595, Grade 3/4 AEs, Grade 3/4 AEs related to GSK3326595, AEs leading to dose reductions of GSK3326595, AEs leading to dose interruptions of GSK3326595, AEs leading to permanent discontinuation of GSK3326595, SAEs, SAEs related to GSK3326595, fatal SAEs, and fatal SAEs related to GSK3326595 Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	IA, SAC
3.2	All Treated	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
3.3	All Treated	AE5B	Summary of All Adverse Events by System Organ Class and Preferred Term and Maximum Grade	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
3.4	All Treated	AE1	Summary of All Adverse Events by Preferred Term	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
3.5	All Treated	AE3	Summary of Common (>=10%) Adverse Events by Overall Frequency	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
3.6	All Treated	AE3	Summary of Common (>=10%) Grade 2-5 Adverse Events by Overall Frequency	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
3.7	All Treated	AE1	Summary of All GSK3326595-Related Adverse Events by System Organ Class and Preferred Term	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose) Please include a footnote describing how these events are selected (i.e. this	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
				table includes events for which the investigator selected as related to GSK only)	
3.8	All Treated	AE5B	Summary of All GSK3326595-Related Adverse Events by System Organ Class and Preferred Term and Maximum Grade	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose) Please include a footnote describing how these events are selected (i.e. this table includes events for which the investigator selected as related to GSK only)	SAC
3.10	All Treated	AE5B	Summary of All Pembrolizumab-Related Adverse Events by System Organ Class and Preferred Term and Maximum Grade	Part 3 only Please include a footnote describing how these events are selected (i.e. this table includes events for which the investigator selected as related to Pembro only)	SAC
3.12	All Treated	AE5B	Summary of All GSK3326595 and Pembrolizumab-Related Adverse Events by System Organ Class and Preferred Term and Maximum Grade	Part 3 only Please include a footnote describing how these events are selected (i.e. this table includes events for which the investigator selected as related to both GSK and Pembro)	SAC
3.13	All Treated	AE3	Summary of Common (>=10%) GSK3326595-Related Adverse Events by Overall Frequency	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose) Please include a footnote describing how these events are selected (i.e. this table includes events for which the investigator selected as related to GSK only)	SAC
3.14	All Treated	AE3	Summary of Common (>=10%) GSK3326595-Related Grade 2-5 Adverse Events by Overall Frequency	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose) Please include a footnote describing how these events are selected (i.e. this table includes events for which the investigator selected as related to GSK only)	SAC
3.15	All Treated	AE15	Summary of Common (>=10%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
3.17	All Treated	AE3	Summary of Adverse Events Leading to Dose Reductions of GSK3326595 by Preferred Term	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
3.18	All Treated	AE3	Summary of Adverse Events Leading to Dose Interruptions / Delay of GSK3326595 by Preferred Term	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
Serious and Selected Adverse Events					
3.19	All Treated	AE5B	Summary of Serious Adverse Events by System Organ Class and Preferred Term and Maximum Grade	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
3.20	All Treated	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
3.21	All Treated	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment by System Organ Class and Preferred Term	IDSL Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
3.23	All Treated	AE3	Summary of Serious Adverse Events Related to GSK3326595 by Preferred Term	Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose) Please include a footnote describing how these events are selected (i.e. this table includes events for which the investigator selected as related to GSK only)	IA, SAC
3.24	All Treated	ESI2A	Summary of Onset and Duration of First Occurrence of Selected Adverse Events	Anemia, neutropenia, thrombocytopenia (platelet count decrease and thrombocytopenia), fatigue, Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
3.25	All Treated	ESI1	Summary of Event Characteristics of Selected Adverse Events	Anemia, neutropenia, thrombocytopenia (platelet count decrease and thrombocytopenia), fatigue, Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	IA, SAC
3.30	All Treated	DD1	Summary of Deaths	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose) Report time to death from last dose (in days) as in the mock	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Laboratory Results					
3.31	All Treated	LB1	Summary of Chemistry Changes from Baseline	ICH E3 To include grade increase from Baseline Grade Creatinine	SAC
3.32	All Treated	LB15	Summary of Worst-Case Chemistry Results by Maximum Grade Increase Post-Baseline Relative to Baseline	ICH E3 Report only worst-case post-baseline. Don't report by-visit summary rows. For CTCAE graded tests Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
3.33	All Treated	LB16	Summary of Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3 Report only worst-case post-baseline. Don't report by-visit summary rows. For non-graded tests Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
3.34	All Treated	LB1	Summary of Haematology Changes from Baseline	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
3.35	All Treated	LB15	Summary of Worst-Case Haematology Results by Maximum Grade Increase Post-Baseline Relative to Baseline	ICH E3 Report only worst-case post-baseline. Don't report by-visit summary rows. For CTCAE graded tests Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
3.36	All Treated	LB16	Summary of Worst Case Haematology Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3 Report only worst-case post-baseline. Don't report by-visit summary rows. For non-graded tests Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
3.37	All Treated	LB1	Summary of Coagulation Changes from Baseline	ICH E3, Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
3.38	All Treated	LB15	Summary of Worst-Case Coagulation Results by Maximum Grade Increase Post-Baseline Relative to Baseline	ICH E3 Report only worst-case post-baseline. Don't report by-visit summary rows. For CTCAE graded tests Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
3.39	All Treated	LB16	Summary of Worst Case Coagulation Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3 Report only worst-case post-baseline. Don't report by-visit summary rows. For non-graded tests Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
3.40	All Treated	LB1	Summary of Urine Concentration Changes from Baseline	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
3.41	All Treated	UR1	Summary of Worst Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline	ICH E3 Define change categories according to actual values expected from lab dataset Report only worst-case post-baseline. Don't report by-visit summary rows. Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
3.42	All Treated	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	IDSL Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
3.43	All Treated	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	IDSL Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
3.45	All Treated	LB15	Summary of Worst Case Troponin Results Relative to Normal Range Post-Baseline Relative to Baseline	Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
ECG, Vital Signs, and LVEF					
3.47	All Treated	EG1	Summary of ECG Findings	IDSL Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
3.48	All Treated	EG10	Summary of Maximum QTcF Values Post-Baseline Relative to Baseline by Category	ICHE14 Report only worst-case post-baseline. Don't report by-visit summary rows. Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
3.50	All Treated	EG11	Summary of Maximum Increase in QTcF Values Post-Baseline Relative to Baseline by Category	ICHE14 Report only worst-case post-baseline. Don't report by-visit summary rows. Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
3.51	All Treated	VS1	Summary of Change from Baseline in Vital Signs	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
3.52	All Treated	VS6	Summary of Worst Case Vital Signs Results by Maximum Grade Increase Post-Baseline Relative to Baseline	ICH E3 Include blood pressure Report only worst-case post-baseline. Don't report by-visit summary rows. Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
3.53	All Treated	VS3	Summary of Worst Case Vital Signs Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3 Include heart rate and temperature Report only worst-case post-baseline. Don't report by-visit summary rows. Part 1	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
				(by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	
3.54	All Treated	OLVEF1A	Summary of Left Ventricular Ejection Fraction Change from Baseline	IDSL Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
Exposure, Dose Modifications, DLT					
3.55	All Treated	EX1	Summary of Exposure to Study Treatment (GSK3326595)	ICH E3 Include duration of treatment (months) Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 by dose	SAC
3.56	All Treated	OEX5	Summary of Exposure to Study Treatment (Pembrolizumab)	Part 3	SAC
3.57	All Treated	ODMOD1	Summary of Dose Reductions of GSK3326595	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
3.58	All Treated	ODMOD1	Summary of Dose Reductions of Pembrolizumab	Part 3	SAC
3.59	All Treated	ODMOD2	Summary of Dose Interruptions of GSK3326595	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
3.60	All Treated	ODMOD3	Summary of Dose Delays of Pembrolizumab	Part 3	SAC
3.65	All Treated	AE1	Summary of Adverse Events Recorded as Dose-Limiting Toxicities by Preferred Term– Part 1	ICH E3 Part 1	SAC
ECOG Performance					
3.66	All Treated	PS1A	Summary of ECOG Performance Status	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 1/Part 2 300mg/400mg/Total/Overall, Part 3 (by dose)	SAC
Ocular Adverse Events					
3.70	All Treated	from IB 2022	Summary of Adverse Events (Ocular Events) by Preferred Term	Part 1, Part 2, Part 3, Part 1+2	SAC
3.72	All Treated	from IB 2022	Summary of Adverse Events (Bone-Related Events) by Preferred Term	Part 1, Part 2, Part 3, Part 1+2	SAC
Bone Mineral Density Shifts					

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
3.75	All Treated	from IB 2022	Summary of Bone Mineral Density Shifts from Baseline Relative to Normal Range, Among Patients with Pre-Treatment Baseline DEXA Scan – Local Labs	Part 1, Part 2, Part 3, Part 1+2	SAC
3.77	All Treated	from IB 2022	Summary of Bone Mineral Density Shifts from Baseline Relative to Normal Range, Among Patients with First DEXA Scan Performed on Treatment – Local Labs	Part 1, Part 2, Part 3, Part 1+2	SAC

15.12.8. Safety Figures

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
3.1.	All Treated	OEX12	Swimmer Plot of Duration of Study Treatment (RECIST 1.1 Criteria)	IDSL Part 2 (by cohort excluding GBM/NHL)	IA, SAC
3.2.	All Treated	OEX12	Swimmer Plot of Duration of Study Treatment (RANO Criteria)	IDSL GBM cohort	IA, SAC
3.3.	All Treated	OEX12	Swimmer Plot of Duration of Study Treatment (Lugano Criteria)	IDSL NHL cohorts	IA, SAC
3.4.	All Treated	OEX12	Swimmer Plot of Duration of Study Treatment (iRECIST Criteria)	IDSL Part 3	IA, SAC

15.12.9. Pharmacokinetic Tables

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
4.1	PK	PK01	Summary of GSK3326595 Pharmacokinetic Concentration-Time Data by Treatment and Study Day	Use descriptive statistics (n, mean, SD, median, min and max) by planned relative assessment time; concentrations in ng/mL. All planned time points. by dose for Part 1, by cohort for parts 2 and 3 also by 300mg, 400mg QD across all parts, For Part 3, include Pembrolizumab	SAC
4.2	PK	GSK-provided	Summary of Pembrolizumab Immunogenicity Data by Treatment and Study Day	Part 3 only	SAC
4.3	PK	PK06	Summary of Derived GSK3326595 Pharmacokinetic Parameters by Treatment and Study Day	PK parameters: Cmax, Tmax, Ctrough, AUC0-t, tlast, AUC0-tau, AUCinf, t½, λz , TI and AR determined from the concentration-time data in ng/ml; descriptive summaries: mean, SD, median, min, max, geometric mean & SD, CV%, and 95%CI of log-transformed	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
				parameters, if applicable. by dose for Part 1, by cohort for parts 2 and 3 also by 300mg, 400mg QD across all parts	
4.5	PK	custom	Dose Proportionality Comparison (Power Model) for AUC(0-inf:=) and Cmax of GSK3326595	Provide separately for QD regimens and BID regimens of Part 1 only	SAC
4.6	PK	NA	Food Effect Sub-Study	<previously done>	IA
4.7	PK	NA	Relative Bio-Availability Sub-Study	<previously done>	IA

15.12.10. Pharmacokinetic/Biomarker Figures

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
4.1.	PK	PK16A	Individual GSK3326595 Concentration-Time Plots (Linear) by Treatment and Study Day	IDSL ng/mL Day 1 and Day 15 only for Part 1 Day 1 only for Part 2 Part 1 by dose level, Part 2 by cohort (and by dose if applicable), Part 3 by dose level by time point per page, plasma only	SAC
4.2.	PK	PK17	Mean Concentration-Time Plots by Treatment and Study Day	IDSL ng/mL Day 1 and Day 15 only for Part 1 Day 1 only for Part 2 Part 1 by dose level, Part 2 by cohort (and by dose if applicable), Part 3 by dose level 300mg and 400mg (across all parts), different color for dose level, both time points on one plot by time point per page, plasma only	SAC
4.3.	PK	PK18	Median Concentration-Time Plots by Treatment and Study Day	IDSL ng/mL Day 1 and Day 15 only for Part 1 Day 1 only for Part 2 Part 1 by dose level, Part 2 by cohort (and by dose if applicable), Part 3 by dose level by time point per page, plasma only	SAC
4.4.	PK	Custom	Dose proportionality figures	1. Provide separately for GD regimens and BID regimens of Part 1 only	SAC
4.6	Biomarker	Custom	Change in c[CCI] level between Baseline and Day 15	By tumor type: ACC, ERBC, GBM, HPV, mTCC, NHL, TNBC, NSCLC	Publication

15.12.11. ICH Listings

No.	Population	IDSL / Example Shell	Title	Programming notes	Deliverable
Participant Disposition					
1	All Treated	ES2	Listing of Reasons for Study Withdrawal	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
2	All Treated	SD2	Listing of Reasons for Study Treatment Discontinuation	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
84	Enrolled	TBD	Listing of Participants by Country and Site	ICH E3 IDSL Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
Protocol Deviations					
3	Enrolled	DV2	Listing of Important Protocol Deviations	ICH E3 Report all important PDs Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
4	All Treated	IE3	Listing of Participants with Inclusion/Exclusion Criteria Deviations	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
Analysis Populations					
5	Enrolled	SP3	Listing of Participants Excluded from All Treated Population	ICH E3 Report participants enrolled but not treated Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
Demographic and Baseline Characteristics					
6	All Treated	DM2	Listing of Demographic Characteristics	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
7	All Treated	DM9	Listing of Race	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
Exposure					
8	All Treated	EX3	Listing of Exposure Data	ICH E3 should be able to include both GSK3326595 and pembrolizumab in the same listing. Add column for treatment. Note: only part 3 subjects will have pembro. Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
Adverse Events, and Serious Adverse Events					
10	All Treated	AE8	Listing of All Adverse Events	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC

No.	Population	IDSL / Example Shell	Title	Programming notes	Deliverable
11	All Treated	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
12	All Treated	AE8	Listing of Non-Fatal Serious Adverse Events	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
13	All Treated	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
14	All Treated	AE8	Listing of Adverse Events Leading to Permanent Discontinuation of GSK3326595	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose) To include Permanent Discontinuation or Withdrawal in action taken	SAC
16	All Treated	AE8	Listing of Adverse Events Leading to Dose Interruptions of GSK3326595	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
18	All Treated	AE8	Listing of Adverse Events Leading to Dose Reductions of GSK3326595	ICH E3 Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
All Laboratory					
20	All Treated	LB5	Listing of All Laboratory Data for Participants with Any Value of Outside Normal Range	ICH E3 To include chemistry, hematology, coagulation	SAC
21	All Treated	UR2	Listing of Urinalysis Data for Participants with Any Value of Potential Clinical Importance	ICH E3 Display all data for a subject who experienced a value of PCI	SAC

15.12.12. Non-ICH Listings

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Participant Disposition					
22	All Treated	custom	Listing of Part 1 Subjects Summarized in Part 2		SAC
23	Screened	ES7	Listing of Reasons for Screen Failure	required for submission studies only Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
24	All Treated	TA1	Listing of Planned and Actual Treatments	IDSL Report only subjects whose actual starting dose is different from the assigned dose group.	SAC
Disease Characteristics					
26	All Treated	DC4	Listing of Disease Characteristics at Screening	Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
27	All Treated	MD2	Listing of Metastatic Disease at Screening	Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
Anti-Cancer Therapy					
28	All Treated	AC6	Listing of Prior Anti-Cancer Therapy	List all prior anti-cancer therapy (but not radiotherapy or surgery) Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
29	All Treated	FAC3	Listing of Follow-Up Anti-Cancer Therapy	ACC Cohorts only	SAC
31	All Treated	PR2	Listing of On-Study Cancer Related Surgical Procedures	Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
Investigator-Assessed Responses					
43	All Treated	RE5	Listing of Investigator-Assessed Response at Each Assessment with Confirmation (RECIST 1.1 Criteria)	Part 1 (by dose) and Part 2 (by cohort, excluding GBM/NHL)	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
44	All Treated	RE5A instead	Listing of Investigator-Assessed Response at Each Assessment with Confirmation (RANO Criteria)	Part 2 GBM cohort	SAC
45	All Treated	RE5	Listing of Investigator-Assessed Response at Each Assessment (Lugano Criteria)	Part 2 NHL cohorts	SAC
46	All Treated	RE5	Listing of Investigator-Assessed Response at Each Assessment with Confirmation (iRECIST Criteria)	Part 3	SAC
Time-To-Event Analyses					
51	All Treated	TTE9	Listing of Duration of Response Based on Investigator Assessment (RECIST 1.1 Criteria)	Part 2 ACC TN cohort	SAC
52	All Treated	TTE9	Listing of Progression Free Survival Based on Investigator Assessment (RECIST 1.1 Criteria)	Part 2 by cohort (excluding GBM, NHL)	SAC
53	All Treated	TTE9	Listing of Progression-Free Survival Based on Investigator Assessment (RANO Criteria)	Part 2 GBM cohort	SAC
54	All Treated	TTE9	Listing of Progression-Free Survival Based on Investigator Assessment (Lugano Criteria)	Part 2 NHL cohorts	SAC
55	All Treated	custom per GSK	Listing of Time to Response Based on Investigator Assessment (RECIST 1.1 Criteria)	Part 2 ACC TN only	SAC
56	All Treated	TTE9	Listing of Overall Survival	Parts 2 and 3 by cohort	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Adverse Events/Dose-Limiting Toxicity					
61	All Treated	AE8	Listing of Adverse Events Recorded as Dose-Limiting Toxicities	Part 1 (by dose)	SAC
Hepatobiliary					
62	All Treated	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting	Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
63	All Treated	LIVER15	Liver Stopping Event Profile	Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
Troponin, ECG, and Vital Signs					
69	All Treated	OLB7	Listing of Local Troponin Data	Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
70	All Treated	EG3	Listing of All ECG Values from Local Labs	Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
72	All Treated	VS5	Listing of All Vital Signs for Subjects with any Value of Potential Clinical Importance	Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose) List all VS data for any subject with at least one PCI	SAC
Other Safety					
74	All Treated	DD3	Subject Profile for Death	ICH E3	SAC
76	All Treated	Custom	Listing of DEXA Bone Densitometry Data from Local Labs	Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
77	All Treated	Custom	Listing of Optical Coherence Tomography Results	Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
78	All Treated	Custom	Listing of Best Corrected Visual Acuity (Snellen Acuity Equivalent) Results	Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
PK					
79	PK	PK07	Listing of GSK3326595 Plasma Pharmacokinetic Concentration-Time Data	IDSL List all data Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose). Create another listing for Part 3 for Pembrolizumab	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
80	PK	PK09	Listing of GSK3326595 Urine Sample Collections	IDSL List all data Part 1 (by dose)	SAC
81	PK	PK11	Listing of GSK3326595 Urine Excretion Rate Data	IDSL List all data Part 1 (by dose)	SAC
82	PK	PK13	Listing of Derived GSK3326595 Plasma Pharmacokinetic Parameters by Treatment	IDSL List only D1, D15 Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
86	PK	GSK-provided	Listing of Pembrolizumab Immunogenicity Data	Part 3	SAC
Family History					
83	All Treated	FH4	Listing of Family History of Cardiovascular Risk Factors	IDSL Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC
Concomitant Medications					
85	All Treated	CM3	Listing of Concomitant Medications by Ingredient	IDSL Part 1 (by dose), Part 2 (by cohort), Part 3 (by dose)	SAC

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