Protocol Amendment 8

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

NCT ID: NCT02783300

Date of Document: 20 April 2022

TITLE PAGE

Division: Worldwide Development

Information Type: Protocol Amendment

Title:	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

Development Phase: I

Effective Date: 20 Apr 2022

Protocol Amendment Number: 08

Sponsor Name and Legal Registered Address:
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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Medical Monitor Name and Contact Information can be found in the Study Reference Manual

Sponsor Signatory

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Approval Date 20 Apr 2022

Regulatory Agency Identifying Number(s):

Compound Number	IND Number	EudraCT Number
GSK3326595	IND146168	2016-000278-39

REVISION CHRONOLOGY

GlaxoSmithKline Document Number	**Date**	**Version**
2015N237263_00	2015-NOV-30	Original
2015N237263_01	2015-DEC-16	Republished
The original protocol dated 2015-Nov-30 was not submitted outside of GSK and was republished to incorporate clarifications in the Time and Events Table prior to submission. The clarifications were made in the timing and acquisition of PD/Metabolite sampling in the Time and Event Tables. The protocol was republished as the original protocol based on these clarifications but has a different document number to reflect this change.		
2015N237263_02	2016-MAR-17	Amendment No. 1
Changes have been made to the definition of dose-limiting toxicities and toxicity attribution during dose escalation, in response to FDA comments. In addition, clarification has been provided for the timing and modalities of baseline and disease response scans, collection of echocardiograms, and the addition of exploratory objectives and endpoints to the PK/PD cohort.		
2015N237263_03	2017-JUN-16	Amendment No. 2
Changes have been made to the highest permitted dose and the investigational product formulation in light of emerging pharmacokinetic data demonstrating exposures that are approximately 2/3 lower than preclinical modeling predicted. Changes have been made to the endpoints for the glioblastoma multiforme cohort after discussion with area experts, substituting 6-month progression free survival as a more meaningful metric than overall response rate in this population. This change prompted additional changes to the statistical modeling and total study size. In addition, clarification has been provided for inclusion/exclusion criteria, dose-limiting toxicities, objectives/endpoints, and time & events tables.		
2015N237263_04	2018-SEP-11	Amendment No. 3
Changes have been made to include 3 additional cohorts (adenoid cystic carcinoma, human papillomavirus positive solid tumors and hormone receptor-positive adenocarcinoma of the breast) due to the emergence of new pre-clinical and clinical data. Changes have been made to the response criteria for non-Hodgkin's lymphoma (NHL), based on the publishing of new criteria. Details of a new tablet formulation for the compound GSK3326595 has been added. A food effect cohort has been added to evaluate the preliminary effects of fed versus fasted administration on the pharmacokinetics of		

GSK3326595. Changes have been made to add in the collection of Patient Reported Outcomes to ascertain the impact of cancer and its treatment with GSK3326595 on patients' health related quality of life. In addition, clarification has been provided for inclusion/exclusion criteria, collection of unscheduled biological samples, and correction of typographical errors.		
2015N237263_05	2019-OCT-23	Amendment No. 4
The following changes have been made. • Addition of a new cohort in Part 2 (dose expansion) to test GSK3326595 in non-small cell lung cancer. • Addition of a new cohort in Part 2 to test a new tablet formulation of GSK3326595 in adenoid cystic carcinoma. • Addition of Part 3 to test the combination of GSK3326595 with a PD-1 inhibitor in solid tumors. • Changes to the eligibility criteria regarding renal function and asymptomatic brain metastases. • Expansion of the food effect cohort to include a relative bioavailability comparison of capsules to the new tablet formulation. • Changing the starting dose for all new subjects enrolled, including new cohorts to 300 mg QD. • Removal of the 25 mg capsules, as they will no longer be available.		
2015N237263_06	2020-APR-04	Amendment No. 5
The following changes have been made: • Duration of study updated to 6 years. • Cardiac monitoring reduced: LVEF and valvular toxicity stopping criteria removed; echocardiogram and troponin collection removed; cardiac risk and mitigation strategy updated; inclusion/exclusion criteria updated, and withdrawal criteria updated. • Addition of bone and teeth non-clinical findings and risk mitigation strategy. Addition of DEXA scans for bone density assessment and serum sampling to check biomarkers of bone metabolism and turnover. • Revised information for Table 4, Pre-clinical and Clinical Risks and Mitigation Strategies, based on review of safety data as of the IB cut-off date (04 February 2020). • Part 1 FE/rBA cohort: sample size reduced to 12 patients (6 per sequence) and overall subject numbers updated. Wording added to allow subjects to move from capsules to tablets, depending on the results of the rBA study. • Part 2: o ACC tablet cohort: eligibility criteria changed to systemic therapy-naïve		

subjects only and subjects who have progressed per RECIST 1.1 in the previous 13 months. Overall survival moved from exploratory to secondary endpoint.

  - NHL cohort: eligibility criteria changed to indolent subtypes of NHL; subjects ≤75 years of age and subjects who have received ≤4 prior lines of systemic therapy.
  - NSCLC cohort: clarification that subjects whose tumors harbor actionable mutations (e.g., EGFR mutations or ALK rearrangements) must have received prior therapy with targeted agents prior to enrollment

- Part 3:
  - Sites in France are ineligible to participate in Part 3.
  - Pembrolizumab PK and immunogenicity sample collection schedule reduced and clarified.
  - Clarification of inclusion criteria: subjects with SD as best response to prior PD(L)-1 therapy must have documented iRECIST progression on PD(L)-1 therapy to be eligible for this study.
  - Additional adverse event management guidance added to reflect changes in October 2019 pembrolizumab Summary of Product Characteristics.
- Clarification has been provided for inclusion/exclusion criteria and Time & Events tables; new IND number added, and typographical errors corrected.

2015N237263_07	2020-OCT-20	Amendment No. 6

The following changes have been made:

- 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.
- Addition of inhibitors of MATE2-K, OAT3 and OCT2 in prohibited medications in Section 7.1.2.1, in alignment with IB version 4.0 data cut off 4th February 2020.
- Inclusion of Appendix 12 outlining clinical study delivery under circumstances of pandemic caused by COVID19 in future.
- Inclusion of reference to Appendix 12 and COVID 19 in Section 4.8.1 regarding clinical risks and mitigations strategies.
- Addition of language to Section 1 (Type and Number of Subjects), 4.2.1 and 4.5 to allow for approximately 12 but no more than 24 patients for the food effect cohort and relative bioavailability sub-study.
- The following changes have been made to Table 4, Section 4.8.1:
  - Inclusion of statement on conclusions from GLP genotoxicity study and embryo fetal development risks
  - Removal of Cardiac Effects risks

- Inclusion of statement for the preclinical data for hepatic event risks
- Addition of statement to the preclinical data for damage to exocrine tissue

- Section 4.8.2- added additional data for ACC and HPV.
- Section 5.2 clarification circumstances under which HIV and HepB patients may be eligible, as per FDA Guidance
- Section 5.4. Removal of text as confirmation of disease progression is not required for parts 1 and 2 based on RECIST. Part 3 uses iRECIST which requires confirmation of progression
- Section 6.4. Added language to refer reader for further guidance around IP storage and temperature excursions
- In Section 8.4.1 Locally collected ECG may be read centrally
- Correction of Pregnancy information collection from Investigator to GSK within 24 hours (Appendix 10 and Section 8.4.4)
- Inclusion of collection of TSH and free T3 and free T4 for all patients (Section 8.4.2 and SoA)
- In Section 8.4.3 Locally collected DEXA Scans may be read centrally
- Correction of typographical errors

Part 2:

- Inclusion of requirements for all NHL subjects in Part 2 to have local p53 mutational analysis done and results available prior to dosing in the trial unless the subject's tumor has previously been demonstrated to harbor a p53 mutation. If p53 status was not determined, an archival sample or a fresh biopsy must be provided (Section 8.2.1).

- In case one NHL cohort reaches futility at any Interim Analysis, further enrolment into the other NHL cohort will require central confirmation (Section 8.2.1).

Part 3:

- Inclusion of collection of local and central PD-L1 test results (Section 8.7.2).
- Clarification of Pembrolizumab contraceptive requirements for females of reproductive potential (Section 4.9.1).
- Inclusion of cervical cancer patients as additional population for enrolment into the Dose Escalation cohort and relevant changes in the inclusion criteria (Section 5.1).
- Inclusion of language to allow for over-recruitment of 1 patient in Part 3 along with updates to the safety stopping rules for dose escalation decisions within Part 3 (Section 4.4.4). Operating characteristics for Part 3 in the event of over-recruitment were added in Section 11.10.4.7.

- Addition of requirement to replace any subject who fails to receive 80% of planned doses in Part 3 due to reasons other than toxicity (Section 4.4.4).
- Administrative change with regards to change in name of Programme Physician lead name.

TMF-11799334	17-FEB-21	Amendment No. 7

CCI [redacted]

This protocol amendment also serves to include additional safety assessments, reduce the total blood volume drawn per subject and to update the HIV/HCV, HBV exclusion criteria. As such, ophthalmic evaluations, Folate/B12 vitamin testing and clarifications for thyroid function testing have been added and the updated SoAs are applicable to all ongoing subjects.

The following changes have been made (in addition to the correction of minor typographical and formatting errors):

Study Population

- An error has been corrected in Exclusion Criterion 9 to specify the exclusion of subjects with a CD4 count ≥350 cells/uL rather than >300 cells/uL.
- Exclusion Criteria has been updated to specify that subjects with HBV infection may participate in the study provided they are on a suppressive antiviral therapy prior to initiation of cancer therapy.
- An exclusion criterion has been added to exclude patients with a history of optic nerve neuropathy or neuritis.

Part 1:

- There have been two observations of optic neuropathy possibly related to folate deficiency in subjects treated with study drug over a prolonged period (>12 months exposure) in this study. Although no causal relationship has been established, in order to ensure appropriate ongoing monitoring of subjects, the following items have been added to safety testing and are applicable to all ongoing subjects:
    - a requirement for investigators to ask patients about vision symptoms at each routine visit and document responses
    - ophthalmology assessments
    - monitoring of folate/B12 levels

- No further survival follow-up will be conducted in Part 1 except in subjects with a diagnosis of ACC.

Part 2:

- CCI [redacted]
- A review of vision symptoms, ophthalmology assessments and folate/B12 levels have been added to safety testing and are applicable to all ongoing subjects.
- A discrepancy in the instructions for thyroid function testing has been corrected and text made consistent throughout the protocol. Thyroid function testing is now consistently specified as required at screening, Weeks 4 or 6, every 8 weeks starting at Week 8 and at EOT.
- The collection of serum samples for the analysis of circulating biomarkers has been removed from the SoA and no further sample should be collected.
- Instructions for the collection of plasma samples for the analysis of circulating biomarkers has been amended in the SoA and no samples should be collected after a subject's Week 24 visit.
- Collection of plasma samples for circulating biomarkers to be collected as per the SoA until Week 24 only.
- Survival follow-up has been amended to only include subjects in an ACC cohort.

Part 3:

- CCI [redacted]
- A review of vision symptoms, ophthalmology assessments and folate/B12 levels have been added to safety testing and are applicable to all ongoing subjects.
- The collection of serum samples for the analysis of circulating biomarkers has been removed from the SoA and no further sample should be collected.
- Instructions for the collection of plasma samples for the analysis of circulating biomarkers has been amended in the SoA and no samples should be collected after a subject's Week 24 visit.
- No further survival follow-up will be conducted in Part 3.

In addition:

- The list of authors has been removed from the protocol cover page to align with current guidance on the use of Personally Identifiable Information (PII).
- The Sponsor Signature Page has been updated to reflect the current GSK template.
- The Investigator Signature Page has been removed from the protocol and will be

provided as a stand-alone document to the Investigator for signature alongside the final protocol.

- The duration of study has been updated to 8 years.
- The statement concerning the approximate total blood volume to be taken over the course of the study has been removed, as this is information is included in the ICF.
- The list of concomitant medications to be used with caution in conjunction with GSK3326595 have been updated with the most recent nonclinical information.
- The instructions for the assessment of intensity in Section 14.9.5 Evaluating AEs and SAEs have been corrected to provide the NCI-CTCAE terminology.

TMF-13861543	09-AUG-2021	Amendment No. 7/France

France specific requirements are listed in Appendix 13 inclusive of additional cardiac monitoring implemented at the request of Health Authority in France for the remaining ongoing patient on treatment, it was approved on 08-Oct-2021.

TMF-14123404	20-APR-2022	Amendment No. 8

This protocol has been amended to provide updates related to stopping recruitment into the Part 2 ACC tablet cohort, and therefore stopping any further recruitment in the study, updating the end of study definition with final analysis plan (Section 5.5), and clarifying study treatment access for subjects continuing to derive clinical benefit from study drug as per Investigator judgement post final analysis, as described in Section 4.1.

A description of all changes is provided below:

- Additional content to the overall study has been added in the Section 4.1, Section 4.3.3 and synopsis, which includes the stop in recruitment into the ACC tablet cohort in Part 2.
- Amendment of primary endpoint for ACC tablet cohort; “ACC tablet formulation will score ORR by independent central review (ICR)” for Part 2 will be replaced by Investigator assessed RECIST review
- Change in secondary endpoint for Duration of Response read out of the ACC tablet cohort from Independent central review to Investigator assessment
- Moved the following Secondary endpoints to exploratory for Part 2
  - CCI
  - [redacted]
- Revised information for Section 4.8.1 (Risk Assessment) and Section 4.8.3 (Overall Benefit: Risk Conclusion), based on review of safety data as of the IB cut-off date (04 February 2022).
- Additional content added in below Sections to implement Protocol Amendment 8.

  - Section 5.4.1 Discontinuation of Study Treatment
  - Section 5.4.3 Withdrawal from the study
  - Section 5.4.4 End of Survival Follow-up
  - Section 6 Study Treatment
  - Section 8.3 Safety
  - Section 8.7 Efficacy; Post Protocol Amendment 8 implementation, no efficacy assessments will be performed as part of the study.
  - Section 10 Data Management
  - Section 11.9.7 Final Analysis
  - Section 14.9.4 Recording of AEs and SAEs
  - Section 14.9.6 Reporting of SAEs to GSK
  - Section 14.10 Collection of Pregnancy Information
- In section 5.5 (End of study definition), inclusion of end of study definition, a predefined data cut off, following which database will be closed for new data.
- In section 6.7 (Treatment after the End of the Study) inclusion of clarification that patients who are receiving GSK3326595 may continue to receive GSK3326595, if they are continuing to derive clinical benefit as assessed by the Investigator, or can choose to discontinue the study drug.
- Additional content to the time period and frequency for collecting AEs, SAEs, AEs leading to treatment discontinuation and AESIs have been added in Section 8 (Study Assessments and Procedures) and Section 9.2 (Time period and Frequency for collecting AE and SAE Information).
- New Section 9.1.2 (Adverse Events of Special Interest) added to clarify ocular events and bone-related events.
- Additional details added in Section 11.9.6 (Interim Futility Analysis) to clarify on interim analyses.
- Added table on Algorithm for determining combined imaging response based on Lugano criteria in Section 14.4.3

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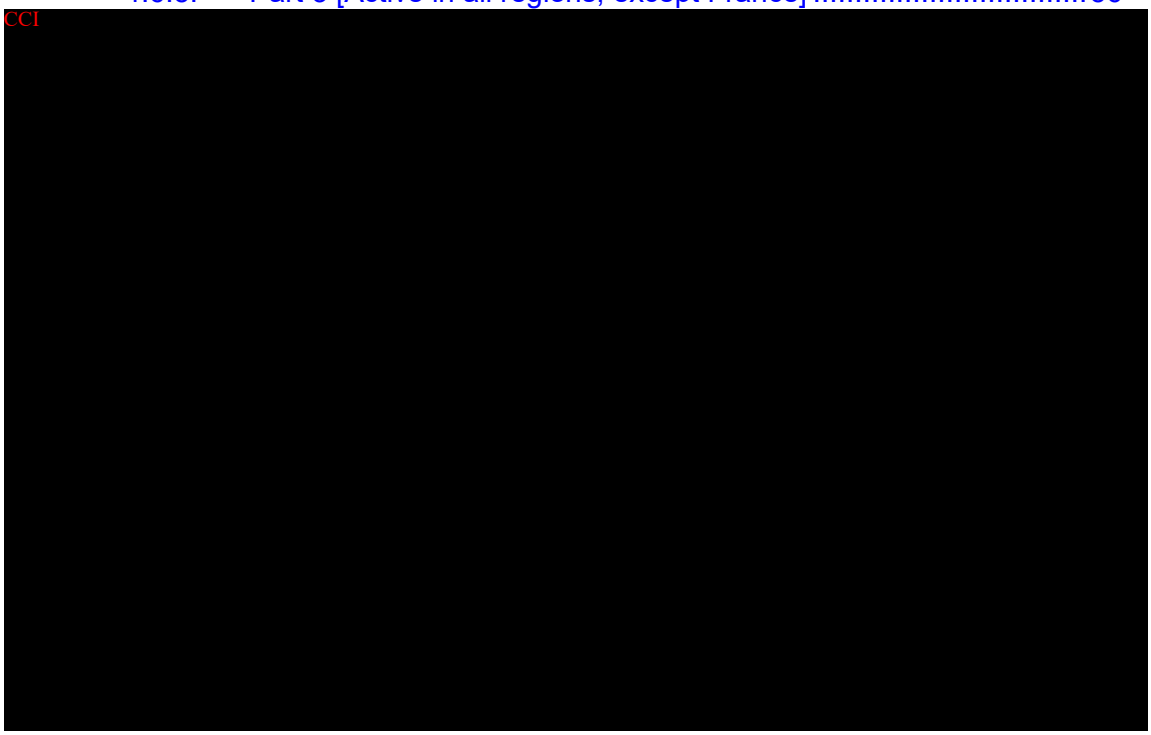

CCI [redacted]

1. PROTOCOL SYNOPSIS FOR STUDY 204653

Rationale

Protein arginine methyltransferases (PRMTs) are a subset of enzymes that methylate arginine residues in various cellular proteins including splicing factors, transcription factors, and histone tails. One of these PRMTs, PRMT5, is aberrantly upregulated in malignant cells compared to wild type, and overexpression of PRMT5 *in vitro* is sufficient for fibroblast transformation. Clinically, upregulation of PRMT5 confers poor prognosis in a number of tumor types including breast cancer and glioma. In preclinical models, PRMT5 inhibition has been associated with potential benefit in multiple human malignancies. The study drug, GSK3326595, is an inhibitor of PRMT5 that potently inhibits tumor growth *in vitro* and *in vivo* in animal models. This first time in human (FTIH), open-label, dose escalation study will assess the safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary clinical activity of GSK3326595 in subjects with advanced or recurrent solid tumors, as well as clinical activity in subjects with a subset of solid tumors and non-Hodgkin's lymphoma (NHL). The study will also assess a tablet formulation of GSK3326595, and clinical activity of GSK3326595 in combination with pembrolizumab in subjects with a subset of solid tumors.

Objectives/Endpoints

Part 1 (Dose Escalation)	
Objectives	**Endpoints**
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	
• To determine the recommended Phase 2 dose (RP2D) of orally-administered GSK3326595	• Safety profile (AEs, SAEs, DLTs), clinical response, and pharmacodynamic (PD) data
• 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: Complete Response (CR) + Partial Response (PR)], based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria

Part 1 (Dose Escalation)	
Objectives	**Endpoints**
• 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	
CCI [redacted]	

Part 2 (Dose Expansion)	
Objectives	**Endpoints**
Primary	
• To determine clinical activity of GSK3326595 in disease-specific expansion cohorts	• Solid tumor (non-glioblastoma multiforme, GBM) cohorts: Overall response rate (ORR, defined as % of subjects achieving 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
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 assessment • 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
• 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	
CCI [redacted]	

Part 2 (Dose Expansion)	
Objectives	**Endpoints**
CCI [redacted]	

Part 3 (Combination with Pembrolizumab)	
Objectives	**Endpoints**
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	
• 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
• 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 immune-based RECIST (iRECIST) 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	
CCI [redacted]	

Part 3 (Combination with Pembrolizumab)	
Objectives	**Endpoints**
CCI [redacted]	

Overall Design

This is an open-label, repeat-dose, multicenter, three-part study to establish the maximally tolerated dose (MTD)/ recommended phase 2 dose (RP2D) (based on 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.

Part 1 is a dose-escalation phase to identify the MTD/RP2D based on the safety, PK, and PD profiles observed after oral administration of GSK3326595, and to preliminarily identify whether or not there is an effect of fed versus fasted state, and of tablet versus capsule formulation, on the PK of GSK3326595. This Part will be conducted in adult subjects with relapsed and/or refractory solid tumors.

Disease-specific expansion cohorts (Part 2) are planned to further explore clinical activity of GSK3326595 in subjects with select solid tumors and non-Hodgkin's lymphomas. Based on pre-clinical data, as well as clinical data that emerged during Part 1, enrollment will be limited to subjects with triple-negative breast cancer (TNBC), metastatic transitional cell carcinoma of the urinary system (mTCC), Grade IV anaplastic astrocytoma (glioblastoma multiforme [GBM]), non-Hodgkin's lymphoma (NHL), adenoid cystic carcinoma (ACC), hormone receptor-positive adenocarcinoma of the breast (ER+BC), human papillomavirus (HPV) positive solid tumors of any histology (including cervical cancer and squamous cell carcinoma of the head and neck [HNSCC]), and p53-wild type non-small cell lung cancer (NSCLC) of any histological subtype; additional cohorts may be added based on emerging pre-clinical data and clinical responses identified during Part 1 or Part 2 of the study. CCI [redacted]

CCI [redacted].

This Protocol Amendment 8 is the follow up of this decision with the primary intent to update study language related to stopping recruitment into the Part 2 ACC tablet cohort, and therefore stopping any further recruitment in the study, updating the end of study definition with final analysis plan (Section 5.5), and clarifying study treatment access for subjects continuing to derive clinical benefit from study drug as per Investigator judgement post final analysis (Section 4.1).

Part 3 is a dose determination study to evaluate the safety, PK/PD profile, and clinical activity of orally-administered GSK3326595 at daily doses of 100 mg, 200 mg and 300 mg, in combination with pembrolizumab administered at the approved dose. Enrollment in Part 3 will be limited to subjects with NSCLC, mTCC, melanoma, HNSCC that have failed to respond to treatment with prior programmed cell death protein-1 (PD-1) or programmed death-ligand 1 (PD-L1) directed therapy. In addition squamous cell carcinoma of the cervix patients that have progressed on or after PD-1 or PD-L1 directed therapy **OR** are PD-1/PD-L1 treatment naïve will be enrolled in Part 3.
CCI [redacted].

Final Last Subject Last visit will be defined as last subject's treatment discontinuation (including 30-day safety follow up).

The end of this study is defined as the date of the last visit of the last subject undergoing the study.

A final data-cut off (DCO), closure of the study database and final analysis 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 this amendment (Protocol Amendment 8).

When Protocol Amendment 8 is implemented at a site, the collection of data for all enrolled subjects who no longer receive study treatment will stop entirely. Subjects still on treatment at the time of the final DCO date may continue to receive study treatment for as long as they continue to derive clinical benefit from study treatment as assessed by the Investigator and do not meet any protocol-defined study treatment stopping criteria (maximum until the end of availability of study drug which is anticipated to be Q3 2023); subjects may also choose to discontinue study treatment at any time. Subjects in survival follow-up at the time of the final DCO date will be considered to have completed the study.

Subjects who continue study treatment following Protocol Amendment 8 will receive follow-up care in accordance with standard local clinical practice. Assessments will revert to the standard of care at a subject's particular study site with recommendations for local safety laboratory monitoring of GSK3326595. Only SAEs, AEs leading to treatment discontinuation, overdoses, pregnancies, and pre-defined ocular and bone AEs (AESIs) will be reported directly to the Sponsor via a paper process. In addition,

- Ocular assessments will be required and reported via a paper process to the Sponsor only if reporting criteria is met for SAEs, AESIs, or AEs leading to treatment discontinuation.
- Bone (DEXA) assessments will be performed at the discretion of the investigator and reported via a paper process to the Sponsor only if reporting criteria is met for SAEs, AESIs, or AEs leading to treatment discontinuation.

Treatment Arms and Duration

All subjects in the study will receive the investigational agent. Part 1 (including the PK/PD expansion, relative bioavailability and food effect cohorts) will have a single arm. Part 2 will incorporate multiple disease-specific arms. Part 3 will incorporate multiple arms comprising a fixed dose of pembrolizumab and three dose levels of GSK3326595. In Part 1 and Part 2, subjects may continue treatment in the study until disease progression, unacceptable toxicity, or withdrawal of consent. In Part 3, subjects may remain on GSK3326595 until these criteria are met; however, pembrolizumab will only be administered for a maximum of 24 months. The duration of study will depend on recruitment rates and the timing of subjects' duration on study (withdrawal rates due to toxicity or progression), with an approximate duration of 8 years.

Type and Number of Subjects

Part 1: It is estimated that 66 subjects will be enrolled into the dose escalation cohort of the study, including around 42 subjects to identify the MTD, approximately 12 additional subjects in the PK/PD/metabolite/biomarker expansion cohort(s), and approximately 12 subjects but no more than 24 subjects in the food effect and relative bioavailability sub-study. The study population will be adults, with histologically- or cytologically-confirmed metastatic or non-resectable solid malignancies.

Part 2: It is estimated that up to 316 subjects will be enrolled in the disease-specific expansion cohorts of the study. Cohorts will include adult subjects with a diagnosis of one of the following diseases:

- Triple-negative breast cancer (TNBC)
- Metastatic transitional cell carcinoma of the urinary system (mTCC)
- Glioblastoma multiforme (GBM)
- Non-Hodgkin's lymphoma (NHL), all sub-types recruited to Protocol Amendments 1-4, and more indolent subtypes recruited to Protocol Amendment 5 onwards
- Adenoid cystic carcinoma (ACC), dosed with GSK3326595 capsule formulation
- Adenoid cystic carcinoma (ACC), in subjects who have not received any systemic therapy for locally advanced or metastatic disease, dosed with GSK3326595 tablet formulation.
- Hormone receptor-positive adenocarcinoma of the breast (ER+BC)
- Human papillomavirus (HPV) positive solid tumors of any histology

- p53 wild-type non-small cell lung cancer (NSCLC) of any histological subtype

Part 3: It is estimated that approximately 30 subjects will be enrolled in Part 3, all 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, or PD as best response) with prior PD-1 or PD-L1 directed therapy. In addition, squamous cell carcinoma of the cervix patients that have progressed on or after PD-1 or PD-L1 directed therapy or are PD-1/PD-L1 treatment naïve 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]

Analysis

Part 1: A modified toxicity probability interval (mTPI) method will be used to make dose escalation decisions. Dose decisions, including dose increments, will be based on the totality of clinical safety assessment including dose-limiting toxicities, clinical, and laboratory safety data. All data will be pooled and descriptive analyses summarized and listed by cohort at study conclusion. No formal statistical hypotheses will be tested. Analyses will be descriptive and exploratory.

Part 2: The primary goal of Part 2 is to evaluate disease-specific efficacy in subjects with TNBC, mTCC, recurrent GBM, NHL (which will be divided into two cohorts: *TP53* mutated and *TP53* wild-type), ACC, ER+BC, HPV-positive solid tumors and NSCLC. Except for the ACC cohorts, this portion of the study will employ a Bayesian design that allows the trial to be frequently monitored with the constraint of both Type I and Type II error rates. The ACC cohorts will use a Simon's optimal two stage design. For all tumors except GBM, the primary endpoint will be defined as overall response rate (ORR), per standard evaluation criteria. Bayesian hierarchical modeling will be used to investigate the clinical activity of GSK3326595 in the TNBC, mTCC, and NHL cohorts.

Hierarchical modeling allows information about the treatment effect in one cohort to be 'borrowed' when estimating the treatment effect in another cohort. For the GBM cohort, the primary endpoint will be defined as the six-month PFS rate. The NSCLC cohort is intended to explore the clinical activity in the p53 wild-type NSCLC population using a Simon's optimal two-stage design to define the interim futility analysis. The results of the interim futility analysis (performed after 10 evaluable subjects) will be used to inform further development in this population. For all cohorts, clinical activity will be monitored through interim analyses.

A secondary goal of Part 2 is to test the hypothesis that clinical response to GSK3326595 in NHL subjects is influenced by tumor p53 status (wild type versus mutant).

Part 3: No formal statistical hypothesis will be tested in this cohort. Analyses will be descriptive and exploratory.

2. INTRODUCTION

GSK3326595 is a potent, selective, reversible inhibitor of the protein arginine methyltransferase 5 (PRMT5)/Methylosome protein 50 (MEP50) complex that is being tested as an oral treatment for human subjects with cancer.

2.1. Study Rationale

Protein arginine methyltransferases (PRMTs) are a subset of enzymes that methylate arginines in proteins that contain regions rich in glycine and arginine residues (GAR motifs). PRMT5 methylates arginines in proteins involved in various cellular proteins including splicing factors, transcription factors, kinases and others [Karkhanis, 2011]. PRMT5 also methylates histone arginine residues (Histone 3 Arginine 8 [H3R8], Histone 2A arginine 3 [H2AR3] and Histone 4 arginine 3, [H4R3]), and these histone marks are associated with transcriptional silencing of tumor suppressor genes such as *RB1* and *ST7* [Wang , 2008; Pal, 2007].

Additionally, symmetric dimethylation of H2AR3 has been implicated in the silencing of differentiation genes in embryonic stem cells [Tee, 2010]. PRMT5 plays a critical role in the cell-cycle and pro-apoptotic effects of p53 via two mechanisms: direct inhibition of p53 activity via methylation of arginine residues on p53 itself, as well as increased ubiquitylation (and subsequent degradation) of p53 via differential splicing of MDM4, a p53 ubiquitin ligase. Finally, PRMT5 plays a role in cellular signaling through the methylation of epithelial growth factor receptor (EGFR) and phosphoinositol-3 kinase (PI3K) [Hsu, 2011; Wei, 2012].

Increasing evidence suggests that PRMT5 is involved in tumorigenesis. PRMT5 protein is overexpressed in a number of cancer types, including lymphoma, glioma, breast and lung cancer and PRMT5 overexpression alone is sufficient to transform normal fibroblasts [Pal, 2007; Ibrahim, 2014; Powers, 2011; Yan, 2014]. Knockdown of PRMT5 often leads to a decrease in cell growth and survival in cancer cell lines. In breast cancer, high PRMT5 expression, together with high programmed cell death 4 (PDCD4) levels predict overall poor survival [Powers, 2011]. High expression of PRMT5 in glioma is associated with high tumor grade and overall poor survival and PRMT5 knockdown provides a survival benefit in an orthotopic glioblastoma model [Yan, 2014]. Increased PRMT5 expression and activity contribute to silencing of several tumor suppressor genes in glioma cell lines.

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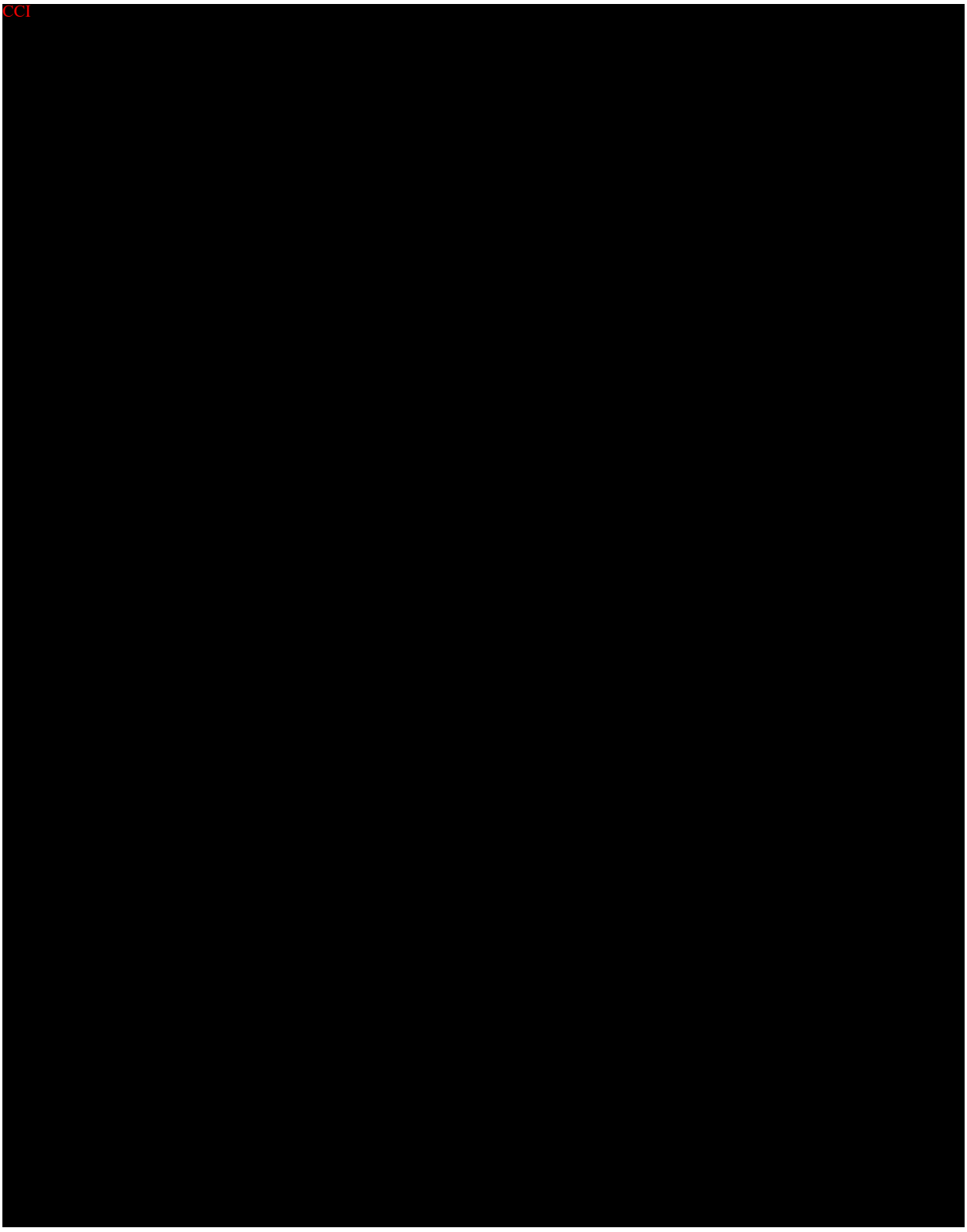


Nevertheless, p53 is not the only mechanism by which PRMT5 has its effect on lymphoma cells, as several p53-mutant cell lines were also highly sensitive to treatment with GSK3326595. For instance, cyclin D1, the oncogene that is translocated in the vast majority of MCL patients, associates with PRMT5 and through a cdk4-dependent mechanism increases PRMT5 activity [Aggarwal, 2010]. PRMT5 mediates the

suppression of key genes that negatively regulate deoxyribonucleic acid (DNA) replication allowing for cyclin D1-dependent neoplastic growth. PRMT5 knockdown inhibits cyclin D1-dependent cell transformation causing death of tumor cells. Thus, because other gene pathways (apart from p53) that are important for lymphomagenesis are regulated by PRMT5, subjects with lymphoma will be enrolled in Part 2 irrespective of p53 status and the response to therapy with GSK3326595 will be compared between cohorts.

Adenoid cystic carcinoma (ACC) is a tumor arising from salivary glands that is clinically distinct from squamous cell tumors of the head and neck. While typically characterized by a long overall survival (OS), it nevertheless portends frequent metastatic progression and steadily progressive disease [Wysocki, 2016]. To date, there are no approved therapies for metastatic or unresectable ACC, as response rates to traditional chemotherapy are typically poor and novel targeted therapies have been unable to improve on this [Dillon, 2017; Goncalves, 2017; Locati, 2016] . Epigenetic agents have recently found favour in ACC therapeutic trials, as recurrent mutations in transcriptional mediators (including myb and NOTCH) have been identified in a subset of ACC tumor samples [Ferrarotto, 2016]. As inactivating p53 mutations are rare in ACC samples, any agent (such as GSK3326595) that increases p53 activity may yield therapeutic benefit in this population.

HPV is a DNA virus that has been associated with numerous squamous cell carcinomas when mucocutaneous squamous cells are infected with high-risk strains of the virus. Tumorigenesis is mediated via viral oncogenes, including E6 and E7, which lead to degradation and/or inhibition of endogenous tumor suppressors. This effect phenocopies inactivating mutations in these tumor suppressors. Critically, viral oncogene expression is dependent on host mRNA-processing machinery (i.e., the spliceosome) [Graham, 2017]. In the absence of viral oncogene expression, the endogenous tumor suppressors would be expected to resume expression, potentially leading to reduction in tumor size. GSK3326595 may be expected to provide therapeutic benefit in HPV-infected solid tumors in multiple ways: either by reducing viral oncogene expression via effects on mRNA splicing of viral oncogenes, or else by direct upregulation of p53 via other PRMT5-dependent processes as described above. As HPV induces tumors via a common mechanism irrespective of the cell type of origin (e.g., cervical, head/neck, etc), PRMT5 inhibition may yield clinical benefit in multiple HPV-infected tumor types.

Recently, immunotherapy has emerged as a significant field for novel therapies in oncology. These agents act via modulation of the acquired immune system in order to drive recognition and destruction of tumors [Gandhi, 2018]. Pembrolizumab, a humanized Immunoglobulin G4 (IgG4) against the Programmed Cell Death protein-1 (PD-1) protein, has been approved as an option for patients with a variety of solid tumors and hematological malignancies, including lung, head and neck, melanoma, bladder, and cervical cancers [KEYTRUDA, Prescribing Information (PI), 2019; KEYTRUDA, Summary of Product Characteristics (SPC), 2019]. Treatment with pembrolizumab is characterized by responses that exhibit significant durability [KEYTRUDA, PI, 2019; KEYTRUDA, SPC, 2019]. However, not all patients respond to pembrolizumab therapy, and wild-type p53 has emerged as a potential biomarker for lack of response [Carlisle, 2018]. Given the preclinical activity of GSK3326595 observed in many pembrolizumab-sensitive tumor types, the unmet medical need of the

pembrolizumab-treated patients who fail to respond to their therapy, and the potential p53-modulating effects of GSK3326595, PRMT5 inhibition may yield clinical benefit when administered in combination with pembrolizumab.

GSK3326595 in combination with Pembrolizumab will be explored in subjects with NSCLC, mTCC, melanoma, squamous cell carcinoma of the head and neck (HNSCC) and with squamous cell carcinoma of the cervix.

Cervical cancer is the fourth leading cause of cancer related mortality in women worldwide (Torre, 2015), third in US (Siegel, 2020) and HPV is the driver behind 97% of invasive cervical cancer (Walboomers, 1999). Response rates associated with first-line treatment of recurrent/metastatic cervical cancer ranged from 19% to 36% for cisplatin alone or in combination with paclitaxel respectively (Moore, 2004) to approximately 50% for bevacizumab containing regimens (Tewari, 2017). Median OS values ranged from 8.8 to 9.7 months for cisplatin alone or in combination with paclitaxel respectively (Moore, 2004) to 16.8 months for bevacizumab-containing regimens (Tewari, 2017). Responses to second-line treatments for recurrent/metastatic cervical cancer are limited. In June 2018, pembrolizumab received accelerated approval in the US for the treatment of patients with recurrent/metastatic cervical cancers expressing programmed death ligand (PD-L1) post chemotherapy showing ORR of 14.3% in Combined Percentage Score (CPS)≥1% population (KEYTRUDA (pembrolizumab) [package insert]). Whitehouse Station, NJ: Merck & Co; June 2019). In addition, Pembrolizumab approval in microsatellite instability-high (MSI-H) or mismatch repair deficient solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options is appropriate for selected cervical cancer patients.

A number of approaches are currently under clinical exploration including a combination of immune oncology agents (Checkmate 358, NCT02488759) or a combination of immunotherapy and chemotherapy (Keynote 826, NCT03635567). Based on preliminary data from HPV positive cohort of study 204653, some tumor shrinkage was seen in cervical cancer patients. A proposed inclusion of cervical cancer patients that have progressed on or after PD-1 or PD-L1 directed therapy or are PD-1/PD-L1 treatment naïve is based on hypothesis that GSK3326595 may augment pembrolizumab activity in this population when compared to pembrolizumab alone. It is anticipated that patients with CPS<1% and CPS≥1% may obtain benefit from treatment, given this novel combination approach and patients will be enrolled irrespective of PD-L1 status.

In summary, relapsed metastatic solid malignancies (including those under investigation in this study), and virtually all relapsed/refractory hematologic malignancies are incurable diseases which will ultimately prove fatal. In particular, recurrent urinary tract cancer and GBM portend a particularly grim prognosis with an overall survival typically measured in months. At this time, there is no standard of care for these diseases, and as such these patients often consider investigational agents in an attempt to provide some clinical benefit. A wealth of data, including genetics, biochemistry, and cellular biology, implicate PRMT5 in a multitude of human malignancies including those investigated in this study. This study is the first in humans to investigate inhibition of PRMT5 in an attempt to treat and ameliorate malignancy in this population with a high degree of unmet medical need.

3. OBJECTIVES AND ENDPOINTS

Part 1 (Dose Escalation)	
Objectives	**Endpoints**
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	
• To determine the recommended Phase 2 dose (RP2D) of orally-administered GSK3326595	• Safety profile (AEs, SAEs, DLTs), clinical response, and pharmacodynamic (PD) data
• 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
• 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	
CCI [redacted]	

Part 1 (Dose Escalation)	
Objectives	**Endpoints**
CCI [redacted]	

Part 2 (Dose Expansion)	
Objectives	**Endpoints**
Primary	
• To determine clinical activity of GSK3326595 in disease-specific expansion cohorts	• Solid tumor cohorts (non-GBM) cohorts: Overall response rate (ORR, defined as % of subjects achieving 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
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 assessment • ACC tablet cohort: Overall survival (OS), defined as

Part 1 (Dose Escalation)	
Objectives	**Endpoints**
	time from first dose until death from any cause in ACC subjects who are systemic-treatment naïve
• 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	
CCI [redacted]	

Part 1 (Dose Escalation)	
Objectives	**Endpoints**
CCI [redacted]	

Part 3 (Combination with Pembrolizumab)	
Objectives	**Endpoints**
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	
• 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
• 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 immune-based RECIST (iRECIST) 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	
CCI [redacted]	

Part 1 (Dose Escalation)	
Objectives	**Endpoints**
CCI [redacted]	

4. STUDY DESIGN

4.1. Overall 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.

Part 1 is a dose-escalation phase to identify the MTD/RP2D based on the safety, PK, and PD profiles observed after oral administration of GSK3326595, and to preliminarily identify whether or not there is an effect of fed versus fasted state, and of tablet versus capsule formulation, on the PK of GSK3326595. This Part will be conducted in adult subjects with relapsed and/or refractory solid tumors.

Disease-specific expansion cohorts (Part 2) are planned to further explore clinical activity of GSK3326595 in subjects with select solid tumors and non-Hodgkin's lymphomas. Based on pre-clinical data, as well as clinical data from Part 1 of the study, enrollment in Part 2 will be limited to subjects with triple-negative breast cancer (TNBC), metastatic transitional cell carcinoma of the urinary system (mTCC), Grade IV anaplastic astrocytoma (glioblastoma multiforme [GBM]), non-Hodgkin's lymphoma (NHL) (all sub-types recruited to Protocol Amendments 1-4, and indolent subtypes of NHL recruited to Protocol Amendment 5 onwards), adenoid cystic carcinoma (ACC), hormone receptor-positive adenocarcinoma of the breast (ER+BC), human papillomavirus (HPV)-positive solid tumors of any histology, and p53-wild type non-small cell lung cancer (NSCLC) of any histological subtype. Additional cohorts may be added, via future protocol amendment, based on pre-clinical data and clinical responses

identified during conduct of the study. CCI [redacted]

[redacted]

[redacted]

This Protocol Amendment 8 is the follow up of this decision with the primary intent to update study language related to stopping recruitment into the Part 2 ACC tablet cohort, and therefore stopping any further recruitment in the study, updating the end of study definition with final analysis plan (Section 5.5), and clarifying study treatment access for subjects continuing to derive clinical benefit from study drug as per Investigator judgement post final analysis.

Part 3 is a dose determination study to evaluate the safety, PK/PD profile, and clinical activity of orally-administered GSK3326595 at daily doses of 100 mg, 200 mg and 300 mg, in combination with pembrolizumab administered at the approved dose. Enrollment in Part 3 will be limited to subjects with NSCLC, mTCC, melanoma, and HNSCC that have failed to respond to treatment with prior PD-1 or PD-L1 directed therapy. In addition, squamous cell carcinoma of the cervix patients that have progressed on or after PD-1 or PD-L1 directed therapy or are PD-1/PD-L1 treatment naïve will be enrolled in Part 3. CCI [redacted].

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Reference Manual (SRM). The SRM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

Final Last Subject Last visit will be defined as last subject's treatment discontinuation (including 30-day safety follow up).

The end of this study is defined as the date of the last visit of the last subject undergoing the study.

A final data-cut off (DCO), closure of the study database and final analysis 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 this amendment (Protocol Amendment 8).

When Protocol Amendment 8 is implemented at a site, the collection of data for all enrolled subjects who no longer receive study treatment will stop entirely. Subjects still on treatment at the time of the final DCO date may continue to receive study treatment for as long as they continue to derive clinical benefit from study treatment as assessed by the Investigator and do not meet any protocol-defined study treatment stopping criteria (maximum until the end of availability of study drug which is anticipated to be Q3 2023); subjects may also choose to discontinue study treatment at any time. Subjects in survival follow-up at the time of the final DCO date will be considered to have completed the study.

Subjects who continue study treatment following Protocol Amendment 8 will receive follow-up care in accordance with standard local clinical practice. Assessments will revert to the standard of care at a subject's particular study site with recommendations for local safety laboratory monitoring of GSK3326595. Only SAEs, AEs leading to treatment discontinuation, overdoses, pregnancies, and pre-defined ocular and bone AEs (AESIs) will be reported directly to the Sponsor via a paper process. In addition,

- Ocular assessments will be required and reported via a paper process to the Sponsor only if reporting criteria is met for SAEs, AESIs, or AEs leading to treatment discontinuation.
- Bone (DEXA) assessments will be performed at the discretion of the investigator and reported via a paper process to the Sponsor only if reporting criteria is met for SAEs, AESIs, or AEs leading to treatment discontinuation.

4.2. 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. As described in Section 4.7, 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. CCI [redacted]. Subjects will also be enrolled at or about the RP2D into a food effect and relative bioavailability sub-study (Section 4.2.6) to evaluate the effects of food and GSK3326595 formulation on GSK3326595 pharmacokinetics.

Dose escalation will be conducted in two stages: dose exploration (Section 4.2.2) and MTD confirmation (Section 4.2.3). Details common to both stages, including DLT definitions and dose increments, are described in Section 4.2.4.

4.2.1. Type and Number of Subjects (Part 1)

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 but no more than 24 subjects in the food effect and relative bioavailability sub-study. The study population will be adults, with histologically- or cytologically-confirmed solid malignancies as described in Section 5.1.

4.2.2. Initial Dose Exploration (accelerated titration)

In order to minimize the number of subjects enrolled at sub-optimal doses, an accelerated titration design will be implemented until the first evidence of a non disease-related ≥ Grade 2 toxicity, with the exception of toxicities listed in Section 4.2.4.2. One subject at each dose level will be enrolled, starting at the dose described in Section 4.7. If the subject enrolled at the first dose level experiences a dose-limiting toxicity (DLT), then lower doses (i.e., Dose Level -1) will be explored and re-escalation may be attempted based on safety and tolerability data. Accelerated titration will continue until a subject experiences a non-disease-related ≥ Grade 2 toxicity, then the implementation of the MTD confirmation stage (Section 4.2.3) will be triggered. Each subject must complete the 21-day DLT evaluation period, and the available safety data must be reviewed before a decision is made on whether to proceed to the next dose level. If a subject fails to receive more than 80% of the planned doses within the 21-day DLT evaluation period for reasons other than toxicity, the subject will be replaced. Guidelines for selecting the next dose level are described in Section 4.2.4.2. Additional subjects may be enrolled at previously cleared dose levels if safety and PK analysis suggest this is warranted for better understanding the safety and PK profile. Safety assessments from these subjects will be included in the MTD determination.

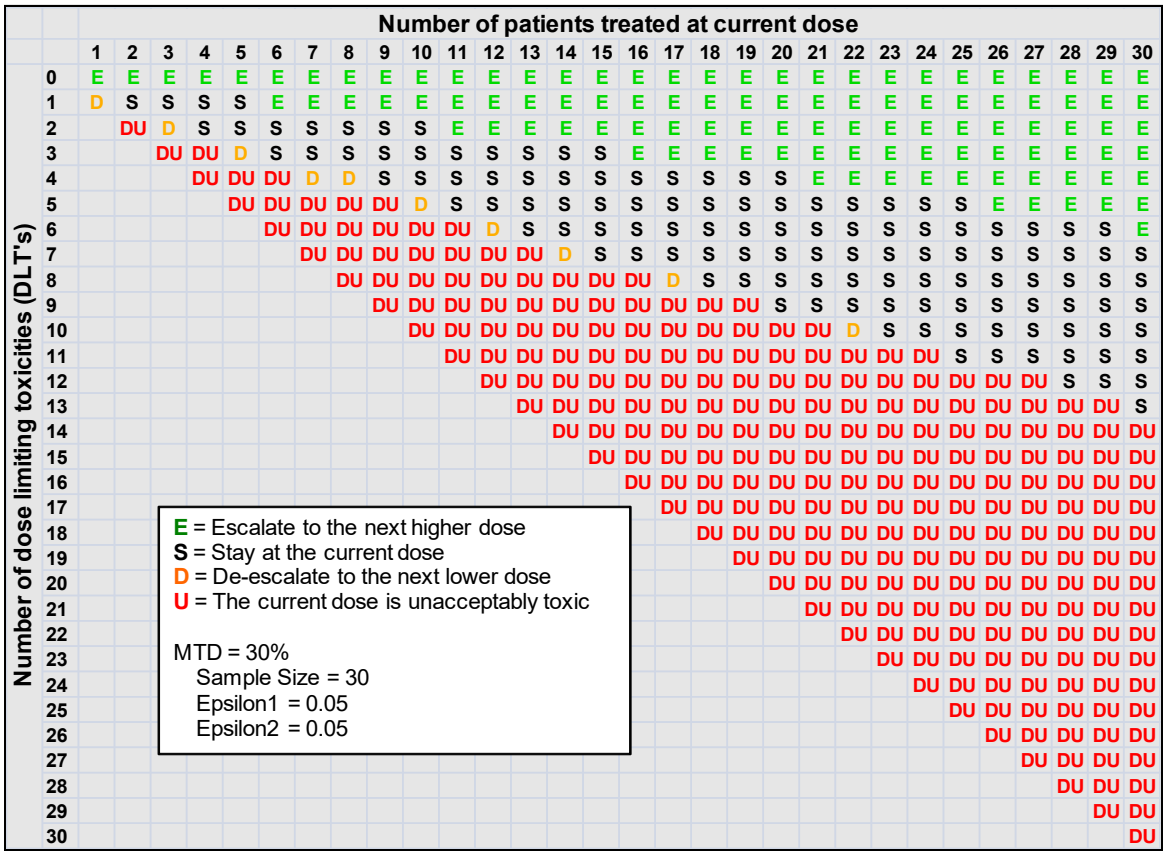
4.2.3. Determining the MTD

Starting with the first cohort exhibiting a non disease-related ≥ Grade 2 toxicity (except for those listed in Section 4.2.4.2), a modified Toxicity Probability Interval (mTPI) design will be implemented (Figure 4-1) [Ji, 2010]. Cohorts will be recruited in blocks of three subjects. The maximum number of subjects assigned to any single dose will be at the discretion of the Sponsor in consultation with the investigators.

The design assumes (i) approximately 38 subjects will complete the DLT evaluation period and (ii) the true underlying toxicity rate for GSK3326595 falls within the range from 25% to 35% and centered at 30%. The monitoring rules guiding dose escalation are provided in Figure 4-1. Columns provide the numbers of subjects treated at the current dose level, and rows provide the corresponding numbers of subjects experiencing toxicity. The entries of the table are dose-finding decisions (i.e., E, S, and D) representing escalating the dose, staying at the same dose, and de-escalating the dose. In addition, decision U means that the current dose level is unacceptable because of high toxicity and should be excluded from the trial. For example, when one of three subjects experiences toxicity, the decision can be located at row 1 and column 3, which is S – to stay at the current dose level. Consequently, the next cohort of subjects will be treated at the same dose level currently being used. If zero of three subjects experiences toxicity, the decision is at row 0 and column 3, which is E – to escalate. Thus, the next cohort of subjects will be treated at the next-higher dose level. If three of three subjects experiences toxicity, the decision is DU – to de-escalate to the next-lower dose level and exclude the current dose from the trial, because the high toxicity level is unacceptable.

During dose escalation, when 2 or more subjects are enrolled in a cohort, no two subjects may start treatment on the same day. This staggered dosing start is not required for subjects enrolling at previously cleared doses or for subjects enrolled in Part 2 of the study.

Figure 4-1 Dose-finding spreadsheet of the modified toxicity probability interval (mTPI) method



The spreadsheet was generated based on a beta/binomial model and precalculated before trial initiation. The letters in different colors are computed based on the decision rules under the mTPI method and represent different dose-finding actions. In addition to actions de-escalate the dose (D), stay at the same dose (S), and escalate the dose (E), the table includes action unacceptable toxicity (U), which is defined as the execution of the dose-exclusion rule in mTPI.

4.2.3.1. Reverting to Accelerated Dose Titration

Subsequent cohorts may revert to one subject per cohort in either of the following scenarios:

- Two additional subjects are added at the dose where the non-disease-related ≥ Grade 2 toxicity is seen in the initial subject, and no non disease-related Grade 2 or higher toxicity is seen in either of the two new subjects.
- All subjects treated at next higher dose level do not have a non-disease-related Grade 2 or higher toxicity.

However, the dose escalation may continue with multiple subjects per cohort per the clinical judgment of the Medical Monitor in consultation with the investigators. The

decision on the number of subjects will be documented in writing together with the dose escalation decision and the rationale.

4.2.4. Dose Escalation Decisions and Determination of MTD

4.2.4.1. Dose-Limiting Toxicity

An event is considered to be a dose-limiting toxicity (DLT) if the event occurs within the first 21 days of treatment and meets the criteria listed in Table 1, unless it can be clearly established that the event is unrelated to treatment.

Table 1 Dose-Limiting Toxicity Criteria

Toxicity	DLT Definition
Hematologic	• Grade 3 neutropenia (absolute neutrophil count [ANC] <1000/mm^3) for ≥5 days or Grade 4 neutropenia of any duration • Grade 3 or greater febrile neutropenia • Grade 4 or greater anemia of any duration • Grade 4 thrombocytopenia (platelets <25,000/mm^3), or Grade 3 thrombocytopenia with bleeding
Non-hematologic	• Alanine aminotransferase (ALT) >3x upper limit of normal (ULN) + bilirubin ≥2xULN (>35% direct) or ALT between 3-5 X ULN with bilirubin < 2xULN but with hepatitis symptoms[a] or rash (See Section 5.4.5 for Liver Stopping Criteria) • Grade 3 nausea, vomiting or diarrhea that does not improve within 72h despite appropriate supportive treatment(s) • Grade 4 or greater nausea, vomiting, or diarrhea • Grade 3 hypertension[b] (uncontrolled despite addition of up to 2 antihypertensive medications) • Grade 4 or greater hypertension • Grade 3 or greater clinically significant non-hematologic toxicity per National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE), v4 except toxicities listed in Section 4.2.4.2.
Other	• Inability to receive at least 80% of scheduled doses in the DLT observation period due to toxicity[c] • Grade 2 or higher toxicity that occurs beyond 21 days which in the judgment of the investigator and GlaxoSmithKline (GSK) Medical Monitor is considered to be a DLT

Toxicity Grading based on NCI-CTCAE v4

a. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)

b. Grade 3 hypertension adequately controlled by antihypertensive medication(s) is not considered to be a DLT.

c. Subjects unable to receive at least 80% of scheduled doses for reasons other than toxicity (e.g., acute illness, disease progression) will not be evaluable for DLT purposes and will be replaced in the cohort

Table 1 provides a list of protocol-defined DLTs; it does not provide guidelines for management of these toxicities. In appropriate clinical circumstances, resumed dosing after a DLT (at a reduced dose level) may be considered after discussion between the

investigator, medical monitor, and GSK medical governance (as necessary). For management of liver toxicity, please refer to Section 5.4.5. For management of cardiac toxicity, see Section 5.4.6. For management of all other toxicities, see Appendix 2.

4.2.4.2. Non-Limiting Toxicities

The following toxicities have been deemed to be non-serious for the purposes of this study. These toxicities will not be taken into account for dose escalation decisions unless, in the opinion of the investigator and the GSK Medical Monitor, they represent a dose-limiting toxicity. For all other toxicities and their management, see Appendix 2.

- Grade 2 or less:
  - Fatigue
  - Rash
  - Alopecia
- Grade 3 or less nausea, vomiting, or diarrhea controlled within 24h
- Electrolyte imbalance or other laboratory abnormalities controlled within 24h

4.2.4.3. Maximum Dose Increment

Built-in safety constraints are in place to prevent exposing subjects to undue risk of toxicity. The maximum allowable dose increment will be determined based on the prior dose level data. The permitted dose increments are a protocol-defined maximum; a smaller increment may always be used based on the decision of the investigators and medical monitor (Section 4.2.4.5). Planned dose levels are detailed in Section 4.2.4.4.

For each individual dose escalation step:

If no grade ≥ 2 non-hematologic non disease-related toxicity (except those listed in Section 4.2.4.2) is observed at the current dose, the dose increment will be no more than 100% of the current dose.

If one or more grade > 2 non-hematologic non disease-related toxicity (except those listed in Section 4.2.4.2), grade > 2 anemia or thrombocytopenia, or DLT is observed, the dose increment to the immediate next dose level will be no more than 50% of the current dose.

4.2.4.4. Planned Dose Levels

Projected daily dose levels 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.

4.2.4.5. Dose Escalation Decisions

The GSK medical monitor, in joint discussion with the participating investigators, will be responsible for determining whether dose escalation during Part 1 should continue as

recommended by the mTPI approach. Prior to the dose escalation decision, the medical monitor, clinical scientist, safety physician, clinical pharmacologist, and investigators will review critical safety data defined in the Dose Escalation Plan, including data on all adverse events including non-DLT toxicities, laboratory assessments and other safety evaluations, as well as PK and PD data. The quality review of critical safety data will be described in the Dose Escalation Plan, which includes ongoing study monitoring visits along with data review of the clinical database.

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).

4.2.4.6. Alternative Dosing Schedules

Alterations may be made to the schedule of administration and/or PK/PD sampling schedule based on the results of emerging PK and safety data.

Schedules that incorporate a recovery period may be explored (e.g., 3 weeks on, 1 week off). This approach will be considered if the safety and PK data suggest that a therapeutic exposure cannot be achieved using the initial schedule without excessive toxicity. The starting dose for the alternate schedule will be the highest completed dose level (at or below MTD) with the initial schedule. Escalation can then proceed as described in Section 4.2.3.

Schedules that use a different daily regimen (e.g., twice daily [BID] dosing) may also be explored. This approach will be considered if the safety, PK, and PD data suggest that a sufficient therapeutic exposure cannot be achieved using the initial schedule. If a shorter recovery period is used, the initial dose level will be ≤50% of the highest completed dose level (at or below MTD) with the initial schedule. Escalation can then proceed as described using in Section 4.2.3. If BID dosing is to be utilized, study events will occur as detailed in Table 11 and Table 12.

The dosing schedule may also be adjusted to expand a prior dose cohort to further evaluate safety, pharmacokinetic and/or pharmacodynamic findings at a given dose level, or to add cohorts to evaluate additional dose levels. The study procedures for these additional subject(s) or cohort(s) will be the same as that described for other study subjects.

Any changes to the dosing schedule may be made only after review of all available data and clearance by the GSK medical monitor. Any planned changes will apply to a cohort of subjects and not an individual subject. Changes will be communicated to the site in writing along with justification and data supporting the change. A modified SRM, including updated Time and Events Table, will be provided to the sites prior to initiation of the alternative regimen.

4.2.4.7. Intra-subject Dose Escalation

In Part 1, intra-subject dose escalations may be considered on a case-by-case basis, provided that the subject has completed at least the DLT observation period without

≥ Grade 2 non disease-related toxicity in the first 21 days of therapy, that all subjects at the next highest dose level have completed the DLT observation period, and that prior approval has been obtained from the GSK Medical Monitor. Subjects may be dose-escalated to the highest cleared dose. Individual subjects may dose-escalate multiple times provided that the above criteria are met at each intra-subject dose escalation step. Safety assessments from these subjects will be included in the MTD determination.

Subjects approved for intra-subject dose escalation will initiate daily dosing from Day 1 of the higher dose (i.e., no dose interruption from Day 2 until Day 4) and will require additional PK sampling on Day 15 at the higher dose, as specified in Time and Events table (see Section 8.1). Additional safety assessments may be specified at the time of dose escalation or schedule modification based on the safety profile in previous subjects at the higher dose level. Intra-subject dose escalations or schedule modification will be discussed with investigators and approved by the GSK Medical Monitor and safety monitoring required will be specified in writing.

4.2.4.8. Completion of Dose Escalation and Determination of MTD/RP2D

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.

4.2.5. 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 (Section 4.3) has been initiated.

Refer to Section 8.1, Time and Events Table (Table 10), which highlights the additional sampling requirements for this cohort. In addition to the safety and PK evaluations necessary for all subjects in Part 1, blood and urine will be collected at time points specified in Section 8.1 (Table 10) for PD, biomarker, and metabolite profiling. Pre-dose

and post-dose tumor biopsies will be required from subjects in this/these cohort(s). Subjects consenting to pre- and post-dose biopsies will be prioritized to enrollment in these cohorts. ^{18}fluorodeoxyglucose (FDG) positron emission tomography (PET) (FDG-PET)/computed tomography (CT) scan (PET/CT scan) will be required for all subjects in this cohort, as described in Section 8.6.3. CCI [redacted]

4.2.6. 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) (refer to Section 4.3.2). 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. All subjects enrolled to the sub-study, on completion of their participation in this segment of the study, will continue on a daily dosing schedule until discontinuation criteria are met, as described in Section 5.4. Further details will be provided in the SRM. The sub-study will be open to adults, with histologically- or cytologically-confirmed solid malignancies as described for Part 1 in Section 5.1.

The high-fat (approximately 50% of the total caloric content of the meal), high-calorie meal (approximately 800 to 1000 calories) will be the representative example given by the 2002 US Food and Drug Administration (FDA) guidance [FDA, 2002]. Additional details of the required meal will be provided in the SRM.

Subjects enrolled in the sub-study will be assigned to one of two sequences, as described in Table 2; equal numbers will be assigned to each sequence. The schedule of visits for subjects enrolled in the sub-study is detailed in Table 13 in Section 8.1. Upon completion of the sub-study, all subjects will continue to undergo scheduled assessments as described in Table 9. Additional details, including the process of sequence assignment, will be provided in the SRM.

Table 2 Food Effect and Relative Bioavailability Sub-Study

Food-Effect Sub-Study: Single Dose Administrations				
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.

As described in Section 8.2.2, 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.

4.3. 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. Other tumor types may be added via protocol amendment, based on additional pre-clinical data and/or clinical responses observed during Part 1 or Part 2 of the study. 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 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 may be 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.

4.3.1. Type and Number of Subjects (Part 2)

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 (see Section 5.1 for all required disease characteristics); 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:

- Triple-negative breast cancer (TNBC)
- Metastatic transitional cell carcinoma of the urinary system (mTCC)
- Glioblastoma multiforme (GBM)
- Non-Hodgkin's lymphoma (NHL) – 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[-])
- 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[+])
- Adenoid cystic carcinoma (ACC), dosed with GSK3326595 capsule formulation
- Adenoid cystic carcinoma (ACC), dosed with GSK3326595 tablet formulation, in a population that is systemic therapy-naïve.
- Hormone receptor-positive adenocarcinoma of the breast (ER+BC)
- Human papillomavirus (HPV)-positive solid tumors of any histology
- p53 wild-type non-small cell lung cancer (NSCLC) of any histological subtype

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 transformed follicular lymphoma (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.

4.3.2. R2PD Dose Selection

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.

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.

Subsequent evaluation of safety and tolerability data was performed, using data from the 04 February 2019 data cut included in the IB for GSK3326595 [GlaxoSmithKline Document Number 2017N314773_03]. As of that date, 71 subjects had been treated at the 400 mg RP2D in the 204653 study. Of those 71 subjects, 33 (46%) required at least one dose reduction. Of the 33 subjects requiring dose reduction, the majority (23 subjects [70%]) remained on 300 mg for their duration on study. Overall, only 10 subjects (14% of the total number treated at 400 mg) required more than one dose reduction (i.e., to doses below 300 mg).

Clinical activity was observed in Part 1, in subjects with ACC who were treated at doses of 300 mg and below. Of the three patients who exhibited confirmed partial responses, two were started at a dose of 200 mg QD and remained at that dose throughout their time on study. The third responder began treatment with GSK3326595 at 400 mg QD, but dose reduced to 300 mg QD after the first month on treatment.

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.

4.3.3. Statistical Design

Continued recruitment into each disease-specific expansion cohort is determined using the rules described in this section. CCI

[redacted]

4.3.3.1. GBM Cohort

In Part 2, the GBM cohort will employ a Bayesian adaptive design that allows the study to be frequently monitored with the constraint of both Type I and Type II error rates. The first interim analysis will be conducted after a minimum of 10 evaluable subjects who have had at least three post-baseline assessments, have progressed or died, or have permanently discontinued from study treatment. Up to 28 subjects may be enrolled in the GBM cohort; for details of the design and decision rules, refer to Section 11.3.

4.3.3.2. mTCC, TNBC, and NHL Cohorts

For mTCC, TNBC and NHL cohorts, a "basket" Bayesian hierarchical modeling design that allows the trial to be frequently monitored with the constraint of both Type I and Type II error rates will be used. Clinical response will be defined as ORR, per standard evaluation criteria (see Section 14.4 for definitions of response assessments and criteria). Bayesian hierarchical modeling will be used to investigate the clinical activity of GSK3326595 in the four tumor-specific cohorts of subjects. Hierarchical modeling allows information about the treatment effect in one cohort to be 'borrowed' when estimating the treatment effect in another cohort [Berry, 2013].

Clinical activity will be monitored through frequent interim analyses. The first interim analysis will be conducted when about 40 evaluable subjects are enrolled across the four tumor-specific cohorts (mTCC, TNBC, p53 WT NHL, and p53 mutant NHL) at a dose level based on RP2D or at least 10 evaluable subjects are available in any cohort. Subjects treated at the RP2D in Part 1, with disease subtypes under study in Part 2, will be incorporated into clinical activity analysis provided that they are evaluable. Each subsequent interim analysis can be conducted after every five additional subjects become evaluable. The timing of subsequent interim analyses will be based on the enrollment rate into each of the cohorts with the expected duration of Part 2 of the trial to be 104 weeks. A subject is evaluable for the interim futility analysis if they have either

progressed or died, withdrawn from the study treatment, or are ongoing and have completed at least two post baseline disease assessments.

Decisions are based on whether the posterior probability that the ORR exceeds its corresponding historical control is sufficiently low compared to fixed statistical thresholds. If this posterior probability is sufficiently low within a given cohort (≤0.15), then enrollment may be halted early for futility. At the final analysis and after the study has been closed, if the posterior probability is sufficiently high (≥0.87), then the dose will be declared efficacious for that cohort. Separate from model estimates, the observed ORR will also be reported for each cohort.

Enrollment into each disease-specific cohort will continue during the conduct of each interim analysis subsequent to the decision of whether or not to declare futility. The total number may be increased up to a total of 32 evaluable subjects for the TNBC cohort, up to a total of 25 evaluable subjects for each of the two NHL cohorts, and up to 40 evaluable subjects for the mTCC cohort, depending on the results observed; a separate decision will be made for each disease cohort. Enrollment into each tumor specific cohorts can only be terminated for futility (i.e., lack of clinical activity), notwithstanding the provisions of Section 5.5; otherwise enrollment will continue to the planned maximum sample size in each cohort. Inference stemming from the Bayesian hierarchical model of GSK3326595 efficacy in subjects harboring these four tumor types are intended to inform decision making. Actual decisions will depend on the totality of the data.

Subjects enrolled in Part 1 may be included in the Part 2 efficacy analysis provided that they were treated at the RP2D and have a disease under study in Part 2.

The decision to terminate a disease-specific cohort will not depend solely on the results of the statistical model but will take all factors into account, including the results of the model, safety, tolerability, PK, and PD data. In some cases (e.g., under-representation of a given predictive biomarker in the subjects treated at the time of interim analysis), additional subjects in a cohort may be enrolled even if the model suggests a low likelihood of activity in that tumor type.

4.3.3.3. ACC Cohorts (Capsule and Tablet Formulation)

The Simon's optimal two stage design will be utilized for the ACC cohorts. Up to 38 subjects in the capsule cohort will be enrolled, and up to 50 subjects in the tablet cohort will be enrolled. One interim analysis will be performed in each cohort after at least the first 10 treated subjects for the capsule cohort and the first 17 treated subjects for the tablet cohort become evaluable (i.e. who have had at least three post-baseline assessments, have progressed or died, or have permanently discontinued from study treatment). Please refer to Section 11.5 for details of the design and decision rules.

4.3.3.4. Hormone Receptor-Positive Breast Cancer Cohort

The ER+BC cohort will employ a Bayesian adaptive design that allows the study to be frequently monitored with the constraint of both Type I and Type II error rates. The first interim futility analysis will be conducted after a minimum of 10 evaluable subjects who

have had at least two post-baseline assessments, have progressed or died, or have permanently discontinued from study treatment. If the cohort does not meet the futility criteria, then up to 25 additional subjects may be enrolled in this cohort; for details of the design and decision rules, refer to Section 11.6.

4.3.3.5. HPV-Positive Solid Tumor Cohort

The HPV-positive cohort will employ a Bayesian adaptive design that allows the study to be frequently monitored with the constraint of both Type I and Type II error rates. The first interim futility analysis will be conducted after a minimum of 10 evaluable subjects who have had at least two post-baseline assessments, have progressed or died, or have permanently discontinued from study treatment. If the cohort does not meet the futility criteria, then up to 18 additional subjects may be enrolled in this cohort; for details of the design and decision rules, refer to Section 11.7.

4.3.3.6. NSCLC Cohort

The p53 wild-type NSCLC cohort will be used to estimate the clinical activity for GSK3326595 for this population. The analysis will be performed on a minimum of 10 and maximum of 15 evaluable subjects with confirmed p53 wild-type status. The additional 5 subjects are intended to account for any discrepancies between local p53 testing and central, comprehensive testing to ensure a minimum of 10 evaluable p53 wild-type subjects. Only those evaluable subjects whose central test results confirm p53 wild-type status will be included in the analysis. A subject is evaluable for analysis if they have either progressed or died, withdrawn from the study treatment, or are ongoing and have completed at least two post-baseline disease assessments. A Simon's optimal two stage design will be utilized as a framework for the analysis of this cohort, where one interim analysis will be performed after at least the first 10 treated subjects become evaluable. Please refer to Section 11.5 for details of the design and decision rules.

4.4. Part 3: GSK3326595 + Pembrolizumab Combination Study [Active in all regions, except France]

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. As described in Section 4.4.4, three cohorts will be evaluated. All subjects will receive pembrolizumab at the approved dose (200 mg IV every 3 weeks [q3w]), in combination with GSK3326595 dosed orally at 100 mg QD, 200 mg QD, or 300 mg QD.

CCI [redacted]

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, as described in Section 4.4.4.

4.4.1. Type and Number of Subjects (Part 3)

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, 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. In addition, squamous cell carcinoma of the cervix patients that have progressed on or after PD-1 or PD-L1 directed therapy or are PD-1/PD-L1 treatment naïve will be enrolled in Part 3. For full details of eligibility criteria, please refer to Section 5.1.

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. For details of subject enrolment, please refer to Section 4.4.4 and to the SRM. CCI [redacted]

4.4.2. Treatment Arms and Duration

All subjects in Part 3 will receive GSK3326595 in combination with pembrolizumab. Subjects may continue therapy with GSK3326595 until progression, unacceptable toxicity, or withdrawal of consent. Subjects may continue therapy with pembrolizumab until progression, unacceptable toxicity, or withdrawal of consent, for a maximum of 24 months.

4.4.3. Dose Selection

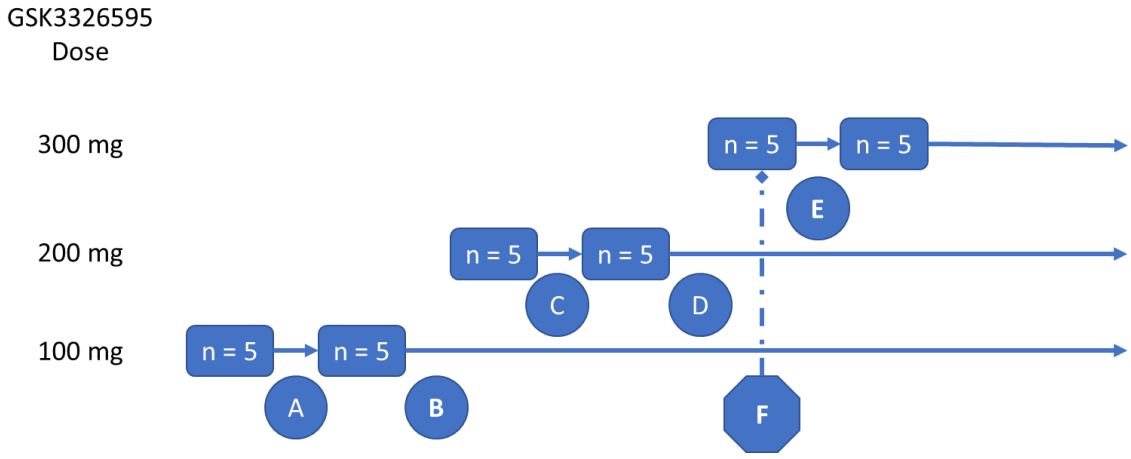
Subjects will be assigned prior to first dose to receive either 100 mg, 200 mg, or 300 mg of GSK3326595 administered once daily, based on the dose escalation schema described in Section 4.4.4. All subjects will receive pembrolizumab at the approved dose (200 mg IV every 3 weeks). Subjects may dose-interrupt and/or dose-reduce GSK3326595 and/or dose interruption of pembrolizumab for toxicity as described in Section 14.2. There will be no intra-subject dose escalation. Subjects who require dose interruption of GSK3326595 and/or pembrolizumab, and/or dose reduction of GSK3326595 for toxicity may continue on protocol at the lower dose or delayed schedule.

4.4.4. Cohort Design

Overall, approximately 10 subjects per dose level may be enrolled. Allowing for late screen failures and early (non-AE related) withdrawals/discontinuations, up to 6 subjects may be enrolled to deliver a minimum of 5 evaluable subjects for each dose decision meeting. Each subject must complete the 35-day DLT evaluation period, and the available safety data must be reviewed before a decision is made on whether to proceed to the next dose level. If a subject fails to receive more than 80% of the planned doses of

GSK3326595 or full first cycle of pembrolizumab within the 35-day DLT evaluation period for reasons other than toxicity, the subject will be replaced. Refer to Table 15 for the schedule of activities for subjects enrolled in Part 3. Dosing will commence in the 100 mg cohort. Safety will be reviewed on an ongoing basis by, at a minimum, the GSK medical monitor and GSK Global Safety representative.

Figure 4-2 Part 3 Schema



CCI [redacted]

Enrollment into Part 3 will occur in two stages at each dose level. The target sample size for each stage is 5 subjects, however, an additional subject may be enrolled at stage 1 and stage 2 of each dose level, to deliver a minimum of 5 subjects per stage and at least 10 subjects per dose level. Hence, it is possible that six subjects may be dosed in stage 1 or stage 2, resulting in 11 total subjects at any one dose level. At the analysis of each stage, the full number of subjects dosed will be included, i.e. if 6 subjects are dosed in stage 1, data from all 6 subjects will be used to make the decision to either stop or continue enrolment at the current dose level.

Five (or six) subjects may be enrolled immediately at the 100 mg dose level (stage 1). Planned analysis of the cohort safety data will take place in a dose decision meeting (see Section 4.4.4.1) after all subjects dosed in stage 1 complete 35 days of study treatment (i.e., 5 weeks of GSK3326595, as well as the first cycle of pembrolizumab treatment) or discontinue prior to 35 days Figure 4-2; A). It is recommended that the cohort stop enrolling for safety reasons if the following criterion is met:

- 3 or more subjects out of the first 5 or 6 enrolled experience a toxicity (at any time on-study) as described in Section 4.4.4.1

If the safety stopping criteria (as defined in Section 4.4.4.1) are not triggered by the first 5 (or 6) subjects, enrollment may continue, with continuous evaluation of safety after each subject enrolled. The additional 5 subjects may all be enrolled immediately at the same dose level. The cohort will be recommended to stop for safety and higher dose cohorts will not be opened (Figure 4-2; B) if the following criterion is met:

- 4 or more subjects in the 100 mg dose level (i.e. 10 or 11 subjects) experience a toxicity (at any time on-study) described in Section 4.4.4.1

Once 10 (or 11) subjects at the 100 mg dose level have completed at least 35 days of study treatment (Figure 4-2; B), the safety data from the cohort will be reviewed in a dose decision meeting, in accordance with the Dose Escalation Plan. All safety events from all Part 3 subjects on treatment will be reviewed prior to dose escalation. Upon the agreement at the dose decision meeting, the 200 mg cohort may open.

Five (or six) subjects may be enrolled in the 200 mg cohort immediately (stage 1), and evaluation and further enrolment will proceed as described above for the 100 mg cohort (Figure 4-2; C). Once all 10 (or 11) subjects have been enrolled in the 200 mg cohort (Figure 4-2; D), then all available safety data will be reviewed in a dose decision meeting prior to making a decision about opening the 300 mg cohort.

Five (or six) subjects may be enrolled in the 300 mg cohort, and evaluation and further enrolment will proceed as the 100 mg and 200 mg cohorts (Figure 4-2; E). Approximately 10 (or 11) subjects may be enrolled in the 300 mg cohort.

If, at any time, more than 4 subjects per cohort at a lower dose meet the stopping criteria described in Section 4.4.4.1, then further enrolment in higher dose cohort(s) may be terminated upon review of all available safety data (Figure 4-2; F). In the event that a dose cohort is closed to further enrolment, subjects already enrolled in Part 3 may continue to receive treatment until disease progression, unacceptable toxicity, or withdrawal of consent as described in Section 4.4.2.

4.4.4.1. Safety Stopping Criteria

As described above, all available safety data will be reviewed in dose decision meetings: after the first 5 (or 6) subjects in each cohort complete 35 days of study treatment, or discontinue prior to 35 days (Figure 4-2; A, C, and E); and after all 10 (or 11) subjects in each cohort complete 35 days of study treatment, or discontinue prior to 35 days (Figure 4-2; B and D). Dose decision meetings will be attended by the GSK medical monitor, GSK clinical scientist, GSK safety physician, GSK clinical pharmacologist, and the Investigators. Agreement to proceed with dosing in the cohort, or to open the next cohort to enrolment, will be made in accordance with the Dose Escalation Plan. Safety data will also be reviewed on an ongoing basis (Figure 4-2; F).

The number of subjects with adverse events meeting one or more of the following criteria, emerging at any time during study treatment, will be defined. In all cases, "drug-related" may pertain to either GSK3326595 or pembrolizumab alone, or the two administered in combination:

- Any drug-related Grade 4 non-hematological toxicity
- Any drug-related Grade 4 hematological toxicity, or any drug-related Grade 3 hematological toxicity that does not recover to Grade 2 or better within 1 week of interrupting therapy.

- Any drug-related hepatic toxicity that meets liver stopping criteria as defined in Section 5.4.5
- Any drug-related Grade 2 or greater toxicity that, in the opinion of the Investigator and Medical Monitor, should limit further enrolment into the study
- Inability to receive at least 80% of scheduled doses in the DLT observation period due to drug-related toxicity.

If it is clearly established that the event is unrelated to treatment, the event will not meet the above criteria. Grade 4 toxicities that are known to occur with pembrolizumab therapy and are controlled within 2 weeks using the recommended supportive measures (refer to Section 14.2.2 and Section 14.2.3) do not meet the above criteria (though could be considered cause for stopping based on the clinical judgement of the Investigator(s) and Medical Monitor). These known toxicities will be evaluated during dose decision meetings, to assess for parameters that include increases in frequency or severity.

Subjects who are unable to receive at least 80% of scheduled doses during the 35-day DLT observation period for reasons other than drug-related toxicity (e.g. acute illness, disease progression) will not be evaluable for DLT purposes and will be replaced in the cohort.

The safety stopping criteria were chosen to align with an mTPI-2 [Guo, 2017] design with a target toxicity rate of 40%, considering the longer watch period for observing adverse events. This will allow for higher accumulation of events and renders the traditional design too conservative for the purpose of this study. The safety stopping criteria were confirmed via simulation of the operating characteristics of the model (provided in Section 11.10.4). If the decision is made to close enrolment at a particular dose, then further enrolment in higher-dose cohorts may also be terminated at that time.

4.4.5. Statistical Design

No formal statistical hypothesis will be tested in this cohort. Analyses will be descriptive and exploratory.

4.5. Type and Number of Subjects (Overall)

All subjects enrolled in this study will have a diagnosis of relapsed or refractory cancer for which no standard therapy is expected to provide a significant response. It is estimated that a maximum of 412 subjects will be enrolled in the study, divided as follows: As planned, approximately 42 subjects will be enrolled in the dose escalation phase of Part 1. In addition, approximately 12 subjects will be enrolled in the PK/PD/biomarker/metabolite cohort(s) and approximately 12 subjects but no more than 24 subjects will be enrolled in the food effect and relative bioavailability cohort. An additional 316 subjects may be enrolled in the disease-specific efficacy cohorts of Part 2. Approximately 30 subjects may be enrolled in Part 3. Further details of the type and number of subjects are available in Section 4.2.1, Section 4.3.1, and Section 4.4.1.

4.6. Design Justification

Given the high unmet medical need of relapsed/refractory advanced solid tumors and non-Hodgkin's lymphoma, this three-part Phase I study (204653) is proposed. The study comprises a dose-escalation part, followed by a series of cohorts to determine preliminary efficacy in selected tumor types, as well as a dose-finding study of GSK3326595 plus pembrolizumab to identify a starting dose of GSK3326595 for future study(s).

4.6.1. Part 1

Part 1 is a conventional dose-escalation study using the mTPI approach, a well-validated method to identify the MTD/RP2D of a given compound. While preliminary efficacy data will be collected as part of the course of this Part, it will not be a primary endpoint. In addition to identification of MTD/RP2D, blood and urine collections will be performed to characterize the pharmacokinetic parameters of GSK3326595 as well as to partially characterize the biomarker profile of GSK3326595 treatment.

4.6.2. Additional Pharmacodynamic, Metabolic & Biomarker Profiling

All subjects in Part 1 will be evaluated for pharmacodynamic data. CCI [redacted] (CCI [redacted] has been identified and validated as a pharmacodynamic biomarker of PRMT5 inhibition in multiple preclinical *in vitro* and *in vivo* studies. Analysis of CCI [redacted] will provide valuable information regarding target engagement by GSK3326595.

A cohort of subjects in Part 1, treated at or close to the MTD, will be evaluated more extensively for metabolic and biomarker profiling (Section 4.2.5). This cohort will provide samples for biomarker, pharmacodynamic, and metabolite assessment. Analysis of human samples will provide first-hand information on metabolism and disposition of GSK3326595 in humans.

CCI [redacted].

4.6.3. Food Effect and Relative Bioavailability Profiling

A subset of subjects in Part 1, treated at 300 mg, will be evaluated more extensively to preliminarily evaluate the effect of food on the pharmacokinetics of GSK3326595 (Section 4.2.6). A relative assessment of bioavailability between capsules and tablets will also be conducted in this group. This cohort will provide data that can be used to modify dosing instructions for subjects in this and future studies (e.g., GSK3326595 may be taken without respect to food, or GSK3326595 must be taken on an empty stomach). It will also be used to support development of GSK3326595 tablet formulation. If the GSK3326595 tablet bioavailability is comparable to that of the GSK3326595 capsules, then any newly enrolled or ongoing subjects in any of the cohorts may be allowed to move over from the capsules to the tablets, once they have been notified by the Sponsor.

4.6.4. Part 2

Part 2 is a disease-specific preliminary study of efficacy, examining the effect of GSK3326595 on tumor growth (as measured by ORR [mTCC, TNBC, ACC, ER+BC, HPV-positive solid tumor, NSCLC and NHL cohorts] or six-month PFS rate [GBM cohort]). Interim analyses and rules for stopping for futility are described in Section 11 and in the Report and Analysis Plan (RAP).

4.6.5. Part 3 [Active in all regions, except France]

Part 3 is a dose-escalation study using a continuous assessment approach, a well-validated method to identify safety and toxicity of a given regimen. While efficacy, PK, and PD will be collected in the course of this part, these will not be primary endpoints. However, all available data will be used to identify a recommended dose for further evaluation in future clinical studies.

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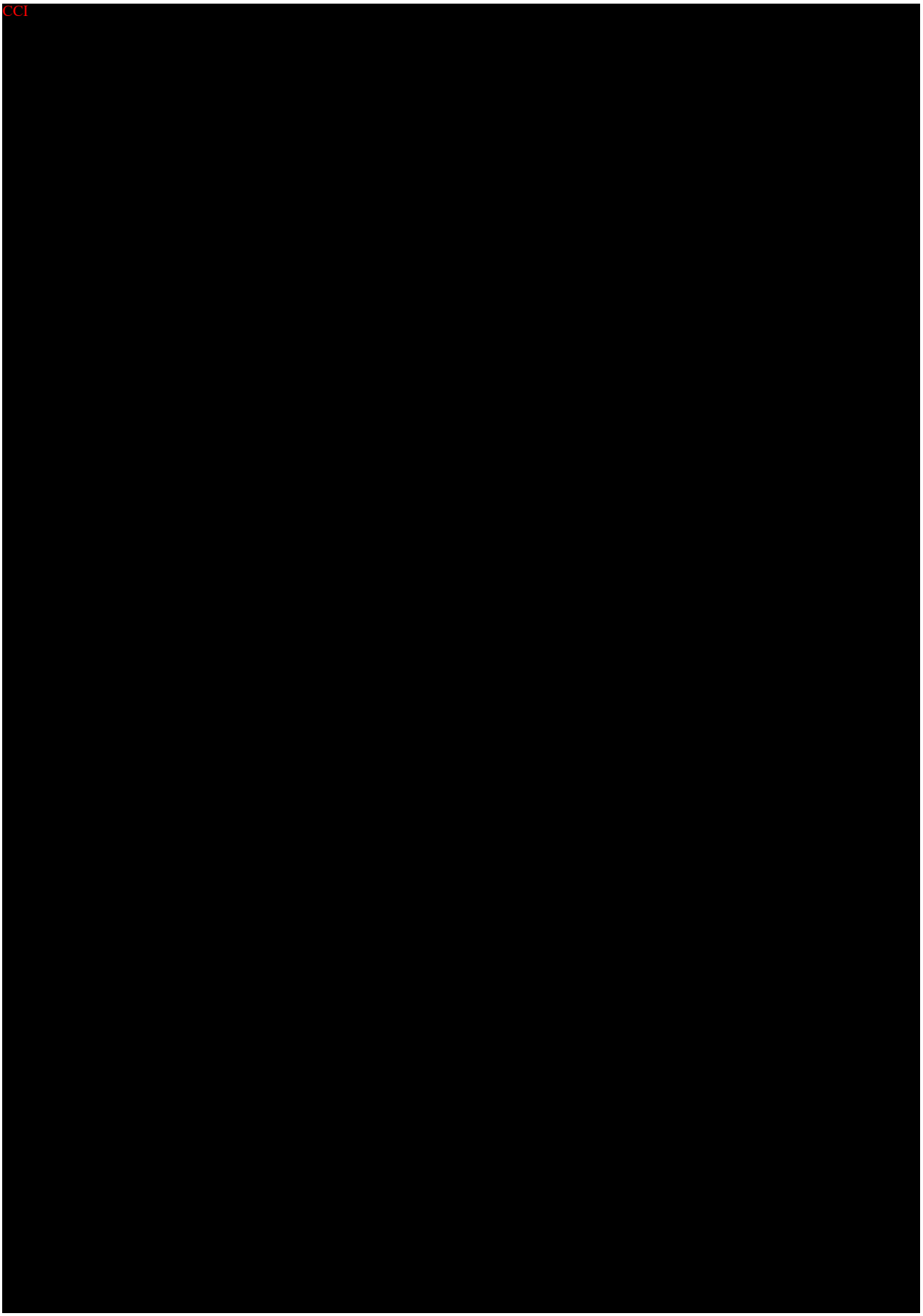

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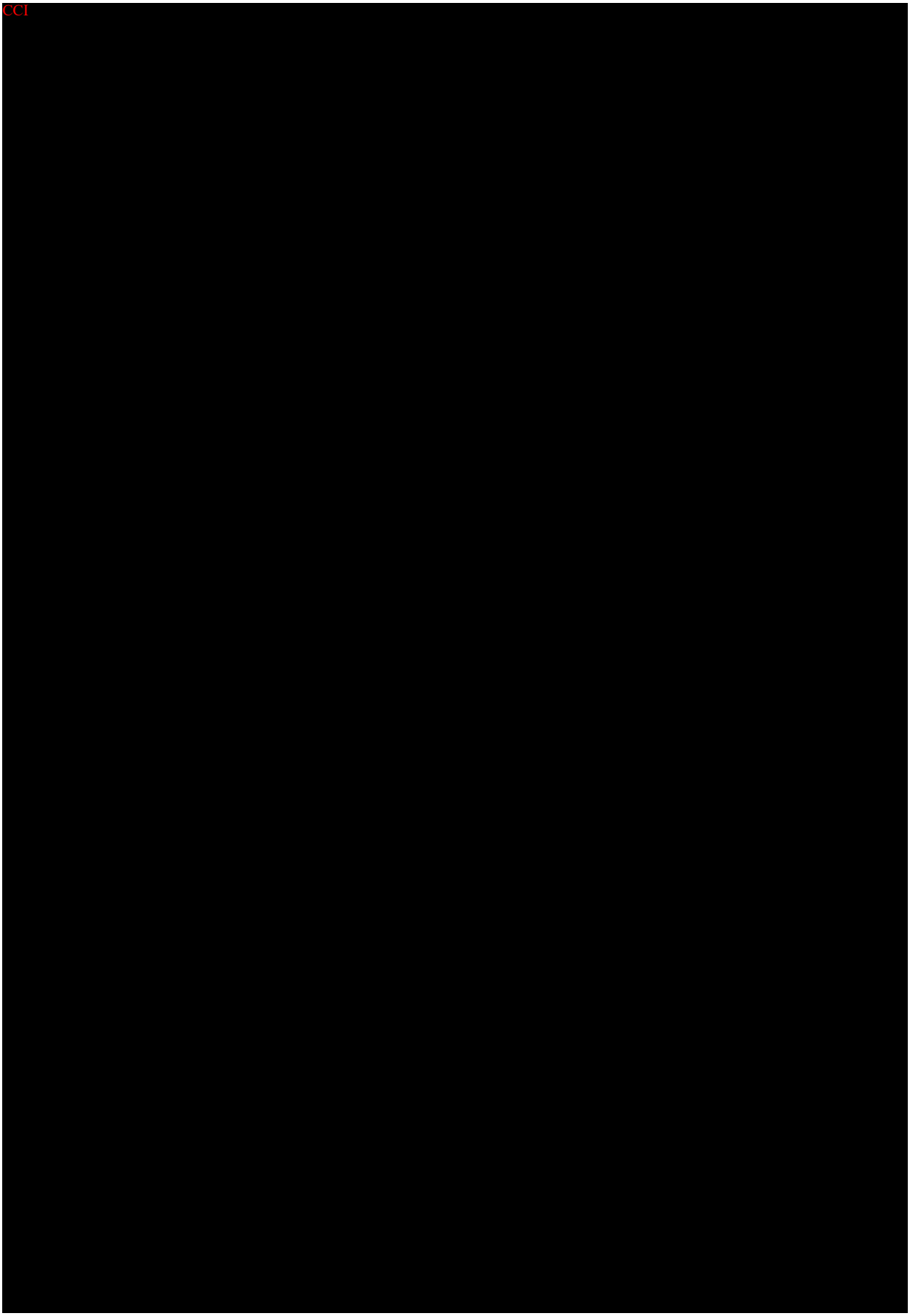

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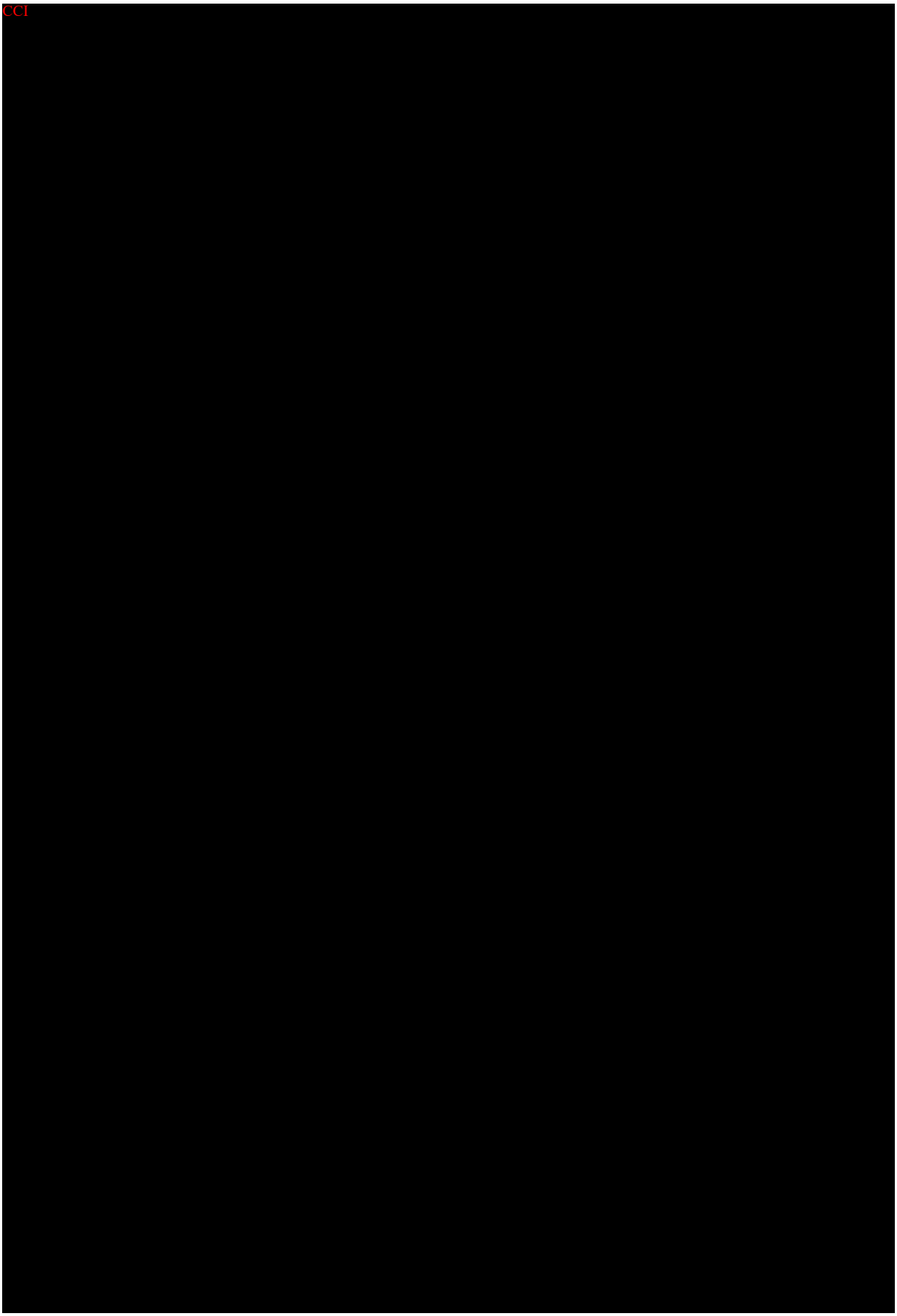

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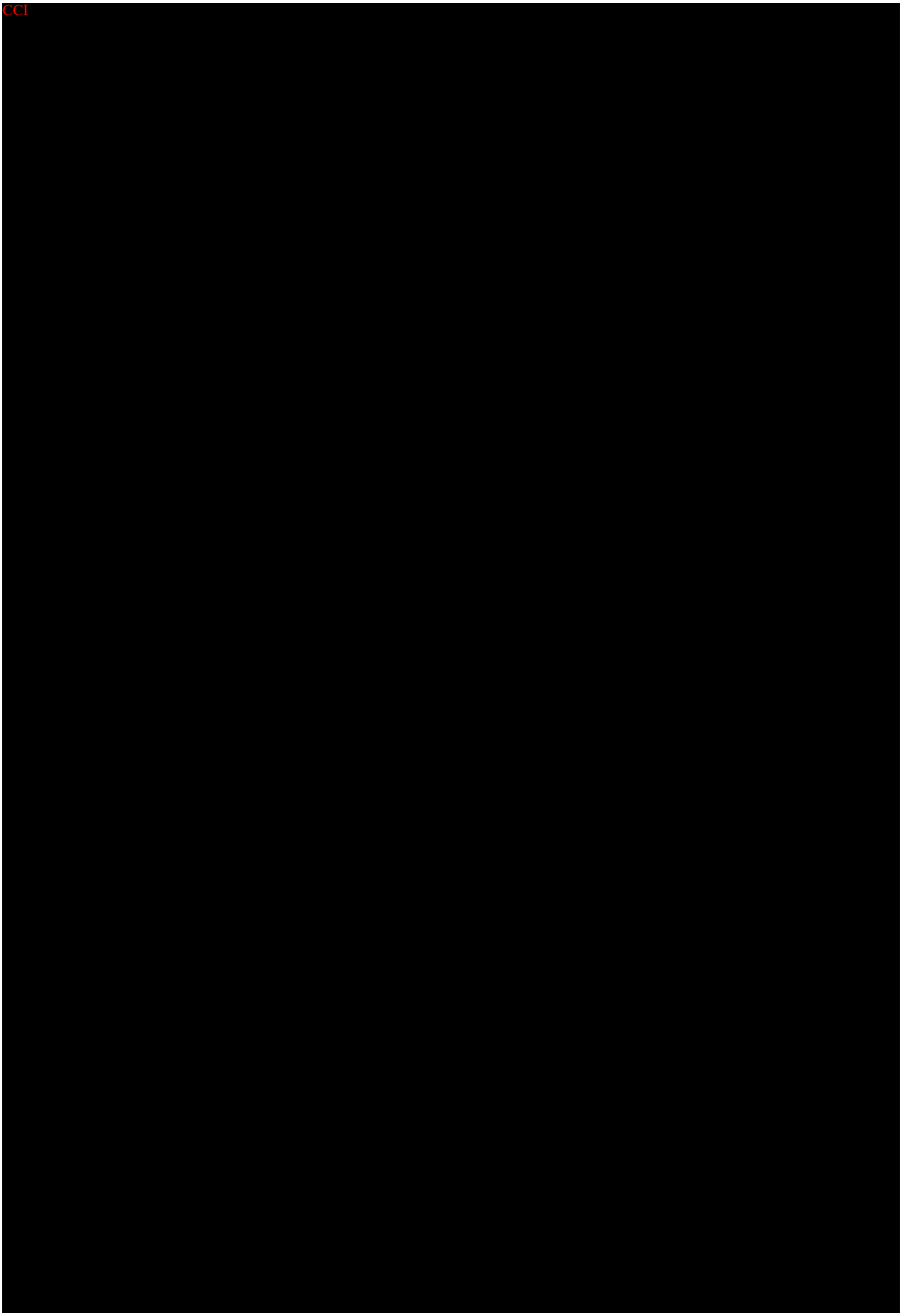

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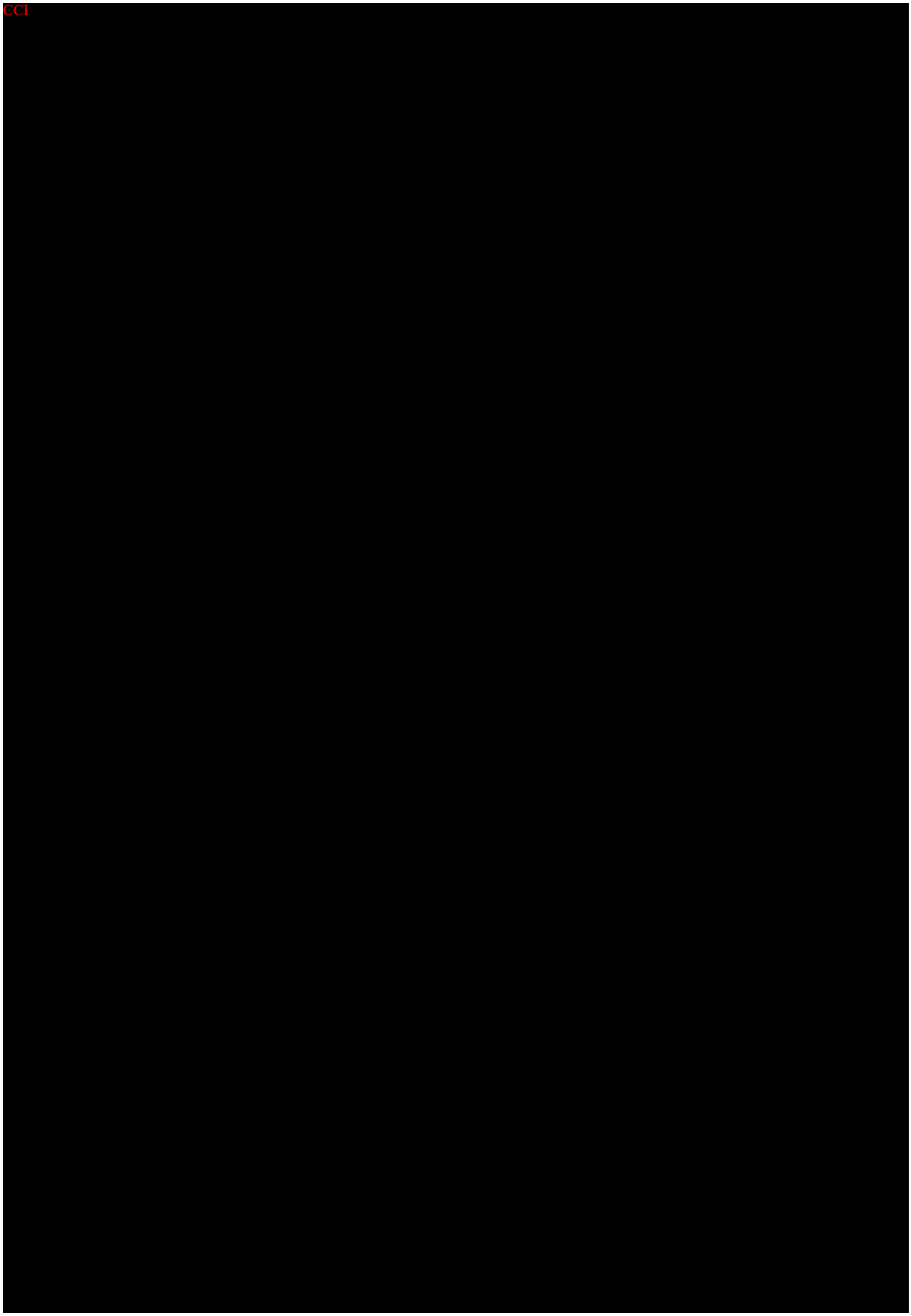

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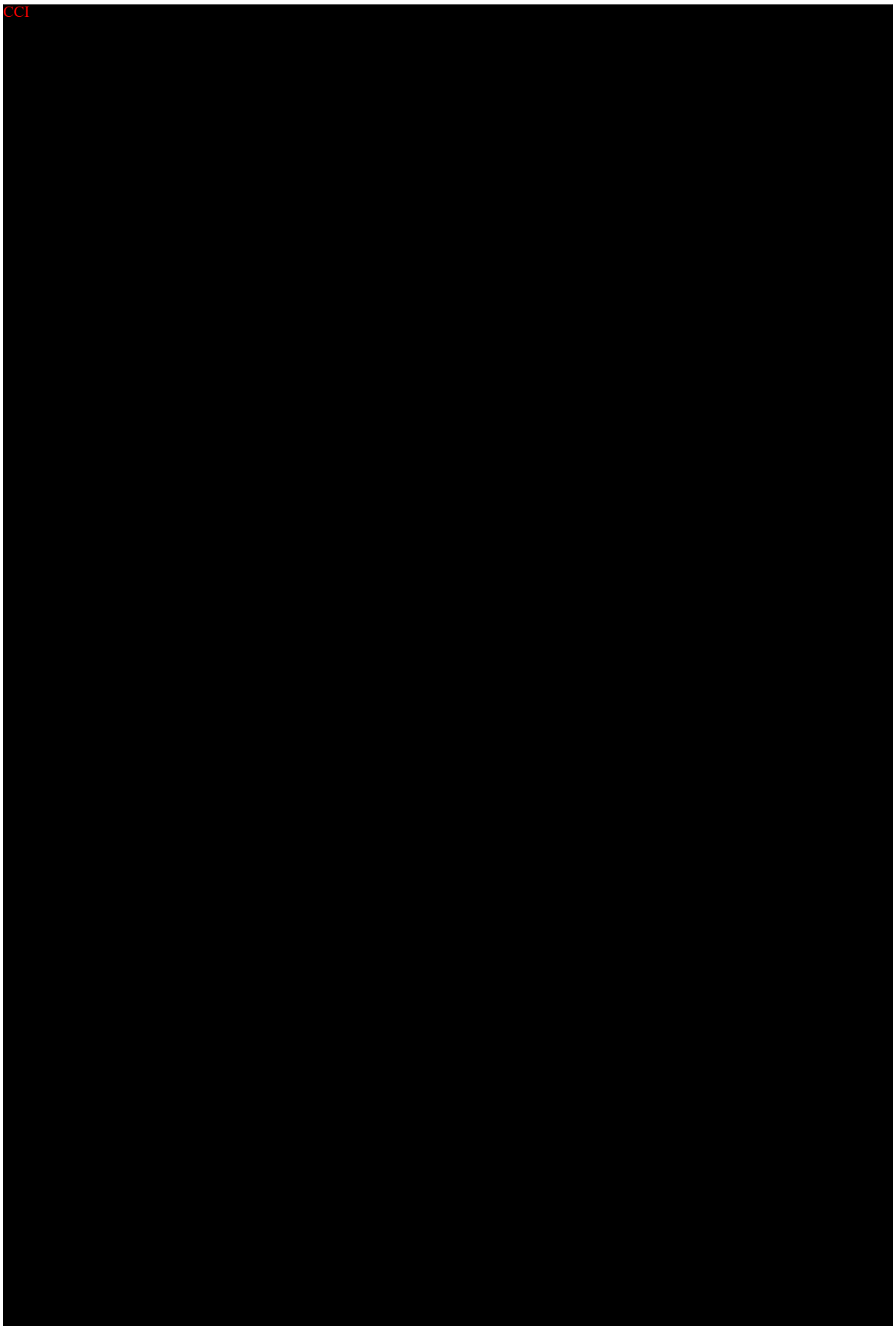

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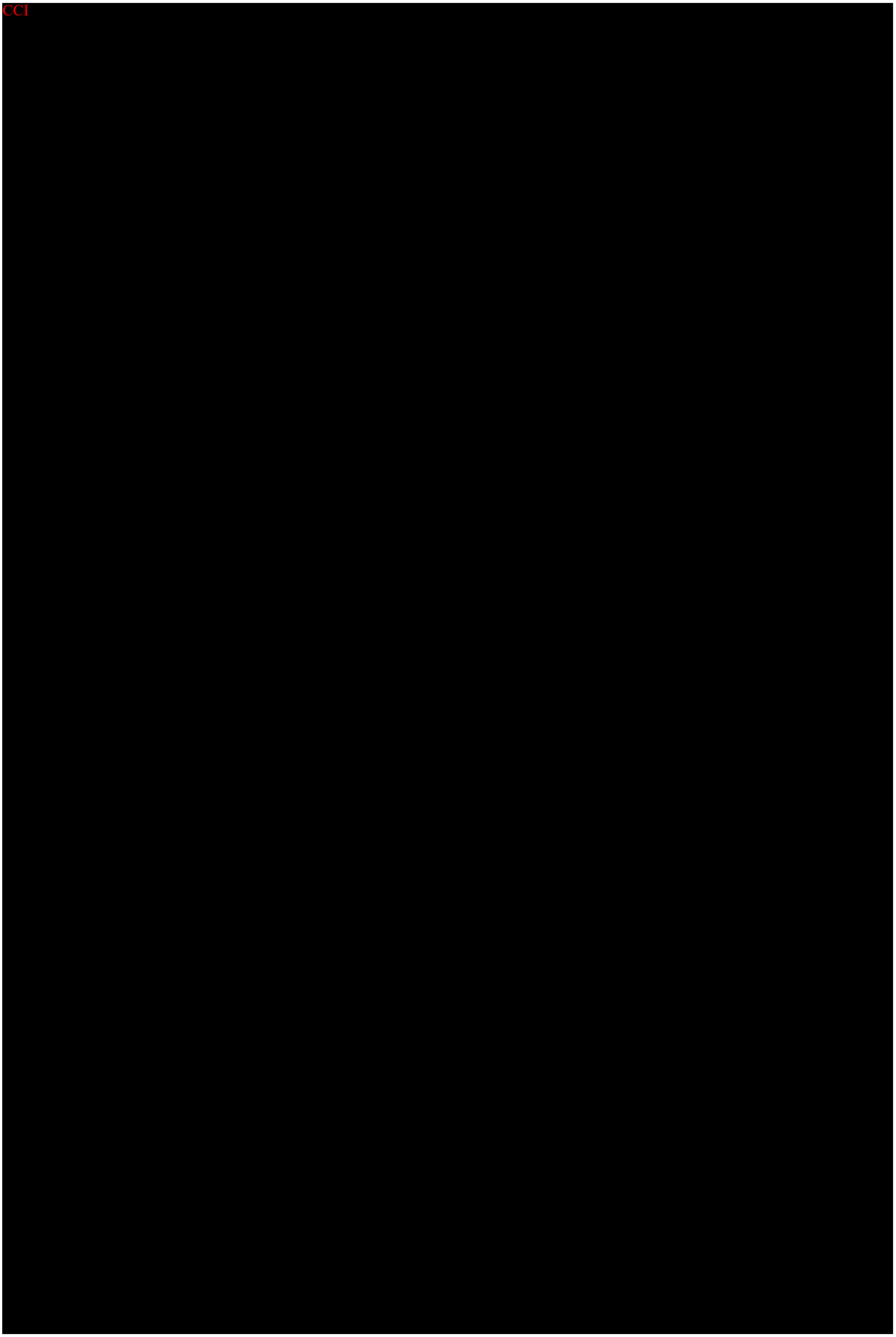

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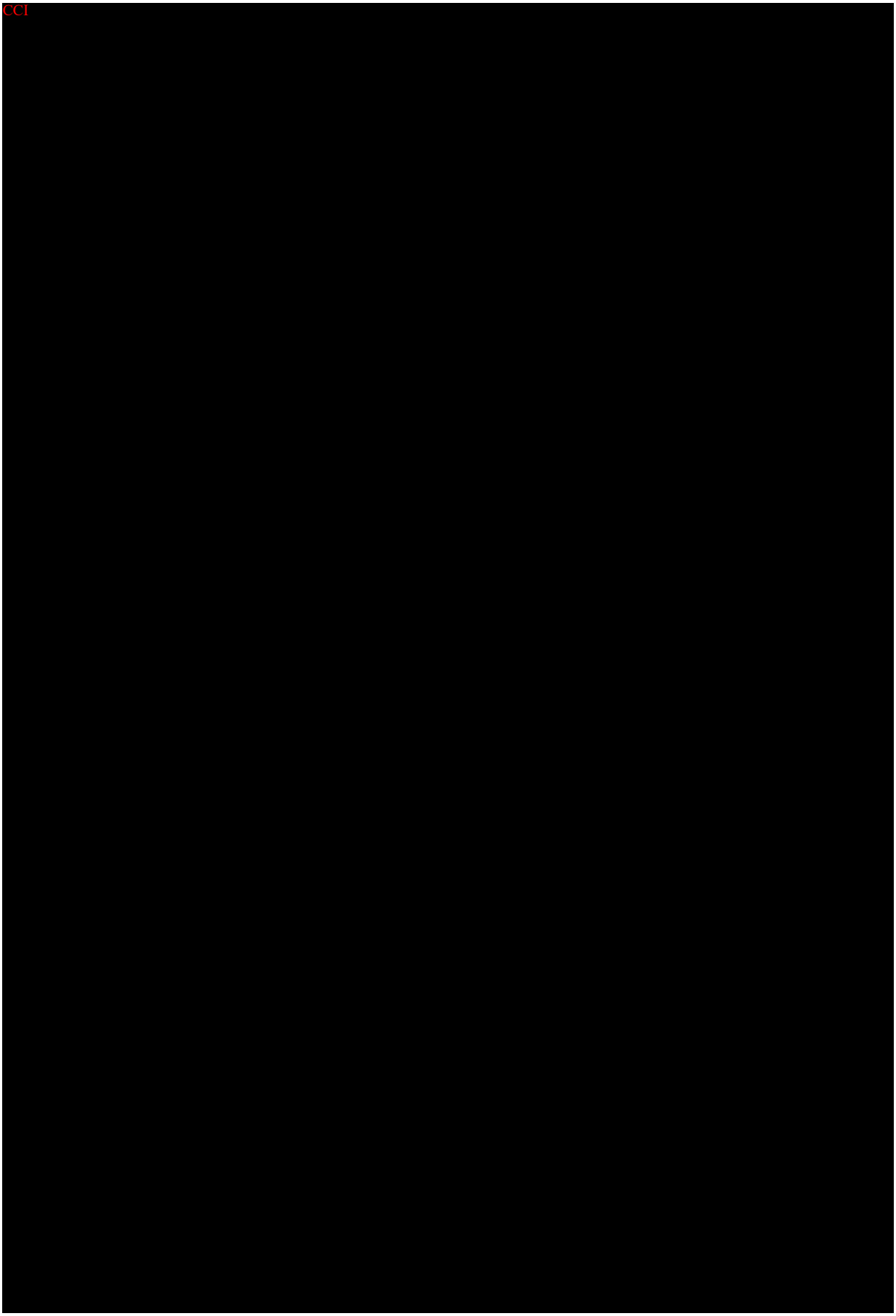

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5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB/IB supplement(s).

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. Males and females ≥18 years of age (at the time consent is obtained)
   NOTE: For NHL cohort ONLY, subjects must be ≤75 years of age at the time consent is obtained
2. Capable of giving signed informed consent
3. Able to swallow and retain orally-administered medication
4. Eastern cooperative oncology group (ECOG) performance status (defined in Appendix 3) of 0 to 2
5. Diagnosis of one of the following:
   a. Part 1: Histologically- or cytological-confirmed diagnosis of non-resectable or metastatic solid malignancy that has progressed on prior therapy (radiographic documentation of progression is adequate for study participation)
   b. Part 2: Histologically- or cytologically-confirmed diagnosis of metastatic or non-resectable disease that has progressed on or after prior therapy (ACC tablet

cohort does not require prior therapy for enrollment; for all tumors, radiographic documentation of progression is adequate for study participation):

- TNBC [estrogen receptor negative (ER-), progesterone receptor negative (PR-) and human epidermal growth factor receptor 2 negative (Her2-), as defined by local laboratory standards];
- ER+BC [estrogen receptor positive (ER+) or progesterone receptor positive (PR+), human epidermal growth factor receptor 2 negative (Her2-), as defined by local laboratory standards];
  NOTE: Subjects in this cohort must have previously received therapy with a cyclin-dependent kinase (CDK) 4/6 inhibitor or be considered ineligible to receive therapy with these agents
- metastatic or non-resectable transitional cell carcinoma of the bladder, ureter, or renal pelvis;
- recurrent GBM;
  NOTE: Subjects with prior low-grade glioma with subsequent imaging demonstrating progression to GBM may be enrolled without confirmatory biopsy on a case-by-case basis after discussion with the medical monitor
- ACC requiring systemic therapy. In order to be eligible for enrolment, ACC subjects must:
  - have shown progression by local evaluation of scans, as per RECIST 1.1, within the 13 months prior to enrolment, AND
  - have measurable disease, as confirmed by independent central review of baseline scans prior to first dose.
- HPV-positive solid tumor of any primary histology
  NOTE: HPV-positive status may be determined locally via any generally accepted test [e.g., HPV DNA OR p16 immunohistochemistry]. A minimum of 10 subjects must be enrolled with cervical cancer;
- non-Hodgkin's lymphoma that is NOT one of the following subtypes, as determined by local laboratory testing:
  - Burkitt's lymphoma or other high-grade lymphoma
  - Double- or triple-hit large B-cell lymphoma
    NOTE: Any questions regarding eligibility of subtypes should be directed to the medical monitor
- OR NSCLC, of any histologic sub-type; with local mutational analysis demonstrating wild-type status of TP53 (i.e., p53 wild-type NSCLC)
  NOTE: Subjects in the cohort must have previously received treatment with an anti-PD1 and/or PD-L1 therapy or be considered ineligible to receive therapy with these agents
  NOTE: Subjects whose tumors harbor actionable mutations (e.g., EGFR mutations or ALK rearrangements) must have received prior therapy with targeted agents prior to enrollment.

c. Part 3: Histologically- or cytologically-confirmed diagnosis of metastatic or non-resectable NSCLC (of any histologic sub-type), mTCC, HNSCC, or melanoma that failed to respond to prior treatment with PD-1 or PD-L1 targeted therapy and recurrent/metastatic cervical squamous cell carcinoma that have progressed on or after PD-1 or PD-L1 directed therapy or are PD-1/PD-L1 treatment naïve.

- NOTE: NSCLC, mTCC, HNSCC or Melanoma Subjects must have had SD (with subsequent documented progression as per iRECIST) or PD as best response to prior PD-1 or PD-L1 targeted therapy to be eligible for enrollment.

6. Prior therapy
    - ACC tablet cohort: subjects must be systemic therapy-naïve. Prior surgery and/or radiation is permitted
    - NHL cohort: subjects may have received up to 4 prior lines of systemic therapy for disease
    - Tumors with actionable mutations (e.g., BRAF V600E in melanoma; EGFR mutations or ALK rearrangements in NSCLC) must have received prior therapy with targeted agents prior to enrollment
    - Apart from ACC tablet cohort, subjects must have received at least one line of prior systemic therapy (or have a disease for which no approved therapy exists), AND have no standard-of-care therapy that would be expected to achieve a durable clinical response, OR refuse standard therapy, OR are not candidates for standard therapy.
7. Evaluable disease
    a. During Part 1, evaluable disease is required; measurable disease per RECIST v1.1 is recommended but not required
    b. Subjects enrolled in Part 2 and Part 3 must demonstrate measurable disease per the disease-specific criteria described in Appendix 4.
8. PK/PD/biomarker/metabolite expansion cohort(s) only (Section 4.2.5): Subjects must consent to pre- and post-dose tumor biopsies and additional sample collection procedures as specified in the Time and Events Table (Section 8.1).
9. Food effect and relative bioavailability sub-study only (Section 4.2.6): Subjects must consent to additional procedures as specified in the Time and Events Table (Table 13).
10. Part 3 only: Subjects must consent to additional procedures (including paired biopsies) as specified in the Time and Events Table (Table 15)
11. All prior treatment-related toxicities must be NCI-CTCAE v4 ≤ Grade 1 (except alopecia [permissible at any Grade] and peripheral neuropathy [which must be ≤ Grade 2]) at the time of treatment allocation.
    NOTE: Subjects with treatment-related toxicities that are unlikely to resolve in the opinion of the treating physician may be enrolled on a case-by-case basis after discussion with the medical monitor
12. Adequate organ function, as defined in Table 7:

Table 7 Definitions for Adequate Organ Function

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥1.5 X 10^9/L
Hemoglobin[a]	Solid malignancy: ≥9 g/dL Non-Hodgkin's Lymphoma: ≥8 g/dL
Platelets[a]	Solid malignancy: ≥100 X 10^9/L Non-Hodgkin's Lymphoma: ≥75 X 10^9/L,
PT/INR and PTT	≤1.5 X upper limit of normal (ULN), unless subject is receiving systemic anticoagulation
Hepatic	
Albumin	≥2 g/dL
Total bilirubin	≤1.5 x X ULN **NOTE**: Isolated bilirubin >1.5 X ULN is acceptable if: • bilirubin is fractionated and direct bilirubin <35% OR • subject has a diagnosis of Gilbert's syndrome
Alanine aminotransferase (ALT)	≤2.5 × ULN OR <5 x ULN is acceptable for subjects with documented liver metastases/tumor infiltration
Renal	
Estimated Glomerular filtration rate (eGFR)[b]	≥50 mL/min/1.73 m^2 **NOTE:** Participants with eGFR of <60 mL/min/1.73m^2 will require additional monitoring as described in Section 8.3.5.

a. Subjects with solid tumors that require transfusion or initiation of growth factor support in order to achieve necessary platelet and/or haemoglobin must maintain adequate values for at least 7 days without transfusion or while on growth factor in order to be eligible for participation
Subjects with NHL may receive transfusions and/or growth factor support in order to achieve necessary platelet and/or haemoglobin values.

b. Estimated GFR should be calculated using the Chronic Kidney Disease Epidemiology Collaborative (CKD-Epi) method. Details are provided in Appendix 5. Glomerular filtration rate (GFR) may also be directly determined via 24-hour urine creatinine clearance or other equivalent method

NOTE: Laboratory results obtained during Screening should be used to determine eligibility criteria. In situations where laboratory results are outside the permitted range, the investigator may opt to retest the subject and the subsequent within range screening result may be used to confirm eligibility.

13. Reproductive criteria:

    a. A male subject with female partner of child bearing potential must agree to use one of the methods of contraception specified in Section 7.3.2 for the duration specified in that section.

b. A female subject is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotrophin [hCG] test), not nursing, and at least one of the following conditions applies:

- Reproductive potential: subject must agree to follow one of the options and the duration specified in Section 7.3.1.

- Non-reproductive potential defined as:
- Pre-menopausal females with one of the following:
- Documented tubal ligation
- Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
- Hysterectomy
- Documented Bilateral Oophorectomy
- Postmenopausal defined as 12 months of spontaneous amenorrhea with an appropriate clinical profile or females over 60 years of age. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. Malignancy attributed to prior solid organ transplant
2. Leptomeningeal disease, spinal cord compression, or brain metastases that require immediate CNS-specific treatment in the opinion of the Investigator (e.g., for symptomatic disease).

   NOTE: Subjects who require local therapy for CNS metastases may be considered for eligibility once local therapy is completed and acute treatment-related toxicities have resolved

   NOTE: Subjects with untreated lesions should be followed with intracranial imaging (e.g., MRI) at each disease assessment, as detailed in Section 8.1.

   NOTE: This criterion does not apply to subjects with GBM. In Part 1, subjects with GBM may enroll provided that they are on a stable to decreasing dose of corticosteroids for at least 14 days prior to the first dose of GSK3326595. In Part 2, subjects with GBM may enroll irrespective of steroid dose.
3. Recent prior therapy, defined as follows:

   - Any non-monoclonal anti-cancer therapy within 14 days or 5 half-lives, whichever is longer, prior to the first dose of GSK3326595. Any nitrosoureas or mitomycin C within 42 days prior to the first dose of GSK3326595. Prior therapy with biologic agents (including monoclonal antibodies) is permitted so long as 28 days have elapsed since therapy and all therapy-related AEs have resolved to ≤ Grade 1, with the exception of those listed in Section 4.2.4.2. Note that subjects

with immunotherapy-related endocrinopathies, currently managed with replacement therapy, will be allowed on study.

- Any radiotherapy within 14 days or major surgery within 28 days prior to the first dose of GSK3326595. For subjects in the GBM cohort, subjects must have completed radiation therapy at least 28 days prior to the first dose of GSK3326595.
- Anti-androgen therapies for prostate cancer, such as bicalutamide, must be stopped 4 weeks prior to enrollment. Second-line hormone therapies such as enzalutamide or abiraterone should be stopped 2 weeks prior to enrollment. Subjects with prostate cancer should remain on luteinizing hormone releasing hormone (LHRH) agonists or antagonists. Subjects with prostate cancer may also remain on low-dose prednisone or prednisolone (up to 10 mg/day) and still be eligible for this study.

4. Part 3 only: History of any of the following:
   - Recent history (within the past 2 years) of autoimmune disease or syndrome that required systemic treatment
     Note: Replacement therapies which include hormone replacement (e.g., thyroid hormone) or physiological doses of corticosteroids for treatment of endocrinopathies (e.g., adrenal insufficiency) are not considered systemic treatments.
   - A diagnosis of immunodeficiency or administration of systemic steroids (≥10 mg oral prednisone or equivalent) or other immunosuppressive agents within 7 days prior to randomization
     Note: Physiologic doses of corticosteroids for treatment of endocrinopathies or steroids with minimal systemic absorption, including topical, inhaled, or intranasal corticosteroids may be continued if the participant is on a stable dose. Steroids as premedication for hypersensitivity reactions (e.g., computed tomography [CT] scan premedication) are permitted.
   - Receipt of any live vaccine within 30 days prior randomization
   - Prior allogeneic/autologous bone marrow or solid organ transplantation
   - Current pneumonitis or history of non-infectious pneumonitis that required steroids or other immunosuppressive agents
     Note: post-radiation changes in the lung related to prior radiotherapy and/or asymptomatic radiation-induced pneumonitis not requiring treatment (Grade 1) may be permitted if agreed upon by the investigator and Medical Monitor.
   - Recent history of allergen desensitization therapy within 4 weeks of randomization
   - History of severe hypersensitivity to monoclonal antibodies
5. History of a second malignancy, excluding non-melanoma skin cell cancer, within the last three years. Subjects with second malignancies that were indolent, *in situ* or definitively treated may be enrolled even if less than three years have elapsed since

treatment. Consult the GSK Medical Monitor if there are questions whether second malignancies meet the requirements specified above.

6. Current use of a prohibited medication or planned use of any forbidden medications during treatment with GSK3326595 (see Section 7.1.2 for the list of medications).
7. Evidence of severe or uncontrolled systemic diseases (e.g., unstable or uncompensated respiratory, hepatic, renal, cardiac disease, or clinically significant bleeding episodes). Any serious and/or unstable pre-existing medical (aside from malignancy), psychiatric disorder, or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures, in the opinion of the Investigator.
8. Any clinically significant gastrointestinal (GI) abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach and/or bowels.
9. History of known human immunodeficiency virus (HIV) infection or positive HIV test result at screening. **NOTE:** HIV – Patients may be eligible if they fullfill all of the requirements below: Have started on antiviral therapy for at least 4 weeks prior to start of study drug treatment, Not be taking HIV related therapy (antivirals, antibiotics) that is on the prohibited list per protocol, Have a CD4 count ≥350 cells/uL, Have a HIV viral load <400 copies/ml.
10. Presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test result at screening.

    NOTE: Subjects with chronic hepatitis B virus (HBV) infection, who meet the criteria for anti HBV therapy may be eligible if subject is on a suppressive antiviral therapy prior to initiation of cancer therapy.

    NOTE: Subjects with positive Hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative Hepatitis C RNA polymerase chain reaction (PCR) is obtained. Also Hep C - Patients may be eligible if they have both: completed curative therapy, have a HCV viral load <quantifiable limit.
11. Any of the following cardiac abnormalities:
    - Recent history (within 6 months of first dose of study drug) of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting
    - Presence of a cardiac pacemaker
    - Baseline Corrected QT (Fridericia's formula) interval (QTcF) ≥450 msec
    - Uncontrolled arrhythmias. Subjects with rate-controlled atrial fibrillation for > 1 month prior to first dose of study drugs may be eligible.
    - Class II, III or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system.
12. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.

13. History of optic nerve neuropathy or neuritis.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently enrolled. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events.

5.4. Withdrawal/Stopping Criteria

5.4.1. Discontinuation of Study Treatment

Subjects will receive study treatment until disease progression, death or unacceptable adverse event, including meeting stopping criteria for liver chemistry, hematologic/non-hematologic toxicity, or corrected QT interval duration (QTc) prolongation, as defined in Section 5.4.5 through Section 5.4.7.

In addition, study treatment may be permanently discontinued for any of the following reasons:

- deviation(s) from the protocol
- request of the subject or proxy
- investigator's discretion
- subject is lost to follow-up
- study is closed or terminated.
- study drug is no longer available

Note that discontinuation from study treatment does NOT equal complete withdrawal from the study (all efforts should be made to keep subjects with a diagnosis of ACC who withdraw from treatment on study for survival follow-up).

Subjects in Part 3 may be treated past progression as described in Section 14.4.4.

Subjects in Parts 1 and 2 with equivocal progression or with rising tumor markers in the absence of radiographic progression may continue on study therapy provided that safety related stopping criteria are not met.

Subjects in Parts 1 and 2 with progressive disease (PD) may remain on study on a case-by-case basis (e.g., as long as the Investigator and the GSK Medical Monitor concur that the subject could continue to receive benefit, the subject is not experiencing serious toxicity, and there is no alternative treatment that is likely to benefit the subject). Discussion between the Investigator and the Medical Monitor must occur in order for a subject to continue study treatment once PD has been confirmed. Subjects who continue on study beyond confirmed progression should continue to undergo all assessments described in the Time and Events Table. Subjects who demonstrate continued progression

at subsequent scheduled scans may be required to discontinue therapy at the discretion of the Investigator and the Medical Monitor.

For subjects in all Parts of the study, the primary reason study treatment was permanently discontinued must be documented in the subject's medical records and electronic case report form (eCRF).

If the subject voluntarily discontinues from treatment due to toxicity, 'adverse event' will be recorded as the primary reason for permanent discontinuation on the eCRF.

Once a subject has permanently discontinued from study treatment, the subject will not be allowed to be retreated.

All subjects who discontinue from study treatment will have safety assessments at the time of discontinuation and during post study treatment follow-up as specified in Time and Events Tables (see Section 8.1).

Any subject in the ACC tablet cohort who has not yet shown objective radiological disease progression at treatment discontinuation should be continued to be followed as per RECIST 1.1 for radiological progression.

All subjects who permanently discontinue study treatment will be followed for survival and new anti-cancer therapy (including radiotherapy) every 6 months until death or termination of the study by the sponsor. If subjects are unable or unwilling to attend clinic visits during follow-up, the investigator should inform the subject of modified follow-up options (eg, telephone call, email, contact with a relative or treating physician, or information from medical records).

Note: following Protocol Amendment 7, survival follow-up should only be conducted for subjects with a diagnosis of ACC.

Following Protocol Amendment 8 implementation, all recruited subjects who no longer receive study treatment will be considered to have completed the study and only subjects still deriving benefit from GSK3326595 as assessed by the Investigator may continue to receive study treatment.

5.4.2. Lost to Follow-up

A subject will be considered potentially lost to follow-up if he fails to return for scheduled visits and is unable to be contacted by study sites.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last

known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

Efforts to reach the subject should continue until the end of the study. Should the subject continue to be unreachable at the end of the study, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

5.4.3. Withdrawal from the study

A subject may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral or administrative reasons, as described above.

If a subject withdraws consent, the investigator/site staff must specifically ask if they are withdrawing consent to:

- Further participation in the study including any further follow-up (eg, survival calls, consultation of medical records for vital status)
- Further participation in study assessments *excluding* survival follow-up [relevant for Part 2 and Part 3 subjects only] (eg, survival calls, consultation of medical records for vital status)
- The use of optional and/or mandatory biological samples that have not already been analysed (remaining unanalyzed samples must be destroyed)

The investigator must document consent withdrawal in the site study records and CRF.

If the subject has actively withdrawn consent to the processing of their personal data, the vital status of the subject can be obtained by site personnel from publicly available resources, where it is possible to do so under applicable local laws.

Following Protocol Amendment 8 implementation, all recruited subjects who no longer receive study treatment will stop entirely and only subjects still deriving benefit from GSK3326595 as assessed by the Investigator may continue to receive study treatment. At the point of discontinuation of study treatment (including 30-day safety follow up), subjects will be considered to have completed the study. If a subject withdraws consent, the investigator/ site staff must document consent withdrawal in the site study records.

5.4.4. End of Survival Follow-up

In Part 2 or Part 3 (whichever is latest), unless a disease cohort is closed early, survival follow-up will continue in each cohort until approximately 70% of the total number of subjects have progressed or died. At such time, the cohort will be closed and any further follow-up on subjects enrolled in that cohort will cease. Subjects with radiologically confirmed lack of disease progression who are still receiving GSK3326595 at the time of study completion may continue treatment through a separate mechanism (e.g., roll-over protocol).

Note: following Protocol Amendment 7, survival follow-up will only be conducted for subjects in Part 1 and Part 2 with a diagnosis of ACC. Survival follow-up with continue until approximately 70% of ACC subjects have died.

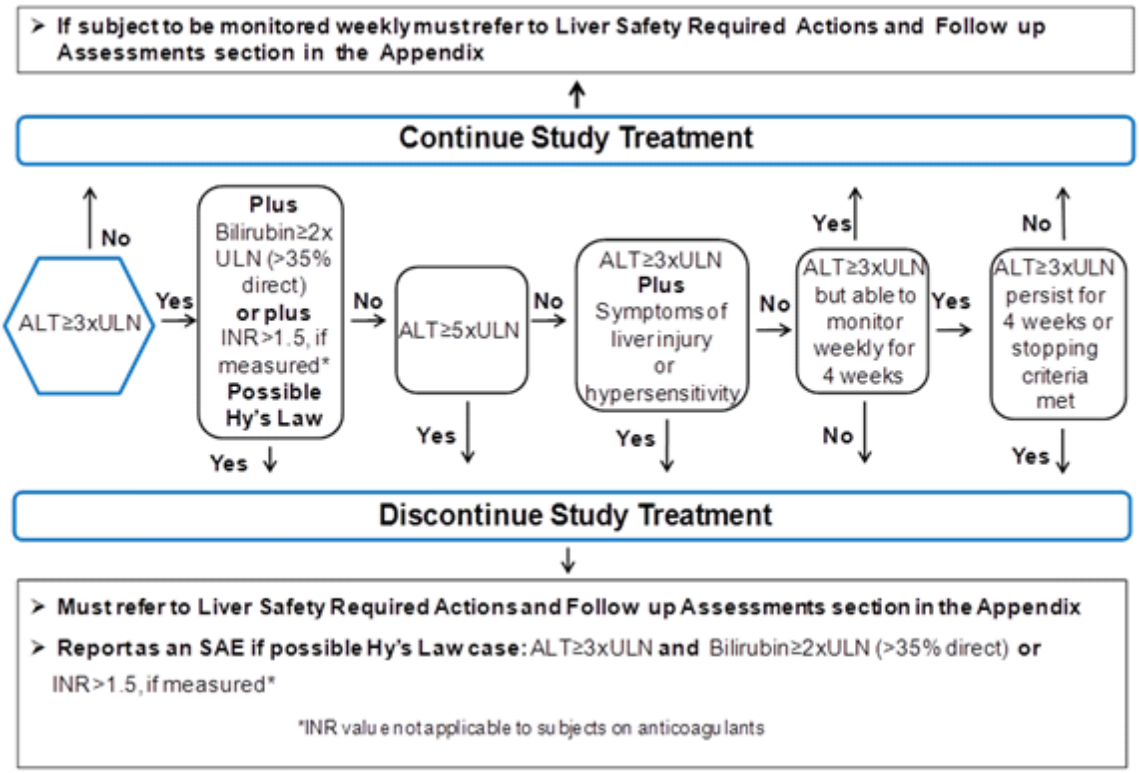
Following Protocol Amendment 8 implementation, all recruited subjects who no longer receive study treatment will stop entirely and only subjects still deriving benefit from GSK3326595 as assessed by the Investigator may continue to receive study treatment.

5.4.5. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance [www.fda.gov, 2009]).

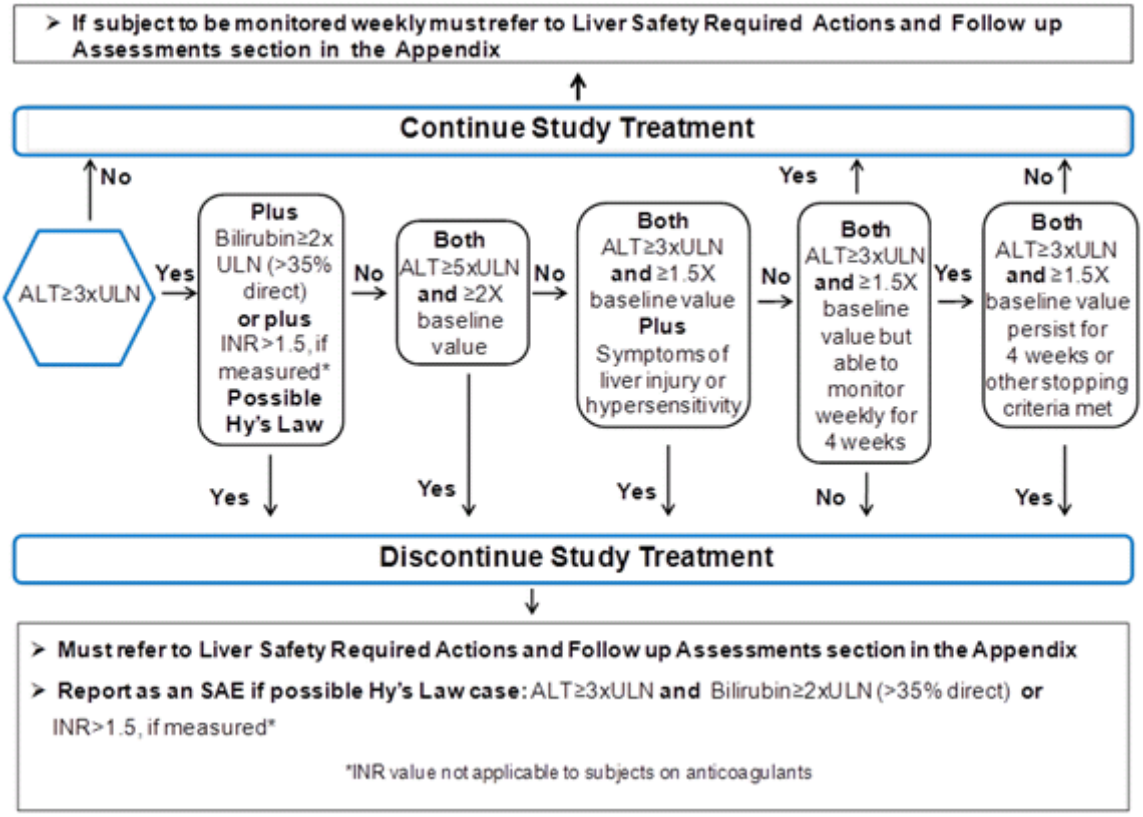
See Figure 5-1 and Figure 5-2 for liver stopping criteria for subjects without and with liver metastases, respectively.

Figure 5-1 Phase I/II Liver Chemistry Stopping and Increased Monitoring Algorithm for Subjects WITH entry criteria ALT ≤2.5xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6.

Figure 5-2 Phase I/II Liver Chemistry Stopping and Increased Monitoring Algorithm including Subjects WITH documented liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5xULN but ≤5xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6.

5.4.5.1. Study Treatment Restart or Rechallenge

If subject meets liver chemistry stopping criteria do not restart/rechallenge subject with study treatment unless:

- GSK Medical Governance approval is granted
- Ethics and/or institutional review board (IRB) approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

  Refer to Appendix 7 for full guidance.

5.4.6. QTc Stopping Criteria

If a subject meets the corrected QT (QTc) interval duration criteria below, study treatment(s) will be withheld.

- QTcF interval ≥ 500 msec OR interval increase from baseline ≥ 60 msec: GSK3326595 will be discontinued unless the benefits of therapy outweigh the risk of rechallenge in the opinion of the investigator, the GSK Medical Monitor, as well as the GSK medical governance. In this situation, rechallenge may be permitted (see Appendix 2 for rechallenge guidelines).

NOTE: In order to determine whether QT interval meets stopping criteria, the QT interval duration criteria should be based on the average QTc value of triplicate electrocardiograms (ECGs), including manual over-read. Routine ECG monitor does not require triplicate measurement. However, if an ECG demonstrates a prolonged QT interval, obtain 2 additional ECGs over a brief period (e.g., within approximately 10 minutes of the abnormal ECG, if possible, and approximately 10 minutes apart from each other), and then use the averaged QTc values of the 3 ECGs to determine whether the subjects should have study treatment discontinued.

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

- For eligibility and withdrawal, QTcF will be used for all subjects.
- For purposes of data analysis, QTcF will be used.

5.4.7. Other Stopping Criteria

Stopping criteria for hematologic toxicities are detailed in Table 24. To monitor for hematologic toxicity, CBCs will be drawn weekly for the first three weeks of study, and then every three weeks, as described in the Time and Events table. Subjects who develop Grade 2 or greater anemia or thrombocytopenia may be monitored more frequently, as clinically indicated. Please see Appendix 2 for suggested management of hematologic toxicity.

Safety will be reviewed on an ongoing basis by the Safety Review Team (SRT) which will be compromised of, at a minimum, a GSK medical monitor, GSK Global Safety representative, and GSK clinical study representative (including a representative from Biostatistics). Deaths, SAEs, and Grade 3/4 adverse events will be carefully evaluated for the possibility of causality.

If clinically significant adverse events or toxicities are observed in more than one third of the subjects, and/or if deaths related to study drug are observed, enrollment may be terminated and/or a lower-dose cohort may be opened or expanded.

5.5. Subject and Study Completion

In Part 1, a subject who is not treated with the RP2D will be considered to have completed the study if:

- they complete screening assessments, at least 21 days of study treatment and the post-treatment follow-up visit, or
- they discontinue study treatment for progression or reasons listed in Section 5.4.

A subject who is treated at RP2D will be considered to have completed the study if:

- they discontinue study treatment for reasons listed in Section 5.4, or
- they die while receiving study treatment, or
- are receiving ongoing study treatment at the time of the Sponsor's decision to close the study/perform the final analysis.

In Part 2 and Part 3, a subject will be considered to have completed the study if:

- they withdraw consent to any further study participation
- they die while on study treatment or during the survival follow-up
- they are ongoing on study at the time of the Sponsor's decision to close the study/perform the final analysis.

The end of the study is defined as the completion of all cohorts as defined in 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.

Final Last Subject Last Visit will be defined as patient's treatment discontinuation (including 30-day safety follow up).

Following Protocol Amendment 8, the end of this study is defined as the date of the last visit of the last subject undergoing the study.

A final DCO, closure of the study database and final analysis 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 this amendment. When the Protocol Amendment 8 is implemented at a site, the collection of data for all enrolled subjects who no longer receive study treatment will stop entirely. Those subjects still benefiting from GSK3326595 in the opinion of their treating Investigator may continue to receive study treatment until the end of availability of study drug which is anticipated to be Q3 2023.

6. STUDY TREATMENT

6.1. GSK3326595 and Pembrolizumab

The term 'study treatment' is used throughout the protocol to describe GSK3326595 (or GSK3326595 plus pembrolizumab for subjects in Part 3) received by the subject as per the protocol design. Post Protocol Amendment 8 implementation, study drug GSK3326595 will be provided until the end of availability of study treatment, which is anticipated to be Q3 2023.

Study Treatment			
Product name:	GSK3326595 Capsules	GSK3326595 Tablets	Pembrolizumab

Study Treatment			
Product name:	GSK3326595 Capsules	GSK3326595 Tablets	Pembrolizumab
Dosage form:	Capsules	Tablet	Solution for infusion
Unit dose strength(s)/Dosage level(s):	100 mg as free base	100 mg as free base	100 mg/4 mL
Route of Administration	Oral		IV infusion
Dosing instructions:	The dosing regimen is detailed in Section 8.1 and is designed to permit collection of detailed safety and PK data. GSK3326595 is to be administered orally with water (approximately 200 mL) at approximately the same time of day (± 4 hours) with no food or antacids for 1 h before and 2 h after each dose. If a dose is delayed by more than 4 hours, the subject should not take that dose and should mark the dose as "not taken". On serial PK days and for two days prior (Days 13 through 16), subjects should attempt to take GSK3326595 within a 1 h window (i.e., 23-25 hours after the last dose). Capsules/tablets should not be chewed or crushed. If dose regimen requires more than one capsule/tablet per dose, the capsules/tablet should be taken one at a time.		Administer diluted product once Q3W (refer to SRM for infusion time)
Physical description:	Opaque white capsules (size 00)	White to almost white film coated tablets with no markings	Concentrate for solution for infusion, clear to slightly opalescent, colourless to slightly yellow solution, pH 5.2 – 5.8.
NOTE: These formulation details are current at the time of protocol finalization and may be updated in other documents (e.g., SRM and/or informed consent form) without requiring protocol amendment			

6.2. Treatment Assignment

Subjects will be assigned to receive GSK3326595, either as monotherapy (Part 1 and Part 2), or in combination with pembrolizumab (Part 3), in an open-label fashion. There will be no placebo arm. Subjects will be identified by a unique subject number that will remain consistent for the duration of the study.

6.3. Packaging and Labeling

GSK3326595 will be provided to the sites by GSK. The contents of the label will be in accordance with all applicable regulatory requirements.

Pembrolizumab will either be provided to the sites in cartons containing vials by GSK or will be sourced locally by the sites themselves. When provided by GSK, the contents of the label will be in accordance with all applicable regulatory requirements.

6.4. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required for GSK3326595. Refer to pembrolizumab prescribing information [KEYTRUDA PI, 2019] for relevant instructions.

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff. Please refer to guidance in the Study Reference Manual with regard to storage of IP and temperature excursion management.

- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (e.g., receipt, reconciliation, and final disposition records).

- Further guidance and information for final disposition of unused study treatment are provided in the SRM.

Precaution will be taken to avoid direct contact with the study treatment. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions for GSK3326595 will be provided to the investigator. In the case of unintentional occupational exposure notify the monitor, Medical Monitor or GSK study contact.

Limited exposure and precautionary action (example: wearing gloves, washing hands post exposure) should be taken by site staff dispensing GSK3326595.

6.5. Compliance with Study Treatment Administration

At each visit, an evaluation of subject compliance with taken medication will be performed. The investigator will make every effort to bring non-compliant subjects into compliance.

Compliance with GSK3326595 will be assessed through querying the subject during the site visits and documented in the source documents and CRF. A record of the number of GSK3326595 capsules/tablets dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.

Following Protocol Amendment 8 implementation, refer to SRM for dispensing of study treatment and drug accountability.

Pembrolizumab will be administered intravenously at site under medical supervision of an investigator or designee. The date and time of administration will be documented in the source documents and reported in the CRF.

6.6. Treatment of Study Treatment Overdose

For this study, any dose of GSK3326595 greater than the protocol-specified dose within a 24 hour time period (± 4 hours) will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose the investigator (or treating physician) should:

- Contact the Medical Monitor immediately
- Closely monitor the subject for AEs/SAEs and laboratory abnormalities until GSK3326595 can no longer be detected systemically (at least 28 days)
- Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis)
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

Post Protocol Amendment 8 implementation, overdoses are required to be reported to GSK via a paper process.

An overdose of pembrolizumab is defined as ≥1000 mg (5 times the dose) of pembrolizumab. In the event of a suspected overdose, it is recommended that the appropriate supportive clinical care be instituted as dictated by the participant's clinical status.

6.7. Treatment after the End of the Study

Post study treatment will not be provided as part of the protocol. Upon discontinuation from assigned study treatment, subjects may receive additional (non protocol) therapy at the discretion of the treating physician. New therapy should be documented on the CRF. Every effort should be made to complete the required withdrawal and follow up evaluations prior to initiating further therapy or dosing of an investigational agent (see Section 8.1 for follow-up assessments and procedures).

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment.

Subjects receiving GSK3326595 at the time of DCO date may continue to receive GSK3326595 under Protocol Amendment 8; GSK3326595 will be provided until the end of availability of study treatment, which is anticipated to be Q3 of 2023.

After the final DCO subjects may continue to receive GSK3326595 for as long as they derive clinical benefit from study treatment as assessed by the Investigator and do not meet any protocol-defined study treatment stopping criteria (maximum until the end of availability of study drug which is anticipated to be Q3 2023); subjects may choose to discontinue study treatment at any time.

7. MEDICATION, LIFESTYLE, AND DIETARY RESTRICTIONS

7.1. Concomitant Medications and Non-Drug Therapies

Subjects will be instructed to inform the investigator prior to starting any new medications from the Screening Visit until the end of the study (Final Study Visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF. The minimum requirement is that drug name, route of administration, dose and frequency of dosing, along with start and stop dates of administration should be recorded. Additionally, a complete list of all prior cancer therapies will be recorded in the eCRF.

Questions regarding concomitant medications should be directed to the GSK Medical Monitor for clarification.

If future changes are made to the list of permitted/prohibited medications, formal documentation will be provided by GSK and stored in the study file. Any such changes will be communicated to the investigative sites in the form of a letter.

7.1.1. Permitted Medications and Non-Drug Therapies

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with erythropoietin, antibiotics, antiemetics, antidiarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

Colony-stimulating factors like filgrastim and pegfilgrastim may be used in Month 2 and beyond as clinically indicated. The only caveat is that subjects should not receive those medications listed as prohibited in Section 7.1.2.1.

Bisphosphonates and denosumab will be allowed if subjects have been on a stable dose for at least three months prior to receiving the first dose of GSK3326595.

7.1.2. Prohibited Medications and Non-Drug Therapies

7.1.2.1. Prohibited Medications

Subjects should not receive other anti-cancer therapy [including chemotherapy, immunotherapy, biologic therapy, investigational therapy, or hormonal therapy (other

than leuprolide, other LHRH agonists/antagonists, or corticosteroids)] while on treatment in this study. Other anti-cancer therapy should not be administered unless one of the following occurs: documented disease progression; unacceptable or unmanageable toxicity; subject is withdrawn from the study at the investigator's discretion or consent is withdrawn; or no further clinical benefit is anticipated which requires permanent discontinuation of study drug.

NOTE: with the exception of other systemic anti-cancer therapies, any medication (including antibacterials, antifungals, or antivirals) which are necessary for the health, well-being, and standard clinical care of oncology patients are exempt from the restrictions below.

No *in vitro* CYP phenotyping data are available for GSK3326595. In the absence of these data, strong and moderate inhibitors or inducers of CYP isoenzymes should not be co-administered with GSK3326595. Any questions regarding co-administration of medications should be directed to the GSK medical monitor.

GSK3326595 was found to be a substrate for P-glycoprotein (P-gp) efflux transporters in bidirectional permeability assays using Continuous cell of heterogeneous human epithelial colorectal adenocarcinoma cells (Caco-2) and madine-darby canine kidney (MDCK)-II monolayers. GSK3326595 should not be co-administered with strong and moderate inhibitors of either P-gp. Such inhibitors include cyclosporine, tacrolimus, and ketoconazole. In addition, GSK3326595 is a substrate of MATE2-K, OAT3 and OCT2 uptake transporters; therefore, GSK3326595 should not be co-administered with strong and moderate inhibitors or inducers of MATE2-K, OAT3 and OCT2. Such inhibitors include, but are not limited to, cimetidine, probenecid, pyrimethamine, metformin and benzylpenicillin (penicillin G).

Any questions regarding co-administration of medications should be directed to the GSK medical monitor.

7.1.2.2. Prohibited Non-Drug Therapies

Non-drug anti-cancer therapies (e.g., radiation therapy, surgery, and/or tumor embolization) will not be permitted from the screening visit through the post-study follow-up visit.

NOTE: Subjects may receive focal palliative treatment (e.g., radiotherapy or radiofrequency ablation; limited to non-target lesions only) and/or surgical intervention (for example to address pain management) during this study. Any proposed focal therapy must be approved by the investigator and the GSK Medical Monitor prior to intervention.

Subjects will abstain from using herbal preparations/medications throughout the study until the final study visit.

Herbal products include, but are not limited to: St. John's Wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, ginseng, and marijuana.

7.1.3. Cautionary Medications

The intrinsic clearance of the GSK3326595 molecule is low in hepatocytes and liver microsomes from humans. Its elimination half-life in plasma ranges from 3 hours to 6 hours. Its bioavailability following oral administration notably varies among species, from 17% in the mouse to 69% in the rat and to 90% in the dog.

GSK3326595 is not an *in vitro* inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6. GSK3326595 inhibited CYP3A4 in vitro at concentrations much higher than clinically relevant.

CCI risk have been identified as a CYP1A2 inducer. Co-administration of GSK3326595 and substrates of CYP1A2 (e.g., alosetron, duloxetine, melatonin, ramelteon, tasimelteon, tizanidine) should be avoided in order to prevent inadvertent under-exposure to these agents. As noted in Section 7.1.2.1, GSK3326595 is a substrate for P-gp. Other P-gp substrates include medications such as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) and digoxin, which may have a narrow therapeutic index. While co-administration of P-gp substrates with GSK3326595 is not prohibited, they should be used with caution and additional monitoring for adverse effects should be utilized.

Though QT prolongation was not identified in pre-clinical animal studies of GSK3326595, the following medications have the potential to induce a prolonged QT and have been associated with torsades de pointes. Co-administration of GSK3326595 and the following medications is not prohibited, but they should be used with caution and with additional monitoring (e.g., more frequent electrocardiograms) as clinically appropriate from the time of the first dose of GSK3326595 until discontinuation from the study.

Table 8 Drugs with a Risk of Torsades de Pointes that Should Be Used With Caution

Amiodarone	Droperidol	Ondansetron
Anagrelide	Erythromycin	Papaverine
Astemizole	Escitalopram	Pentamidine (IV)
Azithromycin	Flecainide	Pimozide
Bepridil	Fluconazole	Probucol
Chloroquine	Gatifloxacin	Procainamide
Chlorpromazine	Grepafloxacin	Propofol
Cilostazol	Halofantrine	Quinidine
Ciprofloxacin	Haloperidol	Roxithromycin
Cisapride	Hydroquinidine	Sevoflurane
Citalopram	Ibogaine	Sotalol
Clarithromycin	Ibutilide	Sparfloxacin
Cocaine	Levofloxacin	Sulpiride
Disopyramide	Levomepromazine	Sultopride
Dofetilide	Levosulpiride	Terfenadine

Domperidone	Mesoridazine	Terlipressin
Donepezil	Methadone	Terodiline
Dronedarone	Moxifloxacin	Thioridazine

Data Source: crediblemeds.org revision date 25 June 2019.

Questions regarding concomitant medications should be directed to the GSK Medical Monitor for clarification.

7.2. Dietary Restrictions

- GSK3326595 will be administered under fasting conditions, with no food or antacids for 1 h before and 2 h after each dose. Requirements for fasting before and after dosing may be modified based on available pharmacokinetics (PK), pharmacodynamics (PD) and safety data. Fasting will consist of avoiding the oral ingestion of calorie-containing products; however, ingestion of water is permitted. Subjects will be instructed to record the time and date of study treatments and meals in relation to dosing in the supplied GSK dosing diary.

Subjects will abstain from ingesting alcohol, tobacco products, caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, chocolate) for 24 hours prior to the start of dosing until collection of the final PK and or PD sample on Day 16. In addition, subjects should also abstain from ingesting these products prior to clinic visits on days scheduled for periodic PK and PD sample collection throughout the study.

Subjects should abstain from consumption of Seville oranges, grapefruit, grapefruit hybrids or grapefruit juice and/or pomelos, exotic citrus fruits, from one day prior to the first dose of study treatment until the last dose of study drug.

- On serial PK sampling days, subjects should fast overnight (i.e., nothing by mouth apart from water and other medications for at least 8 hours) and should continue fasting until at least 2 hours after administration of the morning dose. Fasting is required for 1 hour before and 2 hours after administration of the evening dose for subjects in BID cohorts.

If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose.

For subjects in the food effect sub-study, the administration on the 'fed' days will be performed as described in Section 4.2.6. All other days will be administered as described above.

7.3. Lifestyle Restrictions

7.3.1. Female Subjects

Female subjects of childbearing potential must not become pregnant and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1%. These allowed methods of contraception are only effective when used consistently,

correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

The chosen form(s) of contraception must be used consistently and properly from at least 28 days prior to receiving study drug until at least 5 days plus one menstrual cycle after the last dose of GSK3326595 and for at least 4 months after the last dose of pembrolizumab or in accordance with local prescribing information if longer. (Part 3 subjects only).

Abstinence

Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Contraceptive Methods with a Failure Rate of ≤ 1%

- Intrauterine device (IUD) or intrauterine system (IUS) that meets the <1% failure rate as stated in the product label.
- Hormonal means of birth control that meet the standard operating procedure (SOP) effectiveness criteria including a <1% rate of failure per year, as stated in the product label. Such methods may include: contraceptive subdermal implants, oral combination contraceptives, injectable progestogen, contraceptive vaginal ring, or percutaneous contraceptive patches.
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, “documented” refers to the outcome of the investigator's/designee’s medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject’s medical records.

7.3.2. Male Subjects

Male subjects with female partners of childbearing potential must comply with the following contraception requirements from the time of first dose of study medication until at least at least 5 half-lives plus 90 days (approximately 95 days) have elapsed after the last dose of GSK3326595:

- Vasectomy with documentation of azoospermia.
- Male condom plus partner use of one of the contraceptive options below:
- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Oral Contraceptive, either combined or progestogen alone [Hatcher, 2011] Injectable progestogen [Hatcher, 2011]
- Contraceptive vaginal ring [Hatcher, 2011]

- Percutaneous contraceptive patches [Hatcher, 2011]

This is an all-inclusive list of those methods that meet the following GSK definition of highly effective: having a failure rate of less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label. For non-product methods (e.g., male sterility), the investigator determines what is consistent and correct use. The GSK definition is based on the definition provided by the ICH [ICH (M3) R2, 2009].

The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

8. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 8.1.

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:

  1. 12-lead ECG
  2. vital signs
  3. blood draws.

- Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.
- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic/biomarker or other assessments, may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not require a protocol amendment.
- The IRB/ Independent ethics committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.

Subjects who continue to receive study treatment after the DCO date of the final analyses will be monitored and receive follow-up care in accordance with standard local clinical practice. Assessments will revert to the standard of care at a subject's particular site with

recommendation for local laboratory safety monitoring (refer to SRM). The following assessments will be required and reported directly to the Sponsor via a paper process up to 30 days after last dose of study treatment (refer to SRM and see Section 6.7):

- SAEs
- AEs leading to treatment discontinuation
- AESIs (Pre-defined Ocular and Bone AEs)
- Overdose
- Pregnancy
- Bone (DEXA) assessments will be performed at the discretion of the investigator and reported only if reporting criteria is met for SAEs, AESIs, or AEs leading to treatment discontinuation.
- Ophthalmic Assessments, will be required and reported only if reporting criteria is met for SAEs, AESIs, or AEs leading to treatment discontinuation; approximately every 6 months and at the end of the study treatment (if >8 weeks from previous assessment)

Any SAE or AESI that is ongoing at the time of this data cut-off must be followed up to resolution unless the event is considered by the investigator unlikely to resolve, or the subject is lost to follow-up. GSK retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.1. Time and Events Tables

Table 9 Time and Events for Part 1

Procedure	SCR	DLT Observation Period (Days 1-21)						Weeks 4 & 6	q4w (Starting Week 8)	q8w (Starting Week 8)	q26w (Starting Week 26)	EOT	Survival Follow-up
		D1	D2	D3	D8	D15	D16	D1					
Screening													
Informed consent	X												
Demography	X												
Medical History	X												
Inclusion/Exclusion Criteria	X												
Disease Characteristics	X												
Prior Therapy	X												
Register Subject	X												
Safety													
Pregnancy test (Females of childbearing potential only; must be within 7 days of first dose)	X							X	X			X	
Follicle stimulating hormone (FSH)/Estradiol (Only in women of non-childbearing potential)	X												
HIV, HBsAg, HCV Antibody Screening[1]	X												
Full Physical Examination[2]	X	X										X	
Limited Physical Examination[2]			X	X	X	X		X	X				
ECOG Performance Status[3]	X	X			X	X		X	X			X	
Vital Signs	X	X	X	X	X	X	X	X	X			X	
12-lead ECG	X	PK[4]			X	PK[4]		X	X				
DEXA Bone Densitometry[5]	X									X		X[6]	
Routine Clinical Laboratory Assessments[7]	X	X			X	X		X	X			X	

Procedure	SCR	DLT Observation Period (Days 1-21)						Weeks 4 & 6	q4w (Starting Week 8)	q8w (Starting Week 8)	q26w (Starting Week 26)	EOT	Survival Follow-up
		D1	D2	D3	D8	D15	D16	D1					
Folate and Selected Vitamins[7]	X							X[7]		X		X	
Ophthalmic Assessment[8]	X										X	X	
Study Treatment													
Administer study drug[9]		X		←==========Daily Dosing==========→									
Vision Symptom Review[10]	X	X	X	X	X	X	X	X	X			X	
AE Review		Continuous from the start of study treatment until the follow-up contact											
SAE Review	Continuous from signing of informed consent until the follow-up contact												
Concomitant Medication Review	Continuous from signing of informed consent												
Pharmacokinetics (PK), Pharmacodynamics (PD) & Pharmacogenomics (PGx)													
PK plasma samples[11]		X	X	X		X	X	X	X				
PD plasma samples (CCI [redacted])[12]		X			X	X							
Plasma (circulating biomarkers)[13]		X			X	X							
Tumor biopsy (archival)[14]	X												
PD tumor biopsy (fresh)[14]	X					X						X	
PGx sample (Blood)[15]		X											
Efficacy													
Computed tomography (CT) chest/abdomen/pelvis (see Section 8.2.1 and Section 8.7.1)[16]	X									X[17]		X[18]	
Magnetic resonance imaging (MRI) Brain[19]	X												
Survival Follow-Up[20]													Q6 months

1. If test performed within 3 months prior to first dose of study treatment, testing at screening may not be required. Discuss with Medical Monitor if unclear
2. See Section 8.3.1 for components of full and limited physical examinations
3. See Appendix 3 for definition of ECOG performance status
4. On serial PK days (Day 1 and Day 15), ECGs will be obtained at or about the time of PK sample collection, as described in the SRM. On other days, ECGs will be obtained pre-dose.
5. If possible, DEXA to be performed on same machine for particular subject
6. Only if EOT is > 8 weeks from prior DEXA
7. Refer to Section 8.3.5 (Table 16) for complete listing of protocol-required laboratory assessments. Clinical labs performed during screening within 72 hours of first dose do not need to be repeated on Day 1. Folate and selected vitamins to be drawn at Screening, Week 4, Week 8, every 8 weeks thereafter and at EOT. If a subject's folate or selected vitamins result(s) remain borderline or low at EOT visit, further testing may be requested until no longer deemed necessary in the opinion of the Investigator and Medical Monitor.
8. Refer to Section 8.3.7 for description of components of ocular assessment. If a subject's ocular result(s) remain abnormal at EOT visit, further testing may be requested until no longer deemed necessary in the opinion of the Investigator and Medical Monitor.
9. On serial PK days (Day 1 and Day 15), subjects should fast from 8 hours prior to dose until 2 hours after dose. On all other days, GSK3326595 should be administered on an empty stomach at approximately the same time of day (± 4 h), with no food for 1 hour before and 2 hours after each dose. On serial PK days and for two days prior (Days 13 through 16), subjects should attempt to take GSK3326595 within a 1 hour window (i.e., 23-25 hours after the last dose).
10. At each visit, the investigator should specifically ask the subject about any changes in vision since their last visit/contact (Section 9.2.2). The investigator should document the response, consider if there are any reported events which meet the definition of an AE or SAEs, and intervene as clinically appropriate following discussion with the Medical Monitor if necessary.
11. PK samples following Day 1 dose will be collected at Pre-dose (within 1 hour prior to dosing), 15m±5m, 30m±5m, 1h±5m, 1.5h±5m, 2h±5m, 3h±5m, 4h±10m, 6h±10m, 8h±15m, 12h±2h, 24h±2h (Day 2), and 48h±2h (Day 3; prior to next dose), post-dose. PK samples following Day 15 dose will be collected at Pre-dose, (within 1 hour prior to dosing), 30m±5m, 1h±5m, 2h±5m, 3h±5m, 4h±10m, 6h±10m, 8h±15m, 12h±2h, 24h±2h (Day 16, prior to next dose) post dose. PK samples on days of subsequent visits should be collected within 1 hour Pre-dose.
12. On Day 1, PD plasma samples should be collected within 1 hour Pre-dose. PD plasma samples on Day 8 and Day 15 should be collected 6h post-dose ±3 hours. Samples should be collected and separated per the SRM.
13. Plasma for circulating biomarker analysis will be collected pre-dose on Day 1 and 6h post dose ±3 hours on Days 8 and 15.
14. Refer to Section 8.2.1 for discussion of baseline biopsies. Remaining biopsies are optional unless mandated for individual subject(s) (Section 4.2.5). If a biopsy is required for PD analysis, fresh biopsies must be provided at screening, on Day 15, and at the end-of-study visit.
15. Informed consent for optional substudies (e.g. genetics research) must be obtained before collecting any samples. Appendix 8 describes requirements for genetic research.
16. CT should be performed with oral and IV contrast. CR or PR should be confirmed as per RECIST 1.1 criteria; see Section 14.4.1.
17. After week 32, scan frequencies are reduced. See Section 8.2.2 for details.
18. Repeat scans required at end of treatment (EOT) visit only if the last radiographic assessment was more than 8 weeks prior to the subject's withdrawal from study and progressive disease has not been documented.
19. MRI Brain required at screening and then as clinically indicated thereafter; subjects with untreated CNS lesions should have brain MRI performed at each disease assessment. If MRI is contraindicated for an individual subject, then an equivalent study (e.g., contrast-enhanced MRI of the head) may be performed instead.
20. Survival Follow-Up via telephone, email or other form of communication, every 6 months. Following Protocol Amendment 7, survival follow-up should only be conducted for subjects with a diagnosis of ACC. Follow-up will continue until approximately 70% of subjects with a diagnosis of ACC have died. See Section 5.4 for further details.

Table 10 QD Dosing Time and Events: Part 1 PD/Biomarker/Metabolite Cohort[s]

PK/PD/Biomarker/Metabolite Cohort(s) (Section 4.2.5; samples collected in this section are in addition to any samples, studies, and visits described in Table 9)										
Procedure		**DLT Observation Period (Days 1-21)**								
	SCR	D1	D2	D3	D4	D8	D15	D16	**Week 6**	**EOT**
Plasma (metabolite profiling)[1]		X	X	X			X	X		
Whole blood (Paxgene [PAX] tube for biomarker analysis, e.g., mRNA)[2]		X			X	X	X			
Urine – PK sample[3]		0-12h					0-12h			
Urine – metabolite sample[3]		0-12h					0-12h			
Tumor biopsy (PD; 1 Formalin fixed paraffin embedded (FFPE) and 1 fresh frozen core)4	X						X			X
^{18}FDG-PET/CT scan	X								X	

NOTE: Subjects in the expansion cohort are subject to all screening, safety, PK, and efficacy evaluations detailed in Table 9. Samples collected in this section are in addition to any samples collected in Table 9, with the exception of tumor biopsy for PD, in which the time points in Table 10 supersede those in Table 9.

1. Plasma samples for metabolites will be collected at serial PK timepoints (see Table 9).
2. Whole blood samples for biomarker analysis will be collected pre-dose on day 1 and 6h post dose ± 3 hours on days 4, 8 and 15.
3. Pre-dose urine samples will be collected near the time of dosing on Days 1 and 15 for PK and metabolite profiling. A separate container will be used to collect urine for PK and metabolite profiling from the time of dosing until 12h post-dose on days 1 and 15.
4. Pre- and post-dose biopsies are mandatory for all subjects in this cohort. End-of-treatment biopsy is preferred but not required. Refer to Section 8.2.1 for discussion of baseline biopsies. Biopsies should be collected within 14 days prior to Day 1 of dosing (pre-dose) and paired with Day 15 on-therapy

Table 11 BID Dosing Time and Events: Part 1 (PK and PD/Biomarker/Metabolites cohorts), Week 1[1]

	Day 1						Day 2			Days 3-7	
	Morning Dose			Evening Dose			Morning Dose		Evening Dose[3]	Morning Dose[3]	Evening Dose[3]
	Pre-dose[2]	0h	Post-dose	Pre-dose[2]	12h± 0.5h	Post-dose	Pre dose[2]	0h± 0.5h	12h± 1h	0h± 1h	12h± 1h
Dose		X			X			X	X	X	X
PK plasma sample[4]	X		PK	PK		PK	PK				
PD plasma sample (CCI	X										
PK/PD/Biomarker/Metabolite Cohort(s) ONLY (Section 4.2.5)											
Plasma (metabolite profiling)[5]	X		X	X		X	X				
Plasma (circulating biomarkers, e.g., cell-free DNA)[6]	X										
Whole blood (PAX tube for biomarker analysis, e.g., mRNA)[6]	X										
Urine - PK sample[7]	X	0-12h collection									
Urine metabolite sample[7]	X	0-12h collection									
Tumor biopsy[8]	SCR										
^{18}FDG-PET/CT scan	SCR										

1. Events listed in this table are in addition to all Screening, Safety, and Efficacy evaluations listed in Table 9, with the exception those listed for D3 visit. D3 visit is not required for subjects in BID cohorts. The Dose, PK and PD (CCI sampling schedules are in place of the information in Table 9

2. Pre-dose samples should be collected within 1 hour prior to dosing

3. Evening dose on Day 2 and both daily doses on Days 3 through 7 may be administered at home, by subject, at approximately the same time of day

4. Plasma samples for serial PK ("PK" in the table above) should be collected at the following timepoints on Day 1: Pre-dose (within 1 hour prior to dosing), 15m±5m, 30m±5m, 1h±5m, 1.5h±5m, 2h±5m, 3h±5m, 4h±10m, 6h±10m, 8h±15m, 12h±0.5h (prior to the evening dose), and 24h±0.5h (prior to the Day 2 morning dose). For sites and subjects who are able to accommodate, samples should also be collected at the following timepoints after the Day 1 evening dose: 15m±5m, 1h±0.5h, 2h±0.5h, 3h±0.5h, 6h±0.5h, and 8h±0.5h (these evening samples are in addition to the pre-dose sample on Day 2 described above).

5. Plasma samples for metabolite profiling will be collected at serial PK timepoints (footnote 4, above)

	Day 1						Day 2			Days 3-7	
	Morning Dose			Evening Dose			Morning Dose		Evening Dose[3]	Morning Dose[3]	Evening Dose[3]
	Pre-dose[2]	0h	Post-dose	Pre-dose[2]	12h± 0.5h	Post-dose	Pre dose[2]	0h± 0.5h	12h± 1h	0h± 1h	12h± 1h

6. Plasma and whole blood samples for biomarker analysis will be collected pre-dose on Day 1

7. Pre-dose urine samples will be collected near the time of dosing on Days 1 and 15 for PK and metabolite profiling. A separate container will be used to collect urine for PK and metabolite profiling from the time of dosing until 12h post-dose on days 1 and 15.

8. Refer to Section 8.2.1 for discussion of baseline biopsies. Pre-dose tumor biopsy may be collected up to 14 days prior to first dose ("SCR"). Tumor biopsies in the PK/PD expansion cohort are mandatory.

Table 12 BID Dosing Time and Events: Part 1 (PK and PD/Biomarker/Metabolite cohorts), Weeks 2-3 and Subsequent Visits[1]

	Day 8				Days 9-14		Day 15						Day 16			Days 17-21		W4D1, W6D1, and q4w (starting W8)		
	Morning Dose			Even-ing Dose	Morn-ing Dose	Even-ing Dose	Morning Dose			Evening Dose			Morning Dose		Even-ing Dose	Morn-ing Dose	Even-ing Dose	Morning Dose		Even-ing Dose
	Pre-dose[2]	0h± 0.5 h	Post-dose	12h± 1h	0h± 1h	12h± 1h	Pre-dose[2]	0h± 0.5 h	Post-dose	Pre-dose[2]	12h ± 0.5h	Post-dose	Pre-dose[2]	0h± 0.5 h	12h± 1h	0h± 1h	12h± 1h	Pre-dose[2]	0h± 0.5 h	12h± 1h
Dose[3]		X		X	X	X		X			X			X		X	X		X	X
PK plasma sample[4]							X		PK	PK		PK	PK					X		
PD plasma sample[5]			X						X											
PK/PD/Biomarker/Metabolite Cohort(s) ONLY (Section 4.2.5)																				
Plasma (metabolite)[6]							X		X	X		X	X							
Plasma (biomarkers)[7]			X						X											
Whole blood (PAX tube)[7]			X						X											
Urine - PK sample[8]							X	0-12h collection												
Urine metabolite sample[8]							X	0-12h collection												
Tumor biopsy[9]							Day 15, Any time													
^{18}FDG-PET/CT scan																		W6D1, Any time		

1. Events listed in this table are in addition to all Screening, Safety, and Efficacy evaluations listed in Table 9.
2. Pre-dose samples should be collected within 1 hour prior to dosing
3. Evening dose on Day 8, all doses on Days 9-14, all doses on Days 16-21, and all subsequent doses apart from morning doses (on days noted in table, e.g. W4D1, W6D1, and q4w starting W8) may be administered at home, by subject, at approximately the same time of day. Both doses on Day 15 will be administered in clinic.
4. Plasma samples for serial PK ("PK" in the table above) should be collected at the following timepoints on Day 15: Pre-dose (within 1 hour prior to dosing), 30m±5m, 1h±5m, 2h±5m, 3h±5m, 4h±10m, 6h±10m, 8h±15m, 12h±0.5h (prior to the evening dose), and 24h±0.5h (prior to the Day 16 morning dose). For sites and subjects who are able to accommodate, samples should also be collected at the following timepoints after the Day 15 evening dose: 15m±5m, 1h±0.5h, 2h±0.5h, 3h±0.5h, 6h±0.5h, and 8h±0.5h (these evening samples are in addition to the pre-dose sample on Day 16 described above).
5. Plasma samples for PD analysis will be collected 6h post-dose ± 3 hours on Days 8 and 15 and separated as per the SRM.
6. Plasma samples for metabolite profiling will be collected at serial PK timepoints (footnote 4, above).
7. CCI [redacted]
8. Pre-dose urine samples will be collected near the time of dosing on Days 1 and 15 for PK and metabolite profiling. A separate container will be used to collect urine for PK and metabolite profiling from the time of dosing until 12h post-dose on days 1 and 15.
9. Refer to Section 8.2.1 for discussion of baseline biopsies. Tumor biopsies in the PK/PD expansion cohort are mandatory

Table 13 Time and Events for Food Effect and Relative Bioavailability Sub-Study

Food Effect and Relative Bioavailability Sub-Study (Section 4.2.6; samples collected in this section are in addition to any samples, studies, and visits described in Table 9)											
Procedure	**Screening**	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10 and beyond
Administer study drug[1]		X			X				X	←==========Daily Dosing========→[2]	
Plasma PK samples[3]		X	X		X	X			X	X	Refer to Table 9 for subsequent PK sample requirements
Routine Clinical Laboratory Assessments (Refer to Table 9)	X	X							X		

NOTE: Subjects in the food effect and relative bioavailability sub-study are subject to all screening, safety, PK, and efficacy evaluations detailed in Table 9. Samples collected in this section are in addition to any samples collected in Table 9, with the exception of Day 1-9 PK collections, in which the time points in Table 13 supersede those in Table 9.

1. Study drug should be administered in fed or fasted state, as capsules or tablets based on assignment as described in Section 4.2.6. At least 48 hours should separate each individual dose; in order to accommodate clinic schedules, the Day 4 visit may be performed up to one day late, and the Day 8 visit may be performed ±1 day (note that it may only be performed on Day 8 or Day 9 if the Day 4 visit is performed on Day 5, in order to allow the 48-hour window between doses). Refer to Section 8.2.2 for full discussion of visit windows.
2. Day 9 dose should be administered in clinic following collection of Day 8 24-hour timepoint PK sample.
3. PK samples following Day 1, Day 4, and Day 8 doses will be collected at Pre-dose (within 1 hour prior to dosing), 15m±5m, 30m±5m, 1h±5m, 2h±5m, 4h±10m, 6h±10m, 8h±15m, 12h±2h, 24h±2h and 30h±2h.

Table 14 Time and Events for Part 2

Procedure	Screening	Days 1-21			Weeks 4 & 6	q8w (starting W8)	q12w (starting W12)	q26w (starting W26)	EOT (within 30 days post-last dose)	Survival Follow-Up
		D1	D8	D15	D1					
Screening										
Informed consent	X									
Demography	X									
Medical History	X									
Inclusion/Exclusion Criteria	X									
Disease Characteristics	X									
Prior Therapy	X									
Register Subject	X									
Safety										
Full Physical Examination[1]	X								X	
Limited Physical Examination[1]		X	X	X	X	X				
ECOG Performance Status[2]	X	X	X	X	X	X			X	
Vital Signs	X	X	X	X	X	X			X	
12-lead ECG	X	PK[3]		PK[3]		X			X	
DEXA bone Densitometry	X[4]					X			X[5]	
Pregnancy test (Females of childbearing potential only; must be within 7 days of first dose)	X				X	X			X	
FSH/Estradiol (Only in women of non-childbearing potential)	X									
HIV, HBsAg, HCV Antibody Screening[6]	X									
Routine Clinical Laboratory Assessments[7]	X	X	X	X	X	X			X	

Procedure	**Screening**	**Days 1-21**			**Weeks 4 & 6**	**q8w (starting**	**q12w (starting**	**q26w (starting**	**EOT (within 30 days post-**	**Survival Follow-Up**
TSH, free T3 and free T4[7]	X				X	X			X	
Folate and Selected Vitamins[7]	X				X[7]	X			X	
Ophthalmic Assessment[8]	X							X	X	
Study Treatment										
Administer study drug[9]		←==========Daily Dosing==========→								
Vision Symptom Review[10]	X	X	X	X	X	X			X	
AE Review		Continuous from the start of study treatment until the follow-up contact								
SAE Review	Continuous from signing of informed consent until the follow-up contact									
Concomitant Medication Review	Continuous from signing of informed consent									
Pharmacokinetics (PK), Pharmacodynamics (PD) & Pharmacogenomics (PGx)										
PK Plasma[11]		X		X	X	X				
Tumor Biopsy (archival) for p53 status	X									
Tumor Biopsy (fresh) for p53 and PD[12]	X			X					X	
Plasma (circulating biomarkers)[13]		X	X	X		X				
Whole blood (PAX tube for biomarker analysis, e.g., mRNA)[13]		X	X	X		X				
PGx Sample (Blood)[14]	X									
Efficacy										
Solid tumor cohorts: CT chest/abdomen/pelvis (see Section 8.2.1 and Section 8.7.1)[15]	X					X[16]			X[17]	
Solid tumor cohorts: MRI Brain[18]	X									
GBM cohort: MRI brain (see Section 8.2.1 and Section 8.7.2)	X					X[16]			X[17]	
NHL cohort: Disease assessment (see Section 8.2.1 and Section 8.7.3)[19]	X						X[15]		X[16]	
Patient-Reported Outcomes (ACC Tablet Cohort ONLY)										
CCI [redacted]										

Procedure	**Screening**	**Days 1-21**			**Weeks 4 & 6**	**q8w (starting**	**q12w (starting**	**q26w (starting**	**EOT (within 30 days post-**	**Survival Follow-Up**
EQ-5D-3L		X			X (Week 4 only)	X			X	
Long-Term Follow-Up										
Subsequent cancer treatment following discontinuation of study treatment[20]									X[19]	Q6 months[20]
Survival Follow-Up[20]										Q6 months[20]

NOTE: for visit windows, please refer to Section 8.2.2.

1. See Section 8.3.1 for components of full and limited physical examinations
2. See Section 14.3 for definition of ECOG performance status
3. On serial PK days (Day 1 and Day 15), ECGs will be obtained at or about the time of PK sample collection, as described in the SRM. On other days, ECGs will be obtained pre-dose
4. If possible, DEXA to be performed on same machine for particular subject.
5. Only if EOT is > 8 weeks from prior DEXA.
6. If test performed within 3 months prior to first dose of study treatment, testing at screening may not be required. Discuss with Medical Monitor if unclear.
7. Thyroid function testing including TSH, free T3, and free T4 are to be drawn at Screening, Week 4 or 6, then every 8 weeks starting at Week 8 and EOT. Refer to Section 8.3.5 (Table 16) for complete listing of protocol-required laboratory assessments. Folate and selected vitamins to be drawn at Screening, Week 4, Week 8, every 8 weeks thereafter and at EOT. If a subject's folate or selected vitamins result(s) remain borderline or low at EOT visit, further testing may be requested until no longer deemed necessary in the opinion of the Investigator and Medical Monitor.
8. Refer to Section 8.3.7 for description of components of ocular assessment. If a subject's ocular result(s) remain abnormal at EOT visit, further testing may be requested until no longer deemed necessary in the opinion of the Investigator and Medical Monitor.
9. On serial PK days (Day 1 and Day 15), subjects should fast from 8 hours prior to dose until 2 hours after dose. On all other days, GSK3326595 should be administered on an empty stomach at approximately the same time of day (± 4 h), with no food for 1 hour before and 2 hours after each dose
10. At each visit, the investigator should specifically ask the subject about any changes in vision since their last visit/contact (Section 9.2.2). The investigator should document the response, consider if there are any reported events which meet the definition of an AE or SAEs, and intervene as clinically appropriate following discussion with the Medical Monitor if necessary.
11. Plasma PK samples on Day 1 will be collected at Predose (within 1 hour prior to dosing), 30m±5m, 1h±5m, 2h±5m, 4h±10m, 6h±10m, 8h±15m, 12h±2h, 24h±2h (Day 2 prior to next dose) post dose. Additional PK samples will be collected at the following time points: on Day 15 within 1 hr before dosing and between 1 and 3 hrs post dose, on Day 15 between 5 and 8 hrs post dose (in the NSCLC and ACC tablet cohorts only), and at subsequent scheduled visits within 1 hr before dosing.
12. Refer to Section 8.2.1 for discussion of baseline biopsies. Fresh screening biopsy should be taken within 14 days prior to the first dose. Paired biopsy to be taken on Day 15 after 14 days of GSK3326595 dosing. EOT biopsy to be obtained as able for all subjects. Subjects in GBM expansion cohort may submit archival tumor sample at screening. Day 15 and EOT biopsy not required for GBM cohort. The fresh biopsy will be used to determine p53 status if no archival sample is available
13. Plasma and whole blood samples for biomarker analysis will be collected predose on day 1 and 6h post-dose (±3 h) for all on-treatment samples. Plasma samples for

circulating biomarkers to be collected as per the SoA until Week 24 only.

14. Informed consent for optional sub-studies (e.g. genetics research) must be obtained before collecting any samples. Appendix 8 describes requirements for genetic research
15. CT should be performed with oral and IV contrast. CR or PR should be confirmed not earlier than 28 days from the initial response scan, as per RECIST 1.1 criteria; see Section 14.4.1. Any subject in the ACC tablet cohort who has not yet shown objective radiological disease progression at treatment discontinuation should be continued to be followed as per RECIST 1.1 for radiological progression.
16. After the fourth scheduled scan for disease assessment, scan frequencies are reduced. See Section 8.2.2 for details.
17. Repeat scans required at EOT visit only if the last radiographic assessment was more than 8 weeks prior to the subject's discontinuation of study treatment and progressive disease has not been documented.
18. For subjects in solid tumor cohorts, MRI brain required at screening and then as clinically indicated thereafter; subjects with untreated CNS lesions should have brain MRI performed at each disease assessment. If MRI is contraindicated for an individual subject, then an equivalent study (e.g., contrast-enhanced MRI of the head) may be performed instead
19. CR or PR should be confirmed not earlier than 28 days from the initial response scan, as per international working group criteria; see Section 14.4.3
20. Survival Follow-Up via telephone, email or other form of communication, every 6 months. Following Protocol Amendment 7, survival follow-up should only be conducted for subjects in an ACC cohort. Follow-up will continue until approximately 70% of subjects in the ACC cohorts have died. CCI [redacted] See Section 5.4 for further details

Table 15 Time and Events for Part 3 (Active in all regions, except France)

Procedure	Screening	Days 1-35				q3w (starting W6)	q8w (starting W8)	q26w (starting W26)	EOT (within 30 days post-last dose)
		Day 1	Day 8	Day 15	Day 22				
Screening									
Informed consent	X								
Demography	X								
Medical History	X								
Inclusion/Exclusion Criteria	X								
Disease Characteristics	X								
Prior Therapy	X								
Register Subject	X								
Safety									
Full Physical Examination[1]	X								X

Procedure	**Screening**	**Days 1-35**				**q3w**	**q8w**	**q26w**	**EOT (within**
Limited Physical Examination[1]		X	X	X	X	X			
ECOG Performance Status[2]	X	X	X	X	X	X			X
Vital Signs	X	X	X	X	X	X			X
12-lead ECG	X	PK[3]		PK[3]			X		X
DEXA Bone Densitometry	X[4]						X		X[5]
Pregnancy test (Females of childbearing potential only; screening test must be within 7 days prior to first dose)	X				X	X			X
FSH/Estradiol (Only in women of non-childbearing potential)	X								
HIV, HbsAg, HCV Antibody Screening[6]	X								
Routine Clinical Laboratory Assessments[7]	X	X	X	X	X	X			X
Folate and selected vitamins[7]	X				X		X		X
Ophthalmic Assessment[8]	X							X	X
Study Treatment									
Administer GSK3326595[9]		←==========Daily Dosing==========→							
Administer Pembrolizumab				X		X			
Vision Symptom Review[10]	X	X	X	X	X	X			X
AE Review		Continuous from the start of study treatment until the follow-up contact							
SAE Review	Continuous from signing of informed consent until the follow-up contact								
Concomitant Medication Review	Continuous from signing of informed consent								
Pharmacokinetics (PK), Pharmacodynamics (PD) & Pharmacogenomics (PGx)									
PK Plasma[11]		X		X			X		
Pembrolizumab PK[12]				X	X	X (Q6W starting W6)			X
Pembrolizumab Immunogenicity[13]				X		X (Q6W starting			X

Procedure	Screening	Days 1-35				q3w	q8w	q26w	EOT (within
						W6)			
Tumor Biopsy (archival) for p53 status	X								
Tumor Biopsy (fresh) for p53 and PD[14]	X			X					X
Plasma (circulating biomarkers)[15]		X		X			X		
Whole blood (PAX tube for biomarker analysis, e.g., mRNA)[15]		X		X			X		
PGx Sample (Blood)[16]	X								
Efficacy									
CT chest/abdomen/pelvis (see Section 8.2.1 and Section 8.7.1)[17]	X						X[18]		X[19]
MRI Brain[20]	X								

NOTE: for visit windows, please refer to Section 8.2.2.

1. See Section 8.3.1 for components of full and limited physical examinations
2. See Section 14.3 for definition of ECOG performance status
3. On serial PK days (Day 1 and Day 15), ECGs will be obtained at or about the time of PK sample collection, as described in the SRM. On other days, ECGs will be obtained pre-dose
4. If possible, DEXA to be performed on same machine for particular subject
5. Only if EOT is > 8 weeks from prior DEXA
6. If test performed within 3 months prior to first dose of study treatment, testing at screening may not be required. Discuss with Medical Monitor if unclear.
7. Refer to Section 8.3.5 (Table 16) for complete listing of protocol-required laboratory assessments. Folate and selected vitamins to be drawn at Screening, Day 22, Week 8, every 8 weeks thereafter and at EOT. If a subject's folate or selected vitamins result(s) remain borderline or low at EOT visit, further testing may be requested until no longer deemed necessary in the opinion of the Investigator and Medical Monitor.
8. Refer to Section 8.3.7 for description of components of ocular assessment. If a subject's ocular result(s) remain abnormal at EOT visit, further testing may be requested until no longer deemed necessary in the opinion of the Investigator and Medical Monitor.
9. On serial PK days (Day 1 and Day 15), subjects should fast from 8 hours prior to dose until 2 hours after dose. On all other days, GSK3326595 should be administered on an empty stomach at approximately the same time of day (± 4 h), with no food for 1 hour before and 2 hours after each dose
10. At each visit, the investigator should specifically ask the subject about any changes in vision since their last visit/contact (Section 9.2.2). The investigator should document the response, consider if there are any reported events which meet the definition of an AE or SAEs, and intervene as clinically appropriate following discussion with the Medical Monitor if necessary.
11. GSK3326595 Plasma PK samples on Day 1 will be collected at Predose (within 1 hour prior to dosing), 30m±5m, 1h±5m, 2h±5m, 4h±10m, 6h±10m, 8h±15m, 12h±2h, 24h±2h (Day 2 prior to next dose) post dose. Additional PK samples will be collected at the following time points: Day 15, within 1 hr before dosing and between 1 and 3 hrs post dose, and between 5-8 hrs post dose. At subsequent scheduled visits, PK should be collected within 1 hr before dosing.
12. Pembrolizumab PK samples on Day 15 will be collected predose (within 1 hour prior to dosing), postdose (≤30 min after end of infusion) and 24h±2 h after the start of infusion. For D22, Pembrolizumab PK sample to be collected any time during the visit. At all other visits, predose PK samples will be collected (within 1 hour prior to

dosing).

13. Pembrolizumab samples for immunogenicity will be collected at predose for all visits.
14. Refer to Section 8.2.1 for discussion of baseline biopsies. A fresh screening biopsy is required, even if there is archival tissue available, and should be taken within 14 days prior to the first dose. Paired biopsy to be taken on Day 15 prior to pembrolizumab administration, after 14 days of GSK3326595 dosing. EOT biopsy to be obtained as able for all subjects. The fresh biopsy will be used to determine p53 status if no archival sample is available.
15. Plasma and whole blood samples for biomarker analysis will be collected Day 1 (pre-dose) and 6h post-dose (±3 h) for all on-treatment samples. Plasma samples for circulating biomarkers to be collected as per the SoA until Week 24 only.
16. Informed consent for optional sub-studies (e.g. genetics research) must be obtained before collecting any samples. Appendix 8 describes requirements for genetic research
17. CT should be performed with oral and IV contrast. CR or PR should be confirmed not earlier than 28 days from the initial response scan, as per RECIST 1.1 criteria; see Section 14.4.1
18. After the fourth scheduled scan for disease assessment, scan frequencies are reduced. See Section 8.2.2 for details.
19. Repeat scans required at EOT visit only if the last radiographic assessment was more than 8 weeks prior to the subject's withdrawal from study and progressive disease has not been documented
20. MRI brain required at screening and then as clinically indicated thereafter; subjects with untreated CNS lesions should have brain MRI performed at each disease assessment. If MRI is contraindicated for an individual subject, then an equivalent study (e.g., contrast-enhanced MRI of the head) may be performed instead

8.2. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5. Medical, surgical, and treatment history including date of first diagnosis, best response to prior systemic therapy, histology, and current sites of disease will be taken as part of the medical history and disease status. Details concerning concomitant medication will be recorded starting from screening through post-study follow-up. At a minimum, the drug name, route of administration, dose and frequency of dosing, along with start and stop dates should be recorded. Investigators will be required to provide details of prior response assessments, including the dates of evaluation, size of target lesions used for determination of response, and changes in management made in response to these assessments, for at least two prior lines of therapy (if available) as part of the medical history.

Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging studies, etc.) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

Investigators may be requested to perform additional safety tests during the course of the study based on newly available data to ensure appropriate safety monitoring. Appropriate local regulatory and ethical approvals should be obtained before any additional testing is performed.

For subjects enrolled in the Part 2 ACC cohort, pre-study baseline scans should be provided in order to measure kinetics of tumor growth prior to therapy with GSK3326595. Additional details regarding the number and quality of scans will be provided in the SRM.

8.2.1. Critical Baseline Assessments

The following are required at baseline:

- Imaging/efficacy:
    - Part 1: All subjects should undergo contrast-enhanced CT of the chest, abdomen, and pelvis (and/or other areas as indicated by the subject's underlying disease) as well as an MRI of the brain.

      NOTE: Although CT scan is preferred, MRI may be used as an alternative method of baseline disease assessment for abdomen/pelvis, especially for those subjects where a CT scan is contraindicated due to allergy to contrast, provided that the method used to document baseline status is used consistently throughout study treatment to facilitate direct comparison. An unenhanced CT of the chest

can replace the enhanced CT of the chest, but MRI of the chest is not recommended.

- Part 2, solid tumor cohorts, and Part 3: All subjects should undergo contrast-enhanced CT of the chest, abdomen, and pelvis (and/or other areas as indicated by the subject's underlying disease) as well as an MRI of the brain. If MRI of the brain is contraindicated, then an equivalent scan (e.g., contrast-enhanced CT of the brain) may be performed instead.
- Part 2, GBM cohort: All subjects should undergo MRI of the brain. Refer to the Imaging Acquisition Guidelines (IAG) for scanning guidelines
- Part 2, NHL cohorts: All baseline (and subsequent) scanning should be performed as clinically indicated based on the NHL subtype and the manifestation of the subject's disease. For subjects with measurable tumors, contrast-enhanced CT of the neck, chest, abdomen, and pelvis should be performed. If PET/CT is used to assess disease, the CT component must be performed to diagnostic quality (including the required anatomical coverage and use of IV and oral contrast). Other modalities (e.g., medical photography for cutaneous T-cell lymphoma (TCL) or bone marrow biopsy) may be used after discussion with the medical monitor.

- Disease characteristics (as available):
  - The results of any mutational analysis of tumor or other associated tissue (e.g., cytology, circulating tumor cells, cf-DNA), including p53 status (if available).
  - For Part 2 NHL p53 status and NSCLC p53 WT status is required prior to dosing
  - The size(s) and location(s) of target lesion(s) used for response characterization for at least two prior lines of therapy, as well as a description of the dates of service and changes made to management
- Tumor biopsies:
  - All subjects in Part 1 (dose escalation and, the PK/PD/biomarker/metabolite cohort/s), as well as all subjects in Parts 2 and 3, must submit an archival tumor specimen in addition to any fresh biopsies required in individual cohorts (see below). The archival specimen will be used for retrospective testing for potential markers of sensitivity and/or resistance (e.g., p53). If archival specimen is not available, a fresh biopsy must be performed. Further details regarding processing will be provided in the SRM.
  - NOTE: All NHL subjects in Part 2 must have a local p53 mutational analysis result prior to dosing unless the subject's tumor has previously been demonstrated to harbor a p53 mutation. If local p53 status was not determined, analysis may be performed on archival tissue, but if archival tissue is not available, a fresh biopsy must be performed. NHL subjects with neither archival tumor sample nor accessible tumor for fresh biopsy will not be permitted to enroll. Further details will be provided in the SRM. The intent is to accrue 10 subjects each of WT and mutant p53. As the sub-cohorts are filled, it may become necessary to delay enrollment until p53 status is formally designated. In case one NHL cohort reaches futility at any Interim Analysis, further enrolment

into the other NHL cohort will require central confirmation. NOTE: All NSCLC subjects in Part 2 must have a local genomic p53 mutational analysis result prior to dosing. If local p53 status was not determined, an archival sample or a fresh biopsy must be provided.

- Individual subjects in the dose escalation portion of Part 1 may be required to provide paired biopsies for PD evaluation as described in Section 4.2.5 and Section 8.6.2. For these subjects, a fresh baseline tumor biopsy is required and should be obtained within 14 days of the first dose of GSK3326595. Further details will be provided in the SRM.
- In the Part 1 PD/biomarker/metabolite expansion cohort(s), a fresh baseline tumor biopsy is required from all subjects and should be obtained within 14 days prior to the first dose of GSK3326595. Further details will be provided in the SRM.
- In Part 2, in addition to an archival tumor biopsy, a fresh baseline tumor biopsy is required from all subjects (except those in the GBM cohort) and should be obtained within 14 days prior to the first dose of GSK3326595. If tumor tissue is not accessible, discussion with the GSK medical monitor is required and the medical monitor must assent to subject participation; in this circumstance, the paired biopsy on Day 15 would not be required. Further details will be provided in the SRM.
- In Part 3, in addition to an archival tumor biopsy, a mandatory fresh baseline tumor biopsy is required from all subjects and should be obtained within 14 days prior to the first dose of GSK3326595. The paired on-treatment biopsy should be taken on D15 (W3D1) prior to administration of pembrolizumab (see Section 8.2.2).

8.2.2. Visit Windows

Screening (baseline to pre-dose): All assessments including baseline imaging (e.g., CT, MRI, or PET/CT) should be performed within 14 days prior to first dose. Note for females, pregnancy testing should be performed within 7 days prior to first dose. Also, clinical labs performed during screening within 72 hours of first dose do not need to be repeated on Day 1.

Week 1: Visits for Week 1 Days 1, 2, 3, and 4 must be performed on the day indicated. For subjects in the food effect/relative bioavailability sub-study, the Day 4 visit may be performed on Day 4 or Day 5.

Week 2 to Week 8: Based on subject and clinic schedule, assessments can be ± 2 days. The only exception to this window is the Day 8 visit for subjects in the food effect/relative bioavailability sub-study, for whom this assessment must be performed ± 1 day.

The Week 3 Day 1 (Day 15) PK and PD sample collections are timed to permit evaluation of GSK3326595 PK and PD parameters at steady-state dosing. If a subject is not receiving drug on Week 3 Day 1 (Day 15), either as a consequence of a planned drug holiday or due to toxicity, or has not been receiving drug for 14 days such that they are at

steady state, then these PK/PD collections should be rescheduled for a later timepoint when the subject is again being dosed at steady state, and the alternate collection date noted in the eCRF.

For subjects in Part 3, the preferred order of procedures on Day 15 is: Administration of GSK3326595, on-study tumor biopsy, followed by administration of pembrolizumab. However, this order may be varied based on clinic schedules and other factors. If pembrolizumab is administered prior to the on-study biopsy, the biopsy should be collected within 24 hours of pembrolizumab administration.

The disease assessment at week 8 should be performed ± 2 days. After the fourth scheduled scan for disease assessment (i.e., week 32 for solid tumors/GBM and week 48 for NHL), the frequency of scheduled scans will be reduced to every 16 weeks for subjects with solid tumors/GBM and every 24 weeks for subjects with NHL. For subjects enrolled in the PK/PD/Biomarker/Metabolite cohort, the required ^{18}FDG-PET/CT scan at Week 6 may be performed ± 7 days.

Every 4-week, 8-week, 12-week and 26-week visits after Week 8 until Week 52: After the first disease assessment has been completed, the clinic visits can be scheduled ± 5 days.

In Part 3, all subsequent disease assessments (after the first assessment) may be performed ± 1 week to align with clinic visits for administration of pembrolizumab.

Every 4-week, 8-week, 12-week and 26-week visits after Week 52: After week 52, the every 4-week visits will no longer be required at the discretion of the investigator; any procedures or tests originally required every 4 weeks (q4w) should be performed every 8 weeks (q8w) instead. For the every 8- and 12-week visits, clinic visits can be scheduled ± 7 days.

Discontinuation visit: should be within 30 days from last dose of study drug. If a subject is unable to return to the clinic due to hospitalization, site staffs are encouraged to telephone the subject for assessment of adverse events.

8.3. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 8.1). Additional time points for safety tests may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

Note that this section details the procedures used to evaluate for safety and toxicity for this study. For management of toxicity and management/reporting of any suspected Adverse Events, refer to Section 9, Appendix 9, and Appendix 2.

Post Protocol Amendment 8 implementation, subjects who continue to receive study treatment after the DCO date of the final analyses will be monitored and receive follow-up care in accordance with standard local clinical practice with recommendations provided for local safety laboratory monitoring for GSK3326595 given the absence of a label to define standard of care (refer to SRM). Only pre-specified additional safety assessments will be required (refer to Section 8).

8.3.1. Physical Exams

A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological system, lungs, cardiovascular system, abdomen (liver and spleen), lymph nodes and extremities. Height must be recorded at the screening visit. Weight will also be measured and recorded at the screening visit and at each subsequent visit.

A brief physical examination will include assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). Weight will also be measured and recorded at the screening visit and at each subsequent visit.

Investigators should pay special attention to clinical signs related to previous serious illnesses

8.3.2. Performance Status

The performance status will be assessed using the ECOG scale (Appendix 3) as specified in the Time and Events Table (Section 8.1).

8.3.3. Vital Signs

- Vital sign measurements to be measured, in a consistent fashion, per institutional standard (e.g., in a seated or semi-supine position after 5 minutes rest), will include temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate.
- In case of an abnormal first reading, three readings of blood pressure and pulse rate should be taken and averaged to give the measurement to be recorded in the CRF.
- Vital signs will be measured more frequently if warranted by clinical condition of the subject. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.

Refer to the Study Reference Manual (SRM) for details regarding measurement of vital signs.

8.3.4. Electrocardiogram (ECG)

Section 8.1 indicates the visits at which ECGs must be obtained. At each time point, a single 12-lead ECG will be obtained during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. On serial PK days (Days 1 and 15), ECGs will be obtained at multiple time points as described in the SRM. On all other indicated visits, ECGs will be obtained prior to dosing. Refer to Section 5.4.6 for QTcF calculations, to Appendix 2 for management strategies for QTcF prolongation, and to Section 5.4.6 for QTc withdrawal criteria.

Local ECG may be read centrally at chosen timepoints.

8.3.5. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 16, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed, and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the SRM. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments. The results of each test must be entered into the CRF.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 16.

Table 16 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Haematology	*WBC count with Differential:*	*RBC Indices*:	Platelet Count	Reticulocytes
	Neutrophils	Hemoglobin		
	Lymphocytes	Hematocrit		
	Monocytes	Red blood cells (RBC) Count		
	Eosinophils	Mean corpuscular volume (MCV)		
	Basophils	Mean corpuscular hemoglobin (MCH)		
Clinical Chemistry	BUN/Urea	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose	Total calcium	Alkaline phosphatise	Albumin
	Amylase	Lipase		

Laboratory Assessments	Parameters
Folate and selected vitamins	Serum B12 and Folate. For borderline results of B12 and/or folate, the following 2 additional tests will be performed within 2 weeks of the borderline result: Methylmalonic acid (serum or plasma) and Homocysteine (serum or plasma). **B12:** • >300 pg/mL (above 221 pmol/L) – Normal • 200 to 300 pg/mL (148 to 221 pmol/L) – Borderline • <200 pg/mL (below 148 pmol/L) – Low; consistent with deficiency **Folate:** • >4 ng/mL (above 9.1 nmol/L) – Normal. • From 2 to 4 ng/mL (from 4.5 to 9.1 nmol/L) – Borderline. • <2 ng/mL (below 4.5 nmol/L) – Low; consistent with folate deficiency.
Thyroid Function	Thyroid stimulating hormone (TSH), free Tri-iodothyronine (T3), Free thyroxine (T4)
Coagulation	PTT, PT/INR
Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Urine hCG pregnancy test (only for women of childbearing potential. Note that initial screening test must be serum hCG and subsequent tests may be urine hCG) • Microscopic examination (if available at the participating site)
Additional urine and serum renal biomarkers	Only for participants with screening eGFR <60 mL/min/1.73 m^2: • Neutrophil gelatinase-associated lipocalin (NGAL), Kidney injury molecule-1 (KIM-1) and albumin/creatinine ratio (urine) • Cystatin C (serum)
Additional endocrine studies	• Thyroid stimulating hormone (TSH) • Free T3 • Free T4

Laboratory Assessments	Parameters
Other Screening Tests	• HIV • Hepatitis B (HBsAg) • Hepatitis C (Hep C antibody) • FSH and estradiol (as needed in women of non-childbearing potential only) • Serum hCG Pregnancy test (only for women of childbearing potential. Note that initial screening test must be serum hCG and subsequent tests may be urine hCG)
NOTE: Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 5.4.5 and Section 14.6	

From the first dose of GSK3326595 until 30 days after the last dose of study treatment, all laboratory tests with abnormal values that are considered clinically significant should be repeated as clinically indicated until the values return to normal (per institutional guidelines) or back to the pre-study baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

8.3.6. Bone Mineral Density

In order to assess the clinical bone safety of GSK3326595, dual energy x-ray absorptiometry (DEXA) scans will be performed on all patients at baseline and every 8 weeks thereafter (Section 8.1). This evaluation has been deemed most relevant as it is the clinical gold standard to detect any unexpected changes in bone mineral density (BMD), which may suggest an increased risk of fracture.

For consistency in the assessment, DEXA scans should be performed on the same machine for all evaluations on a particular subject when possible. For more details, please refer to the SRM.

Locally collected DEXA scans may be read centrally.

Post Protocol Amendment 8 implementation, bone assessments (DEXA) will be performed at the discretion of the investigator. The data will be collected via a paper process and submitted to the Sponsor only if reporting criteria is met for SAEs, AESIs, or AEs leading to treatment discontinuation. Locally collected data will not be read centrally.

8.3.7. Ophthalmic Assessment

Study sites must establish a close collaboration with an appropriately qualified eye-care specialist (ophthalmologist/optometrist) who in conjunction with the Investigator will be responsible for carrying out the schedule of ophthalmic assessments, and managing / referring any subject who develops visual symptoms and/or signs potentially associated with GSK3326595 exposure.

Management of subjects with potential treatment-related changes in vision must be performed in close collaboration with the Investigator, appropriately qualified eye-care specialist, and the GSK Medical Monitor.

Subjects will have listed below assessments performed by a qualified eye-care specialist at screening/baseline, then every 6 months and at EOT. The assessments may be expedited in the event that a subject develops any new or evolving ophthalmic symptoms and/or signs in the interval period between assessments. If an abnormal result is recorded at the EOT visit, additional assessment will be required as deemed necessary by the Investigator, appropriately qualified eye-care specialist and the GSK Medical Monitor.

- Full comprehensive exam with best corrected visual acuity (BCVA) at distance for each eye
- Humphrey Visual field assessment (or equivalent as agreed with the Sponsor)
- Optical coherence tomography (OCT) of the optic nerve retinal nerve fibre layer (RNFL) with ganglion complex analysis
- OCT of the macula
- Assessment of color vision by Ishihara method

Primary outputs of the Humphrey Visual Field and OCT assessments will be held centrally by GSK in the event that central or independent evaluation of these is deemed beneficial to support on-going safety evaluation.

Additional examinations, if deemed necessary, may be performed at the discretion of the treating eye-care specialist, and in discussion with the Investigator and Medical Monitor. Further details can be found in the Ocular Manual.

Post Protocol Amendment 8, ophthalmic assessments will be continued approximately every 6 months and at the end of the study treatment (if >8 weeks from the previous assessment). The data will be collected via a paper process and submitted to the Sponsor only if reporting criteria is met for SAEs, AESIs, or AEs leading to treatment discontinuation. Locally collected data will not be read centrally.

8.3.8. Pregnancy

Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of dosing and until 90 days post-last dose.

If a pregnancy is reported then the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 10.

8.4. Pharmacokinetics

8.4.1. Blood Sample Collection

Blood samples (approximately 2 mL each) for pharmacokinetic (PK) analysis of GSK3326595 will be collected at the time points indicated in Table 9, Table 13, Table 14 and Table 15. Blood samples (approximately 2 mL each) for PK analysis of pembrolizumab will be collected at the time points indicated in Table 15.

The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring. Blood samples for pharmacokinetic analysis should be collected at the time of a SAE whenever possible.

Plasma or serum analysis will be performed as described in the Study Reference Manual (SRM). Concentrations of GSK3326595 or pembrolizumab will be determined using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Details of PK blood sample collection, processing, storage and shipping procedures are provided in the SRM.

Once the plasma has been analyzed for GSK3326595 any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate GSK protocol.

8.4.2. Urine Sample Collection

Urine samples for quantitative analysis of GSK3326595 will be collected after single dose and at steady state. The actual date and time of each urine sample collection will be recorded.

Details of PK urine sample processing, storage and shipping procedures are provided in the SRM.

Once the urine has been analyzed for GSK3326595 any remaining urine may be analyzed for other compound-related metabolites and the results reported under a separate GSK protocol.

8.5. Metabolite Analysis

8.5.1. Blood Sample Collection

Subjects enrolled in the PK/PD/Biomarker/Metabolite cohort(s) (Section 4.2.5) will have blood drawn for PK evaluation on the same schedule as all other subjects participating in Part 1. Each collection will require additional volume; approximately 5 mL of whole

blood will be collected at each timepoint from all subjects in the expansion cohorts. Samples will be prepared for shipment according to the SRM and processed/separated at the clinical site.

8.5.2. Urine Sample Collection

Urine samples will be collected from subjects in the PK/PD/Biomarker/Metabolite expansion cohort(s) (Section 4.2.5) into plastic bottles over the time period specified in the Time and Events Table for analysis of GSK3326595 and any metabolite(s). Details of the urine sample processing, storage and shipping procedures are provided in the SRM.

8.5.3. Sample Analysis

Plasma and/or whole blood analysis for circulating biomarkers and metabolites will be performed as described in the SRM.

Plasma and urine samples will be analyzed for GSK3326595 and its metabolites and the results reported under a separate report.

8.6. Pharmacodynamics/Biomarkers

All subjects in Part 1 (both dose escalation and the PK/PD expansion cohort) will have limited PD sampling performed. CCI and other biomarkers may be assessed in blood or tumor to determine the effects of GSK3326595. Change from baseline levels will be measured. In addition, in the PK/PD expansion cohort only, whole blood samples may be utilized for the identification and/or validation of a gene signature panel indicative of modulation in response to GSK3326595. Changes in the gene levels from baseline will be assessed. This signature may serve as a novel PD biomarker of PRMT5 inhibition by GSK3326595. The PD outcome may be correlated to clinical outcome.

All subjects in Parts 2 and 3 will have PD sampling performed. CCI and other biomarkers may be assessed in blood or tumor to determine the effects of GSK3326595. Change from baseline levels will be measured. Whole blood samples may be utilized for the identification and/or validation of a gene signature panel indicative of modulation in response to GSK3326595. Changes in the gene levels from baseline will be assessed. This signature may serve as a novel PD biomarker of PRMT5 inhibition by GSK3326595. PD studies may also help us to better understand the mechanism of action for GSK3326595 and inform future rational combinations. The PD outcome may be correlated to clinical outcome.

8.6.1. Blood Sample Collection

Plasma samples from all subjects in Part 1 will be collected as described in Section 8.4.1. An aliquot from the PK sample will be separated and stored for the purpose of assessing pharmacodynamic biomarkers according to the SRM.

Whole blood and plasma samples will be collected during the PK/PD expansion cohorts, Part 2, and Part 3 as described in the Time and Events table (Section 8.1) and the SRM. Additionally, serum will be collected during Parts 2 and 3. Plasma or serum that is

initially collected for the purpose of PK assessments may be utilized for biomarker assessments when there is remaining sample.

8.6.2. Tumor Biopsy Collection

All subjects will be asked to submit an archival tumor biopsy at baseline in order to conduct retrospective tests for the identification and/or validation of known and novel biomarkers. If archival specimen is not available, a fresh biopsy may be performed. In addition, subjects enrolled in PK/PD expansion cohort(s) must submit fresh tumor biopsies collected pre- and post-dose in addition to the archival tumor biopsy as described in the Time and Events table (Section 8.1) and the SRM. Unscheduled tumor biopsies may be collected based on emerging data (e.g., to evaluate PD in a subject with clinical response).

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In addition, patients enrolled in part 3 are requested to provide results from any PD-L1 test performed, including information on the antibody used and, preferably, the vendor or institution that performed the test. Also, PD-L1 testing will be done centrally.

8.6.3. Assessments for ^{18}FDG-PET/CT

All subjects enrolled in the PK/PD/Biomarker/Metabolite expansion cohort(s) (Section 4.2.5) will have ^{18}FDG PET/CT assessments performed at baseline and on treatment as outlined in the Time and Events table. Additional scans may be performed at different timepoints based on emerging data during the study.

Additional details will be provided in the SRM. Additional analysis may be conducted by an independent central reviewer. Instructions for submission of data are provided in the SRM.

8.7. Efficacy

Post Protocol Amendment 8 implementation, no new efficacy assessments will be performed as part of the study.

8.7.1. Subjects with Solid Tumors (Part 1 and Part 2)

The overall response rate is defined as the percentage of subjects with a confirmed complete response (CR) or confirmed partial response (PR), as per RECIST 1.1.

- Lesion assessment method and timing, evaluation of disease, disease progression and response criteria will be conducted according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [Eisenhauer, 2009] as outlined below and in Section 14.4.1.

- Disease assessment modalities may include imaging (e.g., computed tomography [CT] scan, magnetic resonance imaging [MRI]) and physical examination (as indicated for palpable/superficial lesions). Contrast-enhanced CT of the chest, abdomen, and pelvis is preferred, but other modalities may be used (e.g., in the case of contrast allergy) as described in Section 8.2.1.
- The baseline disease assessment will be completed within 2 weeks prior to the first dose of GSK3326595, then every 8 weeks thereafter and at the final study visit. See the Time and Events Table (Section 8.1) for the schedule of assessments of anti-cancer activity.
- Assessments must be performed on a calendar schedule (Day 1 being the day of the first study treatment administration) and should not be affected by dose interruptions/delays.
- For post-baseline assessments, a window of ±7 days is permitted to allow for flexible scheduling. If the last radiographic assessment was more than 8 weeks prior to the subject's withdrawal from study and progressive disease has not been documented, a disease assessment should be obtained at the time of withdrawal from study treatment.
- Subjects whose disease responds (either complete response [CR] or partial response [PR]) should have a confirmatory disease assessment performed at least 4 weeks after the date of assessment during which the response was demonstrated.
- To ensure comparability between the baseline and subsequent assessments for each subject, the same method of assessment and the same technique will be used when assessing response.
- Any subject in the ACC tablet cohort who has not yet shown objective radiological disease progression at treatment discontinuation should continue to be followed as per RECIST 1.1 for radiological progression, unless consent has been withdrawn.

8.7.2. Subjects with GBM

Response will be assessed by the investigator every 8 weeks, as outlined in the Time and Events Table (Table 14), using standardized Response Assessment in Neuro-Oncology (RANO) Working Group Criteria, as detailed in Section 14.4.2.

8.7.3. Subjects with Non-Hodgkin's Lymphoma

Response will be assessed by the investigator every 12 weeks, as outlined in the Time and Events Table (Table 14), using standardized Lugano Criteria, as described in Section 14.4.3.

8.7.4. Subjects in Part 3

The overall response rate is defined as the percentage of subjects with a confirmed complete response (CR) or confirmed partial response (PR), as per iRECIST guidelines,

as described in Section 14.4.4 [Seymour, 2017]. These guidelines will be used in the assessment of response/progression to account for the unique tumor kinetics observed with immunotherapeutic agents, which may manifest as an increase in tumor burden then later is followed by regression suggesting the apparent observed neoplastic growth representing transient lymphocyte infiltration. Thus, participants with disease progression by RECIST version 1.1 guidelines are required to have a confirmatory disease assessment no sooner than 4 weeks after the date disease progression was declared in order to confirm disease progression by iRECIST guidelines [Seymour, 2017]. The visit level responses and treatment-based decisions will incorporate iRECIST guidelines [Seymour, 2017].

8.8. Pharmacogenetic Analysis

An important objective of the clinical study is pharmacogenetic (PGx) research. Participation in PGx is optional but all subjects who are eligible for the clinical study will be given the opportunity to participate. Subjects may decline participation without effect on their medical care or care during the clinical study. A separate consent signature is required for PGx research.

Subjects who provide consent will have a blood sample taken for analysis. The presence/absence of genetic variations in host DNA from blood will be analyzed to determine their relationship with response (safety, tolerability, pharmacokinetics, and efficacy) to treatment with GSK3326595.

Information regarding pharmacogenetic research is included in Appendix 8. In approving the clinical protocol, the independent ethics committee/institutional review board (IEC/IRB) (and, where required, the applicable regulatory agency) also approve the PGx assessments unless otherwise indicated. Where permitted by regulatory authorities, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx assessments is being deferred and the study, except for PGx assessments, can be initiated. When PGx assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx assessments will not be conducted.

8.9. Immunogenicity Analysis (Part 3)

Blood samples (approximately 2 mL) for immunogenicity analysis of pembrolizumab will be collected at the time points indicated in Table 15. The timing and number of planned immunogenicity samples may be altered during the course of the study, based on newly available data to ensure appropriate safety monitoring. Serum will be used to assess the presence of anti-drug antibodies (ADA). The analysis for the presence of anti-pembrolizumab antibodies will be performed contingent on availability of a validated assay, and if considered clinically relevant. The actual date and time of each blood sample collection will be recorded. Details of blood sample collection (including volume to be collected), processing, storage, and shipping procedures are provided in the SRM.

In the event of a hypersensitivity reaction that is either 1) clinically-significant in the opinion of the investigator, or 2) leads to the participant withdrawing from study

treatment, blood samples may be taken from the participant for immunogenicity testing at the time of the event, and at further timepoints specified in the SRM.

Results of ADA testing may be reported separately at the end of the study.

8.10. Translational and Exploratory Research

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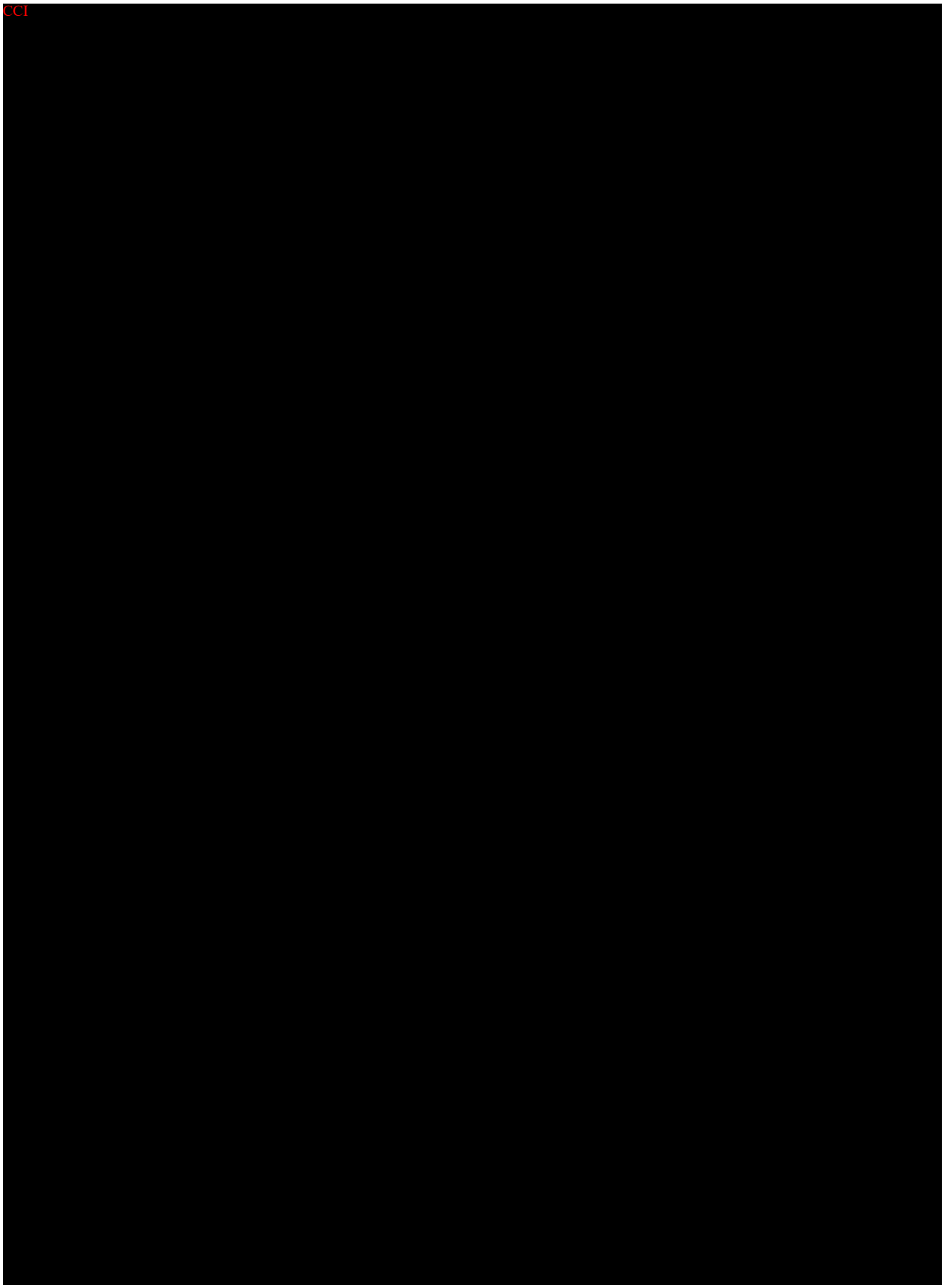

8.11. Patient Reported Outcomes

Planned time points for all assessments related to PROs are listed in the Time and Events Table (Table 14) and will apply to the ACC tablet cohort in Part 2 of the study only. PROs will be available on a rolling basis as they are available and data collection tools are implemented, with select PROs not being completed in the study when unavailable in specific languages.

Cancer can have a profound impact on patients' health related quality of life (HRQoL); both the symptoms of the disease as well as the tolerability profile of treatments impact HRQoL. The patient-reported outcomes (PRO) in this study (Table 17) aim to measure changes in symptoms, physical functioning, and symptomatic side effects, tolerability, and HRQoL.

Completion of PRO Questionnaires

PRO questionnaires are to be administered at the beginning of the visits specified in Section 8.11 in the order presented in the electronic device. To avoid biasing responses, the subjects should not be told the results of diagnostic tests prior to completing the questionnaires. Adequate time must be allowed to complete all items on the questionnaires, and if necessary, the subject must be encouraged to complete any missing items.

Table 17 PRO Outcomes Assessed in Study 204653

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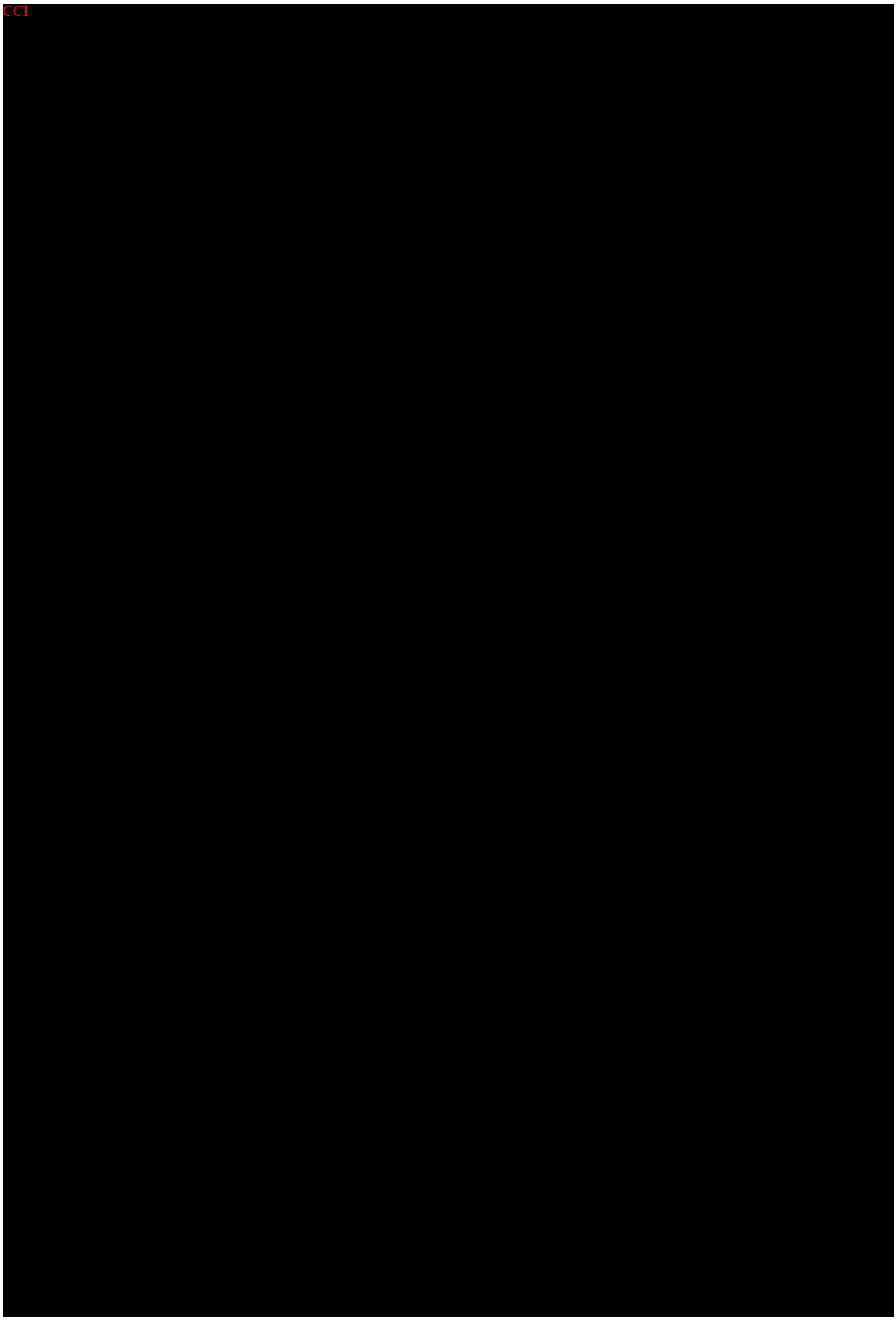

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9. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DATA COLLECTION, REPORTING, AND FOLLOW-UP

9.1. Definition of AE/SAE

The definitions of an AE or SAE can be found in Appendix 9. The severity of adverse events will be graded utilizing the NCI-CTCAE v4. Additional details regarding management of specific AEs or SAEs are described in Appendix 9.

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

9.1.1. Cardiovascular/Death events

For any cardiovascular events detailed in Appendix 9 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV eCRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death eCRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

9.1.2. Adverse Events of Special Interest

Adverse events of special interest (AESIs) for GSK3326595 are ocular events and bone-related events. These AESIs are pre-defined and are derived from the Osteopenia/ Osteoporosis Standardised MedDRA Query (SMQ) and the Optic Nerve Disorders SMQ (see SRM for listing of terms for reporting). Post Protocol Amendment 8 implementation, AESIs will be reported directly to the Sponsor via a paper process. The severity of all AESIs will be graded utilizing the NCI-CTCAE v4 for Adverse Events.

9.1.3. Other Sentinel Events

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, that are felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as an AE or SAE, in accordance with the definitions provided.

In addition, an associated AE or SAE is to be recorded for any laboratory test result or other safety assessment that led to an intervention, including permanent discontinuation of study treatment, dose reduction, and/or dose interruption/delay.

Any new primary cancer must be reported as a SAE.

9.2. Time period and Frequency for collecting AE and SAE Information

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of Study Treatment until the follow-up contact (see Section 8.2.2), at the timepoints specified in the Time and Events Table (Section 8.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.

- All SAEs will be recorded and reported to GSK within 24 hours of the investigator/site staff becoming aware of them, as indicated in Appendix 9.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any AEs or SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.
- Post Protocol Amendment 8 implementation, for those subjects who continue to receive study treatment after DCO date of final analyses, the Sponsor will continue to collect safety information including SAEs, AESIs and AEs leading to treatment discontinuation via a paper process for up to 30 days after last dose of study treatment.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 9.

9.2.1. Method of Detecting Unsolicited AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

9.2.2. Method of Detecting Solicited AEs and SAEs

Vision Symptom Review:

- "Have you had any changes in your vision since your last visit/contact?"

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 9.

9.2.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK or designee of SAEs related to study treatment is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

10. DATA MANAGEMENT

For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system. When the Protocol Amendment 8 is implemented at a site, the collection of data for all enrolled subjects who no longer receive study treatment will stop entirely. Those subjects still benefiting from GSK3326595 in the opinion of their treating Investigator may continue to receive study treatment under Protocol Amendment 8. In the portion of the study continuing treatment under Protocol Amendment 8, only SAEs, AEs leading to treatment discontinuation, overdoses, pregnancies, and pre-defined ocular and bone AEs (AESIs) will be reported directly to the Sponsor via paper process. In addition,

- Ocular assessments will be required and reported via a paper process to the Sponsor only if reporting criteria is met for SAEs, AESIs, or AEs leading to treatment discontinuation.
- Bone (DEXA) assessments will be performed at the discretion of the investigator and reported via a paper process to the Sponsor only if reporting criteria is met for SAEs, AESIs, or AEs leading to treatment discontinuation.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.

Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.

CRFs (including queries and audit trails) will be retained by GSK or designee, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

11. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

11.1. 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 11.9.6.

- 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 (both p53 wild-type and p53 mutant 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]

11.2. mTPI Method

The mTPI design [Ji, 2010] is an extension of the toxicity probability interval method [Ji, 2007] and employs a simple beta-binomial hierarchic model. Decision rules are based on

calculating the unit probability mass (UPM) of three intervals corresponding to under dosing, proper dosing, and overdosing in terms of toxicity. Specifically, the under dosing interval is defined as $(0, p_T - \varepsilon_1)$, the overdosing interval as $(p_T + \varepsilon_2, 1)$, and the proper dosing interval as $(p_T - \varepsilon_1, p_T + \varepsilon_2)$, where ε_1 and ε_2 are small fractions, such as 0.05, to account for the uncertainty around the true target toxicity. A sensitivity analysis reported by Ji et al [Ji, 2010] showed that the mTPI design is robust to the specification of ε values. In addition, ε_1 and ε_2 could take different values to reflect physician preference and the nature of the disease. For advanced diseases with few treatment options, higher toxicity rates might be considered acceptable, implying a specification of $\varepsilon_2 > \varepsilon_1$. For less-advanced diseases, the two ε values could be identical or $\varepsilon_1 > \varepsilon_2$. The three dosing intervals are associated with three different dose-escalation decisions. The under dosing interval corresponds to a dose escalation (E), overdosing corresponds to a dose de-escalation (D), and proper dosing corresponds to staying at the current dose (S). Given an interval and a probability distribution, the UPM of that interval is defined as the probability of the interval divided by the length of the interval. The mTPI design calculates the UPMs for the three dosing intervals, and the one with the largest UPM implies the corresponding dose-finding decision. That decision provides the dose level to be used for future subjects. For example, if the under dosing interval has the largest UPM, decision E, to escalate, will be executed, and the next cohort of subjects will be treated at the next-higher dose level. Ji et al [Ji, 2010] show that the decision based on the UPM is optimal in that it minimizes a subsequent expected loss. Under the mTPI design, a trial is terminated when either the lowest dose is above the MTD or a prespecified maximum sample size is reached.

11.3. Bayesian Predictive Adaptive Design for GBM Cohort

A Bayesian predictive adaptive design [Lee, 2008] that allows the trial to be monitored more frequently at multiple stages 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 is 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 18. These rules are intended as a guideline. Actual decisions will depend on the totality of the data.

Table 18 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
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.

11.4. Bayesian Hierarchical Modelling

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. 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,..., 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 Table 21. 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 Section 4.3.3.

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

11.5. Simon's Two Stage Design for ACC Cohorts

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%.

11.6. 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 19. 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 19 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

11.7. 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 20. 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 20 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

11.8. 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 (Simon, 1989) 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%.

11.9. Sample Size Considerations

11.9.1. Sample Size Assumptions

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

The study will enrol a maximum of approximately 412 subjects with tumor types that may include TNBC, mTCC, GBM, ACC, ER+BC, HPV+, NHL and NSCLC.

In Part 1 approximately 42 subjects will complete the DLT evaluation period. In addition, up to 12 subjects will be enrolled at or near the MTD/RP2D in the PK/PD/Biomarker/Metabolite expansion cohort(s) (Section 4.2.5) and approximately 12 subjects in the food and formulation effect sub-study (Section 4.2.6).

In Part 2, a maximum of 32 subjects, 40 subjects, 38 subjects, 50 subjects, 35 subjects, 28 subjects, 28 subjects and 15 subjects will be enrolled in TNBC, mTCC, ACC (capsule), ACC (tablet), ER+BC, HPV+ solid tumor, GBM and NSCLC cohorts, respectively. A maximum of 25 subject will be enrolled in each of the NHL[+] and NHL[-] cohorts. If all cohorts enroll the maximum number of subjects, this will result in no more than 316 subjects total.

In Part 3 approximately 10 subjects will be enrolled into each of three cohorts: GSK3326595 100mg + pembrolizumab, GSK3326595 200mg + pembrolizumab, and GSK3326595 300mg + pembrolizumab.

To determine the maximum sample size for GBM cohort, Bayesian predictive adaptive design will be used for testing hypotheses and sample size determination:

H_0: 6 months PFS rate $\leq$17%

H_A: 6 months PFS rate $\geq$35%

When maximum sample size is 28, the design will have a Type I error (α) of 0.086 and 80% power.

Enrollment into specific cohorts may be halted early based on results from interim analyses incorporating emerging response data. Response data from a minimum of 10 subjects will be required in a cohort before it may discontinue enrollment for futility. In addition, at the final analysis and after the study has been closed, a minimum of 5 subjects will be required in a cohort in order to meet statistical success at the final analysis. See Section 11.9.6 for more details. Data from evaluable subjects treated in the dose escalation part may be used for futility analysis if the subject is from the same population and treated at RP2D.

Simulation studies were conducted to evaluate the performance of the Bayesian Hierarchical design under various assumptions for the distribution of true ORRs across the TNBC, mTCC, and NHL cohorts. Operating characteristics including power, type I error, estimation of the ORR, and the probability of halting enrollment at interim analyses were assessed.

When the treatment effects are similar across TNBC, mTCC, and NHL histologies, the design maintains power 88% to 97% and type I error rate $\leq$0.1. Estimation efficiencies due to borrowing result in very good operating characteristics in these situations, even in histologies with low sample sizes. Table 21 provides similar operating characteristics for scenarios where not all histologies align in terms of efficacy performance.

11.9.2. Sample Size Sensitivity

No sample size sensitivity assessments will be performed.

11.9.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be performed.

11.9.4. Data Analysis Considerations

Data will be listed and summarized according to GSK reporting standards, where applicable. Complete details will be documented in the RAP. Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report.

In the dose escalation cohorts, the dose will be escalated based on all available data, including biomarker and PK data and the safety profile of prior cohorts. The DLT information on all subjects enrolled in the trial are used to update the estimated dose-toxicity relationship and provide supportive information in addition to the mTPI design in the next escalation/de-escalation decision; the mTPI approach is expected to be used as the primary criteria for dose escalation.

The expansion phases are designed to evaluate preliminary clinical activity. A futility assessment will be conducted and enrollment into a disease-specific cohort may be paused in order to evaluate accumulating data including safety, clinical responses, and

pharmacokinetic and pharmacodynamic data. Response may also be stratified by p53 status and other mutational and gene expression data, as described in the RAP.

Subjects enrolled in Part 1 will be included in a Part 2 disease specific cohort analyses if the subjects were treated at the Part 2 dose and has the same disease as required for the cohort.

11.9.5. Analysis Populations

The **All Treated Population** is defined as all subjects who receive at least one dose of GSK3326595. Safety and anti-cancer activity will be evaluated based on this analysis population.

The **All Evaluable Population** is 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 (both capsule and tablet) and GBM cohorts.

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

Pharmacodynamic Population: The PD Population is defined as subjects in the All Treated Subjects Population for whom paired and evaluable tumor biopsies (pre- and on-treatment time points) or plasma were obtained and analyzed for biomarkers.

Additional analysis populations may be defined in the RAP.

11.9.6. Interim Futility Analysis

Interim data will be evaluated to monitor efficacy and safety. For the GBM cohort, a planned interim analysis for futility will be performed when at least 10 evaluable subjects have been enrolled in this expansion cohort. Enrollment may be stopped early for toxicity or lack of efficacy, should various criteria occur based on accrued data. The design criterion for early stop for futility based on Bayesian Predictive Adaptive Design is described in Section 11.3. For TNBC, mTCC, and NHL cohorts, the decision criteria for early stop for futility based on Bayesian Hierarchical model are described below. The decision will be made for each individual disease-specific cohort. For the ACC capsule cohort, one interim futility analysis will be performed when first treated 10 subjects become evaluable. If there are 1 or fewer responders in these 10 subjects, the cohort will be stopped early for futility. For the ACC tablet cohort, one interim futility analysis will be performed when the first 17 treated subjects become evaluable. 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. For ER+BC cohort, the first interim analysis will be conducted when at least 10 subjects become evaluable. The details about interim decision rules are specified in Section 11.6. For HPV+ cohort, the first interim analysis will be conducted when at least 10 subjects become evaluable. The details about interim decision rules are specified in Section 11.7.

For the NSCLC cohort, one interim futility analysis will be performed when first treated 10 p53 wild-type subjects become evaluable. If there are 1 or fewer responders in these 10 subjects, the cohort will be stopped early for futility.

For TNBC, mTCC, and NHL cohorts, the therapeutic effect will be declared insufficient, and termination of enrollment will be recommended, if a minimum of 10 subjects become evaluable and the posterior probability that the confirmed ORR is greater than its corresponding historical control (C_j) is sufficiently low (<15%) based on the hierarchical model. That is,

$$P(\pi_j > C_j \mid \text{current data}) < 15\%, \text{ for the j-th cohort, j=1,..4}$$

However, as described in Section 4.3.3, the decision to terminate a given cohort will not be made based on the statistical model alone and will require review of all available data, including safety/tolerability, PK, PD, and biomarker data. Operating characteristics associated with declaring early futility are provided for multiple scenarios in Table 21.

For the Part 3 GSK3326595 + pembrolizumab combination cohorts, planned analyses will take place after the first 5 subjects in each cohort complete 35 days of study treatment or discontinue prior to 35 days. The details of this design can be found in Section 4.4. The operating characteristics of the stopping criteria for the Part 3 GSK3326595 + pembrolizumab combination cohorts have been examined and can be found detailed in Section 11.10.4.

Additional interim analyses may also be conducted to share key results at medical conferences, if deemed appropriate.

11.9.7. Final Analysis

Following Protocol Amendment 8 implementation, the final analysis of the study will be performed following the DCO as defined in Section 5.5.

11.10. Key Elements of Analysis Plan

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.

All data up to the time of study completion/withdrawal from study will be included in the analysis, regardless of duration of treatment.

As the duration of treatment for a given subject will depend on efficacy and tolerability, the duration of follow-up will vary between subjects. Consequently, there will be no imputation for missing data.

All data will be summarized and listed.

11.10.1. Primary Analyses

As the primary endpoints of Part 1 of this study are safety and tolerability, the primary analyses will be descriptive in nature. Safety endpoints are described in Section 5.4.

The primary aim of Part 2 is to demonstrate clinically meaningful response rates in each of the disease cohorts. Bayesian predictive adaptive designs will be used to evaluate the GBM, ER+BC and HPV+ cohorts, independently, as described in Section 11.3, Section 11.6, and Section 11.7, respectively. Bayesian-based hierarchical modeling will be used for the mTCC, TNBC, p53 WT NHL and p53 mutant NHL cohorts, as described in Section 11.4. For the NHL cohort, subgroup analyses may also be performed for specific indolent histological subtypes (e.g., follicular lymphoma [FL], transformed FL [tFL], and mantle cell lymphoma [MCL] subtypes only). Simon's Two Stage designs will be used for both the capsule and tablet formulation cohorts for ACC, as detailed in Section 11.5. The primary aim of the NSCLC p53 wild-type cohort is to evaluate the potential of GSK3326595 as a treatment for this population. A Simon's two-stage design will be used as a basis for this cohort, where the results of the interim futility analysis will help determine the scope of any further development of this cohort, as detailed in Section 11.8.

The primary aim of Part 3 is to evaluate the safety and tolerability of GSK3326595 in combination with pembrolizumab in subjects with select solid tumors. The primary analyses will be exploratory in nature.

The All Treated Population will consist of all subjects receiving at least one dose of study drug and will be used for the analysis of safety and efficacy data. Complete details of the analyses will be provided in the RAP.

11.10.2. Secondary Analyses

11.10.2.1. Safety Analyses

Safety endpoints are described in Section 5.4.

The All Treated Population will be used for the analysis of safety data. All serially collected safety endpoints (e.g., laboratory tests, vital signs, electrocardiogram [ECGs]) will be summarized according to the scheduled, nominal visit at which they were collected and across all on-treatment time points using a "worst-case" analysis. Complete details of the safety analyses will be provided in the RAP.

11.10.2.1.1. Extent of Exposure

The number of subjects administered study treatment will be summarized according to the duration of therapy

11.10.2.1.2. Adverse Events

AEs will be coded using the standard MedDRA and grouped by system organ class. AEs will be graded by the investigator according to the NCI-CTCAE v4.

Events will be summarized by frequency and proportion of total subjects, by system organ class and preferred term. Separate summaries will be given for all AEs, treatment-related AEs, SAEs, and AEs leading to discontinuation of study treatment and dose modification. AEs, if listed in the NCI-CTCAE v 4, will be summarized by the maximum grade.

Dose-limiting toxicities will be listed for each subject and summarized by dose cohort for Part 1 subjects.

AEs of special interest will be outlined in the RAP.

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

11.10.2.1.3. Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be summarized using frequencies and proportions according to NCI-CTCAE v4. Laboratory test results outside the reference ranges that do not have an associated NCI-CTCAE criterion will be summarized using proportions. Further details will be provided in the RAP.

11.10.2.2. Pharmacokinetic Analyses

11.10.2.2.1. Pharmacokinetic Parameters

PK analyses will be the responsibility of GSK. The plasma concentrations for individual subjects will be determined using a validated analytical method for GSK3326595. Individual plasma concentrations of GSK3326595 will be listed and summarized.

For subjects participating in serial sampling, plasma GSK3326595 concentration-time data will be analyzed by non-compartmental methods with Phoenix WinNonlin. The following pharmacokinetic parameters will be determined, as data permit:

- maximum observed plasma concentration (Cmax)
- time to Cmax (tmax)
- area under the plasma concentration-time curve (AUC(0-t), AUC(0-∞) and AUC(0-τ))
- apparent terminal phase half-life (t½).
- oral apparent clearance following oral dosing (CL/F)
- time invariance (TI) and accumulation ratio (AR) as calculated by the following equations:

$$TI = \frac{AUC(0-\tau), Day15}{AUC(0-\infty), Day1}$$

$$AR = \frac{AUC(0-\tau), Day15}{AUC(0-\tau), Day1}$$

Sparse plasma concentration-time data from Part 2 may be combined with serial data and further analyzed using a population approach. A nonlinear mixed effects model may be

used to determine population pharmacokinetic parameters and identify important covariates (e.g., age, weight, or disease related covariates). Further details of population PK analysis will be described in the RAP; results of such an analysis may be included in a report separate from the clinical study report.

In a subset of subjects, GSK3326595 concentrations may be determined in urine samples to determine urinary recovery of unchanged drug and renal clearance.

11.10.2.2.2. Statistical analysis of pharmacokinetic parameters

Plasma concentration-time data will be listed by dose, age group, and summarized using descriptive statistics (n, mean, SD, median, minimum and maximum) by planned relative assessment time. Mean and/ or median values will be plotted over time. Individual plasma and urinary (if available) pharmacokinetic parameter values as well as a descriptive summary (mean, standard deviation, median, minimum, maximum, geometric mean, and the standard deviation, coefficient of variance percent (CV%) and 95% confidence interval of log-transformed parameters [if applicable]) by dose cohort will be reported.

Cmax and AUC (AUC(0-∞), single dose, and AUC(0-τ), steady state) will be plotted as a function of the dose administered. If more than 2 dose cohorts are required to reach MTD (or the recommended dose based on available safety, PK and response data), dose proportionality of AUC and Cmax for GSK3326595 following single dose administration and AUC(0-τ) and Cmax following repeat dose administration will be assessed graphically and using the power model as described below:

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

where a is the intercept and b is the slope.

The power model will be fitted by restricted maximum likelihood (REML) using Statistical analysis system (SAS) Proc Mixed. Both the intercept and slope will be fitted as fixed effects. If there is sufficient data, the model may also be fit with the intercept and/or slope as random effects depending on the ability of the model to converge and on estimation of variance-covariance matrix. The mean slope and corresponding 90% confidence interval will be estimated from the power model.

11.10.2.2.3. Food Effect and Relative Bioavailability Sub-Study

Pharmacokinetic (PK) parameters AUC(0-∞), and Cmax will be log-transformed and analyzed separately using a mixed-effects model with fixed-effect term for fed status (fed or fasted)/formulation (tablet or capsule), and subject as a random effect. Point estimates and their associated 90% CIs will be constructed for the differences between fed and in fasted state, between tablet and capsule. For the relative bioavailability analysis, tablets are the test formulation and capsules are the reference. The point estimates and their associated 90% CIs were then back transformed to provide point estimates and 90% CIs for the ratios of fed/fasted and tablet/capsule. Non-parametric methods such as the Hodges and Lehmann estimator 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.

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.

11.10.2.3. Efficacy Analysis

The confirmed overall response rate (ORR) is defined as the percentage of subjects with a confirmed complete response (CR) or a partial response (PR) at any time as per disease-specific criteria (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. Exact methods for calculated confidence intervals will be given in the RAP.

The number and types of responses, as outlined in RECIST 1.1 (for subjects with solid tumors), RANO (for subjects with GBM), and Lugano (for subjects with NHL), will be listed and summarized separately, as appropriate.

The observed confirmed ORR will be reported at the interim and final analysis for each cohort specified in Part 2 treated at RP2D. The estimates along with 95% confidence interval (CI) based on a normal approximation will be provided. Bayesian inference based on summary statistics from the posterior distributions of each ORR will be reported at interim and final analyses. The posterior mean and posterior 2.5% and 97.5% percentiles of the ORR will be calculated for each cohort. In addition, the posterior probability that the ORR exceeds its corresponding historical control will be reported for each cohort.

Progression-free survival rate (PFSR) is calculated from the start of treatment until the date of progression or death from any cause. The PFSRs at 6 months were estimated by the Kaplan-Meier method. These rates estimated the proportion of patients who did not progress and were alive at month 6. The 95% confidence intervals for the PFSR at month 6 will be estimated using Greenwood's estimate of the standard error (SE) and a linear transformation of the progression-free survival function.

Duration of response is defined as the time 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. Duration of response will be summarized descriptively for each cohort, if data warrant, using Kaplan-Meier medians and quartiles. Details on rules for censoring will be provided in the RAP.

For the ACC tablet cohort, duration of response will be analyzed as determined by the Investigator assessment.

For the analysis of Progression-free survival **(**PFS**)**, if the subject received subsequent anti-cancer therapy prior to the date of documented events, PFS will be censored at the last adequate assessment (e.g. assessment where visit level response is CR, PR, or stable disease [SD]) prior to the initiation of therapy. Progressive disease (PD) will also be defined per standard criteria. Otherwise, if the subject does not have a documented date of events, PFS will be censored at the date of the last adequate assessment. Further details on rules for censoring will be provided in the RAP. PFS will be summarized by cohort specified in Part 2, if data warrant, using Kaplan-Meier quantile estimates along with 2-sided 95% CIs at the time of final analysis.

For the analysis of overall survival (OS), the last date of known contact will be used for those subjects who have not died at the time of analysis; such subjects will be considered censored. Further details on rules for censoring will be provided in the RAP. OS will be summarized by cohort specified in Part 2, if data warrant, using Kaplan-Meier quantile estimates along with 2-sided 95% CIs at the time of final analysis.

11.10.3. Other Analyses

CCI

11.10.4. Simulations and Design Operating Characteristics

11.10.4.1. Simulation Description

Extensive simulations have been conducted to develop and understand the performance of the adaptive design; the hierarchical model including clustering mechanism, interim monitoring, and decision criteria.

11.10.4.2. Software Details

Simulations were conducted by the software provided by Berry Consultants. For each assumed scenario, 500 sets of trials were simulated. Posterior distributions were estimated via Markov chain Monte Carlo methods using 50,000 iterations for each analysis, discarding the first 2,000 iterations for each analysis as burn-in.

11.10.4.3. Trial Sample Size and Simulation Scenarios

Sample size requirements for halting enrollment at interim analyses for simulations is based on the number of subjects enrolled; while in practice, they will be based on the number of subjects with available response data. This discrepancy is due to software feasibility but should not have a significant impact on operating characteristics of the design. Simulations assumed interim analyses occurred every 4 weeks, with the first interim analysis occurring once 40 subjects have been enrolled. The time from subject entry until the response assessment was performed is assumed to be 24 weeks. The maximum length of time for each study is 120 weeks ±6 weeks (roughly 2.5 years).

Although actual enrollment may vary, predicted enrollment during a 2-year time period is incorporated into the simulations. Cohort, projected enrollment and the historical control and clinically meaningful response rates used in simulations are shown in Table 21.

Table 21 Simulation Scenarios and Design Characteristics

	Cohorts			
	TNBC	**mTCC**	**NHL[+]**	**NHL[-]**
Project Enrollment in 2-year time period; n	32	40	25	25
Max Sample size; n	32	40	25	25
Scenarios				
All Null	10%	15%	10%	10%
All Positive	25%	30%	30%	30%
All Moderate	20%	20%	20%	20%
2 Null, 2 Positive	25%	15%	30%	10%
3 Null, 1 Positive	10%	15%	30%	10%
Proportion of Trials that Declare each Cohort Efficacious (Measure of Power or Type I Error Rate)				
All Null	0.05	0.10	0.06	0.05
All Positive	0.92	0.88	0.95	0.96
All Moderate	0.67	0.39	0.58	0.57

	Cohorts			
	TNBC	**mTCC**	**NHL[+]**	**NHL[-]**
2 Null, 2 Positive	0.82	0.12	0.87	0.13
3 Null, 1 Positive	0.09	0.10	0.81	0.11
Proportion of Trials that Declares Early Futility				
All Null	0.50	0.52	0.47	0.42
All Positive	0.03	0.05	0.02	0.01
All Moderate	0.09	0.22	0.06	0.08
2 Null, 2 Positive	0.09	0.41	0.04	0.24
3 Null, 1 Positive	0.39	0.45	0.06	0.31
Proportion of Trials that Pick all the Positive Cohorts				
All Null	N/A			
All Positive	0.76			
All Moderate	N/A			
2 Null, 2 Positive	0.74			
3 Null, 1 Positive	0.81			

Due to the 'borrowing' nature of the model, the design is evaluated across a variety of scenarios for the distribution of true ORRs across the four cohorts. These are shown in Table 21.

The "All Positive" scenario assumes all cohorts are responsive at the defined clinically meaningful RR levels. The "Null" case assumes all cohorts are nonresponsive at the historical control RRs. The "All Moderate" scenario assumes all cohorts show moderate RR levels in between the historical control and clinically meaningful RR levels. The other three scenarios consider various situations where cohorts are either responsive (at the clinically meaningful RR level) or not (at the historical control RR level).

11.10.4.4. Operation Characteristics

Power and type I error rate are examined across scenarios for the distribution of assumed true ORRs for each cohort. The power is the probability of declaring efficacy within an individual cohort when the true underlying ORR is greater than its corresponding historical control. Type 1 error rate is the probability of declaring efficacy within an individual cohort when the true underlying response rate is equal to the historical control.

The power and type I error rate are dependent upon the sample sizes and response rates across the distribution of cohorts. When the treatment effects are the same across all cohorts (either all responsive or all non-responsive), estimation efficiencies, due to borrowing, result in very good operating characteristics, even in cohorts with low sample sizes. The type I error rate is controlled to ≤0.08 across all cohorts (All Null scenario). The design maintains power 90% to 97% for all four cohorts (All Great scenario). Also, the design exhibits reasonable power to detect a moderate level of activity (All moderate scenario).

When the treatment effects vary across cohorts, the amount of appropriate borrowing also varies, impacting the operating characteristics. However, under all scenarios, the design

maintains at least 80% power for the positive cohorts. The '2 null, 2 positive' and '3 null, 1 positive' cases investigate design performance where at least half of the cohorts are not responsive. In this situation, the type I error rate is inflated between 0.1 and 0.13 the power is at least 81% for the positive cohorts. Generally, improvement in the overall distribution of treatment effects tends to coincide with slight increases in type I error rate and moderate increases in power.

Overall type I error rate, the probability of claiming efficacy in at least one group under the null hypothesis is 0.23.

11.10.4.5. Stopping Early

Table 21 also presents the proportion of trials that halt enrollment early for futility across simulation scenarios. Since the study requires at least ten subjects in a particular cohort prior to stopping early for futility, the ability for a cohort to stop early is largely dependent upon the projected maximum sample size and enrollment rate per cohort. The overall distribution of treatment effects across cohorts also impacts the likelihood of halting enrollment early.

When the expected 2-year enrollment is greater than 20, non-responsive cohorts stop early for futility between 26% and 47% of the time. Across simulation scenarios, responsive cohorts generally do not stop early for futility.

11.10.4.6. Mean Proportion of Correct Decisions

To evaluate the design performance in correctly evaluating all four cohorts, Table 21 listed the probabilities of making a correct decision on concluding efficacy on all the cohorts whose true underlying ORR is greater than historical control (pick all positive cohorts). In the scenarios where there are positive cohorts, there are 73% to 83% chance that all the positive cohorts will be picked.

11.10.4.7. Operating characteristics of the safety stopping rule in Part 3 (GSK3326595 in combination with pembrolizumab)

Simulations were used to evaluate the design performance of the safety stopping rules planned for the Part 3 dose determination. In these simulations, we simulate 50,000 independent trials and evaluate the performance of the model on average.

Recall that each higher dose cohort is dependent on the result of the previous cohort(s). For example, if cohort 1 is not completed, cohorts 2 and 3 will not begin. Thus, in order to complete cohort 3, cohorts 1 and 2 must have also been deemed safe with respect to our safety stopping criteria.

Table 22 details the scenarios we have evaluated as well as the average number of subjects dosed in each cohort, and the percentage of simulated trials that completed that dose level, assuming that 5 subjects were dosed during each stage resulting in 10 subjects total per dose level. Table 23 details the same scenarios under the assumption that we over-enroll by 1 subject, e.g. dosing 6 subjects in stage 1 and 5 subjects in stage 2 (or vice versa), resulting in 11 subjects total per dose level. Figure 11-1 graphically

represents the operating characteristics of our safety stopping rules for each cohort, assuming that we enroll 10 subjects in each dose level. Cohorts 1, 2 and 3 are shown in separate plots arranged horizontally. Each line of the plot corresponds to a different scenario detailed in Table 22. The scenarios considered range from very low toxicity to very high toxicity. In low toxicity scenarios, the cohorts are likely to fully enroll, and as toxicity increases, cohorts are more likely to stop early for safety. For example, scenario 1 represents a low toxicity scenario and 84.8% of the time, our simulations fully enrolled the final cohort (dose level 3). A similar plot is shown for the case where 11 subjects are enrolled per dose level (Figure 11-2). In the case where we have 11 subjects per dose level, we see a higher percentage of trials that do not complete dose level 3. This is expected, since these trials are larger, and thus have more chances to stop for safety reasons.

Table 22 Simulation Scenarios and Results (10 subjects per dose level)

Scenario	True toxicity of dose 1	Average # of subjects dosed at dose 1	% of trials that completed dose 1	True toxicity of dose 2	Average # of subjects dosed at dose 2	% of trials that completed dose 2	True toxicity of dose 3	Average # of subjects dosed at dose 3	% of trials that completed dose 3
1	0	10	100	0.1	9.9	98.2	0.2	9.5	84.8
2	0.1	9.9	98.2	0.2	9.5	84.9	0.3	7.6	53.2
3	0.2	9.6	86.2	0.2	8.3	74.2	0.2	7.2	64.2
4	0.2	9.6	86.3	0.3	7.7	54.0	0.4	4.3	19.7
5	0.2	9.6	86.2	0.4	6.9	31.6	0.6	1.9	1.6
6	0.4	8.0	36.2	0.4	2.9	13.3	0.4	1.1	4.8

Table 23 Simulation Scenarios and Results (11 subjects per dose level)

Scenario	True toxicity of dose 1	Average # of subjects dosed at dose 1	% of trials that completed dose 1	True toxicity of dose 2	Average # of subjects dosed at dose 2	% of trials that completed dose 2	True toxicity of dose 3	Average # of subjects dosed at dose 3	% of trials that completed dose 3
1	0	11	100	0.1	10.9	97.1	0.2	10.1	78.8
2	0.1	10.9	97.3	0.2	10.1	79.3	0.3	7.5	42.8
3	0.2	10.4	81.1	0.2	8.5	65.7	0.2	6.8	53.1
4	0.2	10.4	81.4	0.3	7.7	43.8	0.4	3.6	12.0
5	0.2	10.4	81.1	0.4	6.8	22.3	0.6	1.5	0.6
6	0.4	8.4	27.7	0.4	2.3	7.5	0.4	0.6	2.1

Figure 11-1 Operating Characteristics for Safety Stopping Rules of Part 3 combination cohort (10 subjects per dose level)

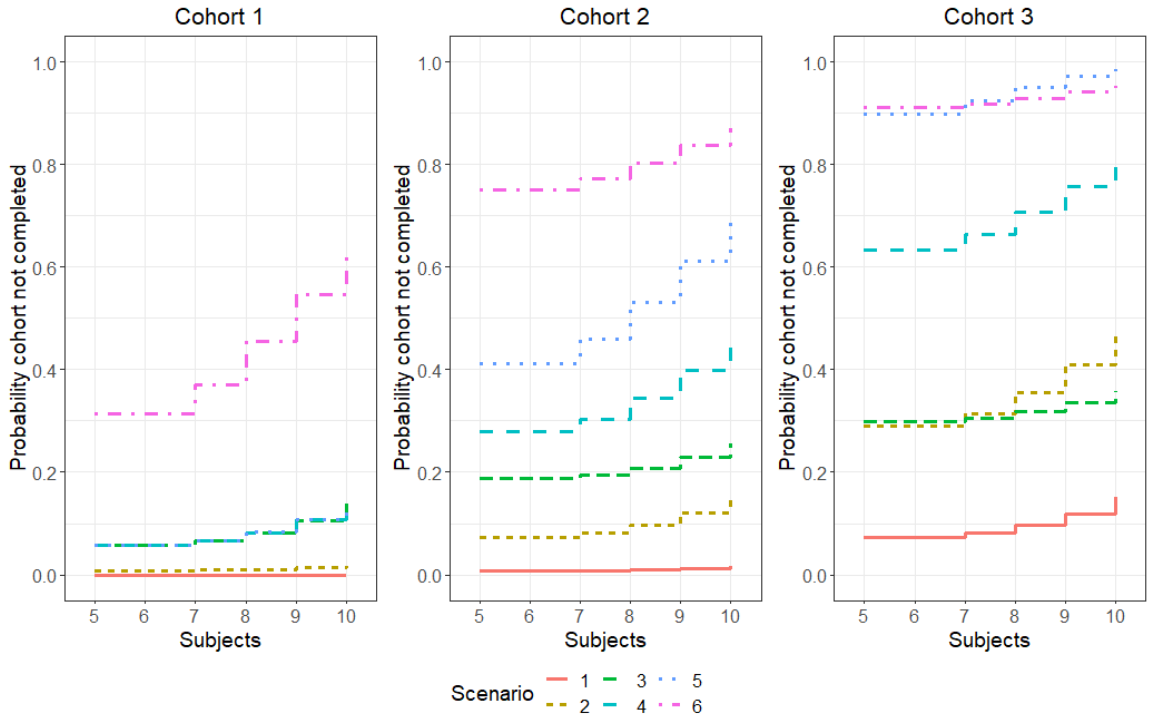
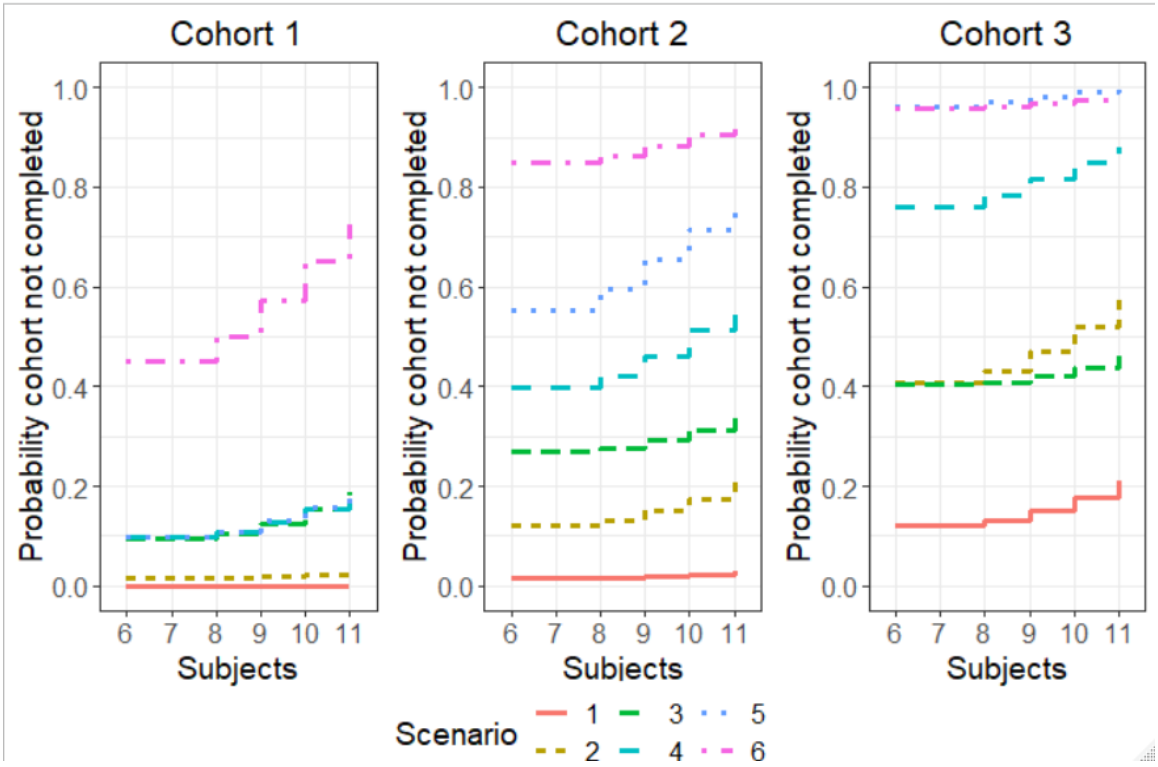


Figure 11-2 Operating Characteristics for Safety Stopping Rules of Part 3 combination cohort (11 subjects per dose level)



12. STUDY GOVERNANCE CONSIDERATIONS

12.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

12.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

12.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.

- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

12.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s), and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

12.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.

- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

12.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

12.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as

appropriate. The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

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14. APPENDICES

14.1. Appendix 1: Abbreviations and Trademarks

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
BCVA	Best corrected visual acuity
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
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
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
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
OCT	Optical coherence tomography
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
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
RNFL	Retinal nerve fiber layer
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]	CCI [redacted]
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
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

Trademark Information

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14.2. Appendix 2: Guidelines for Management of Toxicity

The following dose modification criteria should provide guidance for, but not act as a replacement for sound clinical judgment. The investigator should use clinical judgment to determine which drug may be contributing to the toxicity necessitating dose adjustment and make the appropriate change for that drug. Dose modifications should be made after discussion with the GSK medical monitor. For management of suspected pembrolizumab toxicity in Part 3, please refer to Section 14.2.2, Section 14.2.3, or to the pembrolizumab prescribing information.

14.2.1. Management of Selected Toxicities for GSK3326595

Table 24 Dose Adjustment/Stopping Safety Criteria for GSK3326595

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
Thrombocytopenia	Grade 1 & 2 (platelet count above 50,000)	Continue dosing at same dose level with weekly or more frequent monitoring as necessary
	Grade 3 (platelet count between 25,000-50,000)	For subjects with solid tumors, temporarily interrupt study medication. For subjects with non-Hodgkin's lymphoma, consider interruption of study medication. After discussion with medical monitor and using sound clinical judgement, continue at same dose or adjust dose (e.g. consider reduced daily dosing or dosing on alternate days). Monitor complete blood count (CBC) at least twice a week, more frequently if necessary
	Grade 4 (platelet count below 25,000)	Interrupt study medication and monitor CBC every 2-3 days. 1. If platelet counts recover to Grade 2 and are steady for at least 2 CBC measurements at least 3 days apart, or rising, discuss with the medical monitor. Based on clinical judgement, resume treatment at the same or previously cleared lower dose. 2. Platelet transfusion is allowed based on institutional guidelines. If platelet transfusions are required, hold drug until platelet counts recover to Grade 2, and are steady for at least 2 CBC measurements at least 3 days apart, or rising. Using clinical judgement and after consultation with the medical monitor, consider resuming treatment at same or the

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
		previously cleared lower dose. 3. Discontinue treatment if drug has to be held for >14 days.
Anemia	Grades 1 & 2 (HgB >8.0 g/dL)	Continue dosing at same dose level with weekly or more frequent monitoring as necessary
	Grade 3 (HgB <8.0 g/dL, or transfusion required)	Transfuse and treat as necessary. Monitor CBC at least twice a week, more frequently if necessary. After discussion with medical monitor and using sound clinical judgement, continue at same dose or adjust dose (e.g. consider reduced daily dosing or dosing on alternate days).
	Grade 4 (Life-threatening consequences; urgent intervention indicated)	Transfuse and treat as necessary. Temporarily interrupt study medication and monitor CBC every 2-3 days. If hemoglobin recover to Grade 2 and is steady/rising for at least 2 CBC reads at least 3 days apart, discuss with medical monitor resuming treatment at the same or adjusted dose (see Grade 3) based on sound clinical judgement.
QTcF	If >30msec and < 60 msec change from baseline AND manual QTcF <500 (average of three ECGs over at least 15 minutes)	• Continue current dose of GSK3326595 • Supplement electrolytes, particularly potassium and magnesium, to recommended levels: (1) Maintain serum potassium > 4mol/L (2) Maintain serum magnesium levels >0.85 mmol/L • Discontinue any concomitant medications with potential for QTcF prolongation. • Consider 24 hour or longer telemetry monitoring if clinically indicated.
	If ≥ 60 msec change from baseline occurs OR QTcF ≥500	• Discontinue GSK3326595 and notify the GSK Medical Monitor. (1) Supplement electrolytes to recommended levels: a. Maintain serum potassium > 4mol/L b. Maintain serum magnesium

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
	(average of three ECGs over at least 15 minutes)	levels >0.85 mmol/L (2) Rule out other potential etiologies for prolonged QTcF such as cardiac ischemia (3) Discontinue any concomitant medications with potential for QTcF prolongation. (4) Consider telemetry monitoring if clinically indicated. • This subject may consider restarting study treatment at a previous dose level if the following criteria for QTcF rechallenge are met : • QTcF Rechallenge Procedures: Do not rechallenge with study treatment unless under the following conditions: (1) QTcF event reduced to <450 msec, (2) potassium and magnesium levels are within institutional normal range, (3) a favorable risk/benefit profile (in the medical judgement of the Investigator and the GSK Medical Monitor), (4) approval within GSK medical governance: a. agreement with Safety Evaluation Medical Director and the Project Physician Lead, b. review with Chair or co-Chair of the GSK QT panel, c. Safety Evaluation VP and Clinical VP approval d. Head Unit Physician approval (5) Institutional IRB (or equivalent) approval, and (6) The subject is re-consented regarding the possible increased risk of QTc prolongation. • If approval for re-challenge is granted, the subject must be re-consented (with a separate informed consent specific to QTc prolongation)

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
		• Discontinuation procedures: If the subject is withdrawn due to QTcF event, the subject should complete the following activities post-dose: (1) Evaluation by cardiologist. (2) Weekly assessments for QTcF should be monitored weekly for two weeks, and then next assessment at 4 weeks post-dose. • (3) If QTcF results have not resolved to baseline by 4 weeks post-dose, then continue every 4-5 weeks until resolution
Liver		• Refer to procedures outlined in Section 14.6: Liver Safety Required Actions and Follow up Assessments
Diarrhea	Grade 1	• Initiate supportive care including loperamide.
	Grade 2	• Initiate supportive care including loperamide. • Consider temporary discontinuation of GSK3326595 and discuss with GSK Medical Monitor.
	Grade 3	• Above plus consider intravenous (IV) hydration, hospital admission and prophylactic antibiotics as appropriate. • Hold GSK3326595 and discuss with GSK Medical Monitor. • If diarrhea recovers to Grade 1, discuss with medical monitor; consider resuming treatment at the same or lower dose based on clinical judgement.
	Grade 4	• Above plus consider intravenous (IV) hydration, hospital admission and prophylactic antibiotics as appropriate. • Discontinue GSK3326595 permanently
Nausea/Vomiting	Grade 1	• Initiate supportive care with antiemetics as necessary.

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
	Grade 2	• Initiate supportive care with antiemetics as necessary • Consider temporary discontinuation of GSK3326595 and discuss with GSK medical monitor. If drug is held, subject may resume therapy at same level once nausea/vomiting has resolved to ≤Grade 1.
	Grade 3	• Supportive care as above, plus consider intravenous (IV) hydration, hospital admission and IV nutrition as appropriate. • Hold GSK3326595 and discuss with GSK Medical Monitor. • If nausea/vomiting recovers to less than Grade 2, discuss with medical monitor; consider resuming treatment at lower dose based on clinical judgement.
	Grade 4	• Supportive care as above, plus consider intravenous (IV) hydration, hospital admission and IV nutrition as appropriate • Discontinue GSK3326595 permanently
All Other Toxicity	Grade 1	• Continue dosing with no change
	Grade 2	• Continue dosing with no change • • OR • • Hold GSK3326595 for up to 1 week for toxicity to be < Grade 2, then continue at the same dose (dose reduction is required if the grade 2 toxicity is considered a DLT)
	Grade 3	• 1st episode: Hold dose for one week intervals until ≤ Grade 2, then restart GSK3326595 at the same or reduced dose. • 2nd episode: Utilize an alternative, less frequent schedule or reduce by one dose level. If no recovery to ≤Grade 1* after a 21 day delay, subject should discontinue therapy.

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
	Grade 4	• Discontinue GSK3326595 OR • In rare situations, based on discussion and written agreement between GSK medical monitor and investigator, if the subject is receiving benefit then the episode may be managed as per Grade 3 toxicity.

Note*: Exceptions to ≤ the drug-related Grade 1 requirement may be made for certain AEs as defined in Section 4.2.4.2.

14.2.2. Management of Immune-Related Events, Part 3 pembrolizumab combination

AEs associated with immunotherapy treatment may be immune-mediated. These immune-related AEs (irAEs) may occur shortly after the first dose, several months after the last dose of treatment, or during the treatment course and may affect more than one body system simultaneously. Therefore, early recognition of and initiation of treatment for these events is critical to reduce potential complications. Refer to pembrolizumab documents [KEYTRUDA, PI, 2019; KEYTRUDA, SPC, 2019] for additional information regarding the background and the management of other AEs or potential safety-related issues. The investigator may consult the GSK Medical Monitor on study treatment modifications (i.e., holds or discontinuation) or on the management of AEs.

For suspected irAEs, ensure adequate evaluation to confirm the etiology or exclude other causes. Additional procedures or tests such as, but not limited to, bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue treatment and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with immunotherapies are provided in Section 14.2.3.

Before administration of study treatment, investigators are to review a participant's AEs, concomitant medications, and clinical evaluation results, e.g., vital signs, laboratory results, ECOG PS, physical examination findings, responses, as outlined in the Time and Events table (Table 15), to monitor for new or worsening irAEs and ensure that continued dosing is appropriate.

Table 25 Dose Modification and Toxicity Management Guidelines for Immune-Related AEs

General instructions:

- Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.

- For situations where immunotherapy treatment has been withheld, treatment can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Immunotherapy treatment should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks.
- For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Severity Grade or Conditions	Action Taken with Pembrolizumab	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
Respiratory				
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg methylprednisolone or equivalent) followed by taper	Monitor participants for signs and symptoms of pneumonitis. Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment. Add prophylactic antibiotics for opportunistic infections.
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Gastrointestinal				
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg methylprednisolone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). Participants with ≥ Grade 2
	Grade 4	Permanently discontinue		

Immune-related AEs	Severity Grade or Conditions	Action Taken with Pembrolizumab	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
				diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
Hepatobiliary				
AST / ALT elevation or increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5- 1 mg/kg methylprednisolone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable. Refer to Section 14.6 for liver safety required actions and follow-up
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg methylprednisolone or equivalent) followed by taper	

Immune-related AEs	Severity Grade or Conditions	Action Taken with Pembrolizumab	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
				assessments and study treatment guidelines.
Endocrine				
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	Initiate insulin replacement therapy for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Adrenal insufficiency Symptomatic hypophysitis	Grade 1 or 2	Withhold until adverse reactions recover to Grades 0-1.	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). If treatment-related toxicity does not resolve to Grades 0-1 within 12 weeks after last dose of pembrolizumab, or if corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks, pembrolizumab should be
	Grade 3 or 4	For patients with Grade 3 or Grade 4 endocrinopathy that improved to Grade 2 or lower and is controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if		

Immune-related AEs	Severity Grade or Conditions	Action Taken with Pembrolizumab	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
		needed. Otherwise treatment should be discontinued		permanently discontinued.
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or Permanently discontinue		
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (e.g., levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders.
Renal				
Nephritis and renal dysfunction	Grade 2	Withhold	Administer corticosteroids (methylprednisolone 1-2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function.
	Grade 3 or 4	Permanently discontinue		
Cardiovascular				
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 3 or 4	Permanently discontinue		
Other				
All other immune-related AEs	Grade 3, or intolerable/ persistent Grade 2	Withhold or discontinue based on the type of event. Events that require discontinuation include and are not limited to: Guillain-Barre	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes.

Immune-related AEs	Severity Grade or Conditions	Action Taken with Pembrolizumab	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
		Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

NOTES:
The decision whether to withhold or permanently discontinue immunotherapy treatment is at the discretion of the investigator or treating physician. For participants with Grade 3 or 4 immune-related endocrinopathy where interruption of immunotherapy treatment is required, treatment may be resumed when the event resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or, for T1DM, metabolic control has been achieved.

Abbreviations: AE=adverse events; ALT=alanine aminotransferase; AST= aspartate aminotransferase; CTCAE=common terminology criteria for adverse events; GI=gastrointestinal irAE=immune-related AE; IV=intravenous; kg=kilogram; mg=milligram; T1DM=Type 1 diabetes mellitus

14.2.3. Dose Modification and Toxicity Management of Infusion-Reactions Related to Immunotherapy Treatment, Part 3

Infusion reactions are a well-documented AE associated with the administration of mAb. Infusion reactions typically develop within 30 minutes to 2 hours after initiation of drug infusion, although symptoms may be delayed for up to 48 hours. The incidence of infusion reactions varies by mAb agent, and there are multiple mechanisms known to lead to infusion-related reactions including both IgE-dependent anaphylactic and non-IgE dependent anaphylactoid hypersensitivities. Cytokine release syndrome, and when severe, cytokine "storm", has been identified as a sequela of the immune system activation associated with infusion reactions.

Infusion reactions may affect any organ system in the body; most are mild in severity, although severe and even fatal reactions occur. As a group, infusion reactions (including both cytokine-mediated and allergic) usually occur during or within a few hours of drug infusion. Occasionally, a reaction may occur 1 to 2 days after administration. The NCI-CTCAE for grading adverse reactions during chemotherapy administration has a scale for grading the severity of infusion reactions and separate grading scales for allergic reactions and anaphylaxis. While use of these separate grading scales may be useful for classifying the nature of an infusion reaction for research purposes, they are less useful for clinical care, since it may not be obvious if the participant is having an allergic infusion reaction or a non-allergic infusion reaction.

Clinically, an infusion reaction may present with flushing, itching, urticaria, and/or angioedema, CCI cough, sudden nasal congestion, shortness of breath, chest tightness, wheeze, sensation of throat closure or choking, and/or change in voice quality, faintness, tachycardia (or less often bradycardia), hypotension, hypertension and/or loss of consciousness, nausea, vomiting, abdominal cramping, and/or diarrhea, sense of impending doom, tunnel vision, dizziness, and/or seizure, severe back, chest, and pelvic

pain. Refer to Table 27 for dose modification and treatment guidance for immunotherapy infusion reactions.

To better understand the underlying etiology of these events, serum tryptase, C-reactive protein (CRP), ferritin, and a cytokine panel should be drawn during the occurrence of an infusion reaction/CRS of any grade as outlined in Table 26. The serum tryptase, CRP and ferritin panels should be performed at the investigator's designated local laboratory. The serum cytokine panel will be performed at a GSK designated laboratory. These data will aid in the classifying (albeit retrospectively) the etiology of the AE.

Table 26 Infusion-Related Reaction Laboratory Panel

Analyte	Relationship to Adverse Event
Serum tryptase[a]	IgE-related infusion reaction (Allergic/anaphylaxis) [Schwartz, 2006]
Serum CRP[a]	Elevated in CRS [Lee, 2014]
Serum ferritin[a]	Elevated in CRS [Lee, 2014]
Serum cytokine panel[b] (***IFN***γ*^, ***TNF***α*^, ***IL1***β**,** IL2*, IL4, ***I-6****^, ***IL8****, IL10*, ***IL12p70***, and IL13)	* Reported to be elevated in CRS [Lee, 2014] ^ Consistently reported as elevated in CRS [Lee, 2014]

Abbreviations: CRP = C-reactive protein; CRS = Cytokine release syndrome; IFNγ = Interferon gamma; TNFα =Tumor necrosis factor alpha; IL = Interleukin.

a. Performed by investigator designated local laboratory if available; otherwise performed by GSK designated laboratory
b. Performed by a GSK designated laboratory

The guidelines provided in Table 27 are suggestions. Investigators and site staff may also follow their site standard operating procedures for the treatment of these events.

Table 27 Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy	• **Stop Infusion** • Additional appropriate	Participant may be premedicated 1.5hr (± 30 minutes) prior to

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	medical therapy may include but is not limited to: o IV fluids o Antihistamines o NSAIDs o Acetaminophen o Narcotics • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment**	infusion of study drugs with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 **Grade 3:** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical	• **Stop Infusion** • Additional appropriate medical therapy may include but is not limited to: o Epinephrine** o IV fluids o Antihistamines o NSAIDs o Acetaminophen	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	○ Narcotics ○ Oxygen ○ Pressors ○ Corticosteroids • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator • Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study treatment.**	
Note: Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events at http://ctep.cancer.gov		

Abbreviations: CTCAE=common terminology criteria for adverse events; hr=hour; IV=intravenous; mg=milligram; ml=millilitres; NSAID=nonsteroidal anti-inflammatory drug; po=per os [by mouth]

14.3. Appendix 3: ECOG Performance Status

The performance status assessment is based on the ECOG scale [Oken, 1982]

0 = Fully active, able to carry on all pre-disease performance without restriction.

1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work).

2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

5 = Dead

14.4. Appendix 4: Guidelines for Assessment of Disease, Disease Progression, and Response Criteria

14.4.1. Response Criteria for Solid Tumors (RECIST 1.1 [Eisenhauer, 2009])

14.4.1.1. Assessment Guidelines

Please note the following:

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion. Contrast agents must be used in accordance with the Image Acquisition Guidelines.
- All measurements should be taken and recorded in millimeters (mm), using a ruler or calipers.
- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by CT or MRI is required.
- Fluorodeoxyglucose (FDG)-PET is generally not suitable for ongoing assessments of disease. However FDG-PET can be useful in confirming new sites of disease where a positive FDG-PET scans correlates with the new site of disease present on CT/MRI or when a baseline FDG-PET was previously negative for the site of the new lesion. FDG-PET may also be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and FDG-PET is performed at all assessments.
- If PET/CT is performed then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required anatomical coverage and prescribed use of contrast. The method of assessment should be noted as CT on the CRF.

Clinical Examination: Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules) [Eisenhauer, 2009].

CT and MRI: **Contrast enhanced CT with 5mm contiguous slices is recommended.** Minimum size of a measurable baseline lesion should be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. MRI is acceptable, but when used, the technical specification of the scanning sequences should be optimised for the evaluation of the type and site of disease and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible the same scanner should be used [Eisenhauer, 2009].

X-ray: In general, X-ray should not be used for target lesion measurements owing to poor lesion definition. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung; however chest CT is preferred over chest X-ray [Eisenhauer, 2009].

Brain Scan: If brain scans are required, then contrast enhanced MRI is preferable to contrast enhanced CT.

Bone Scan (typically bone scintigraphy): If a bone scan is performed and a new lesion(s) is equivocal, then correlative imaging (i.e., X-ray, CT, or MRI) is required to demonstrate malignant characteristics of the lesion(s).

Note: PET [FDG or fluoride] may be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and PET is performed at all assessments.

14.4.1.2. Guidelines for Evaluation of Disease

14.4.1.2.1. Measurable and Non-measurable Definitions

Measurable lesion

A non-nodal lesion that can be accurately measured in at least one dimension (longest dimension) of

- ≥10 mm with MRI or CT when the scan slice thickness is no greater than 5mm. If the slice thickness is greater than 5mm, the minimum size of a measurable lesion must be at least double the slice thickness (e.g., if the slice thickness is 10 mm, a measurable lesion must be ≥20 mm).
- ≥10 mm caliper/ruler measurement by clinical exam or medical photography.
- ≥20 mm by chest x-ray.

Additionally lymph nodes can be considered pathologically enlarged and measurable if

- ≥15mm in the short axis when assessed by CT or MRI (slice thickness recommended to be no more than 5mm). At baseline and follow-up, only the short axis will be measured [Eisenhauer, 2009].

Non-measurable lesion

All other lesions including lesions too small to be considered measurable (longest diameter <10 mm or pathological lymph nodes with ≥ 10 mm and <15 mm short axis) as well as truly non-measurable lesions, which include: leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques [Eisenhauer, 2009].

Measurable disease: The presence of at least one measurable lesion. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilized as the only measurable lesion.

Non-Measurable only disease: The presence of only non-measurable lesions.

14.4.1.3. Baseline Documentation of Target and Non-Target Lesions

- All baseline lesion assessments must be performed within (28) days of randomization.

- Lymph nodes that have a short axis of <10mm are considered non-pathological and should not be recorded or followed.
- Pathological lymph nodes with <15mm and but ≥10mm short axis are considered non-measurable.
- Pathological lymph nodes with ≥15mm short axis are considered measurable and can be selected as target lesions, however lymph nodes should not be selected as target lesions when other suitable target lesions are available.
- Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

Note: Cystic lesions thought to represent cystic metastases should not be selected as target lesions when other suitable target lesions are available.

Note: Measurable lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as target lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered measurable. Bone scans, FDG-PET scans or X-rays are not considered adequate imaging techniques to measure bone lesions.
- All other lesions (or sites of disease) should be identified as non-target and should also be recorded at baseline. Non-target lesions will be group by organ. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

14.4.1.4. Response Criteria

14.4.1.4.1. Evaluation of target lesions

Definitions for assessment of response for target lesion(s) are as follows:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes must be <10mm in the short axis.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (e.g. percent change from baseline).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g. percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5mm.

- Not Applicable (NA): No target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the five preceding definitions.

Note:

- If lymph nodes are documented as target lesions the short axis is added into the sum of the diameters (e.g. sum of diameters is the sum of the longest diameters for non-nodal lesions and the short axis for nodal lesions). When lymph nodes decrease to non-pathological size (short axis <10mm) they should still have a measurement reported in order not to overstate progression.
- If at a given assessment time point all target lesions identified at baseline are not assessed, sum of the diameters cannot be calculated for purposes of assessing CR, PR, or SD, or for use as the nadir for future assessments. However, the sum of the diameters of the assessed lesions and the percent change from nadir should be calculated to ensure that progression has not been documented. If an assessment of PD cannot be made, the response assessment should be NE.
- All lesions (nodal and non-nodal) should have their measurements recorded even when very small (e.g. 2 mm). If lesions are present but too small to measure, 5 mm should be recorded and should contribute to the sum of the diameters, unless it is likely that the lesion has disappeared in which case 0 mm should be reported.
- If a lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance. However, if the response status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

14.4.1.4.2. Evaluation of non-target lesions

Definitions for assessment of response for non-target lesions are as follows:

- Complete Response (CR): The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at baseline must be non-pathological (e.g. <10 mm short axis).
- Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline ≥ 10 mm short axis.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.
- Not Applicable (NA): No non-target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the four preceding definitions.

Note:

- In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- In the presence of non-measurable only disease consideration should be given to whether or not the increase in overall disease burden is comparable in magnitude to the increase that would be required to declare PD for measurable disease.
- Sites of non-target lesions, which are not assessed at a particular timepoint based on the assessment schedule, should be excluded from the response determination (e.g. non-target response does not have to be "Not Evaluable").

14.4.1.4.3. New lesions

New malignancies denoting disease progression must be unequivocal. Lesions identified in follow-up in an anatomical location not scanned at baseline are considered new lesions.

Any equivocal new lesions should continue to be followed. Treatment can continue at the discretion of the investigator until the next scheduled assessment. If at the next assessment the new lesion is considered to be unequivocal, progression should be documented.

14.4.1.4.4. Evaluation of overall response

Table 28 presents the overall response at an individual time point for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions for subjects with measurable disease at baseline.

Table 28 Evaluation of Overall Response for Subjects with Measurable Disease at Baseline

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Non-PD or NA or NE	No	PR
SD	Non-PD or NA or NE	No	SD
NE	Non-PD or NA or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response, PR = partial response, SD=stable disease, PD=progressive disease, NA= Not applicable, and NE=Not Evaluable

Table 29 presents the overall response at an individual time point for all possible combinations of tumor responses in non-target lesions with or without the appearance of new lesions for subjects with non-measurable only disease at baseline.

Table 29 Evaluation of Overall Response for Subjects with Non-Measurable Only Disease at Baseline

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non CR/Non PD	No	Non CR/Non PD
NE	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR=complete response, PD=progressive disease, and NE=Not Evaluable

Note: Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

14.4.1.4.5. Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence and will be determined programmatically by GSK based on the investigators assessment of response at each time point.

- To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after first dose at a minimum interval of 49 days (based on the expected 56 ± 7 day window)
- 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.

14.4.1.4.6. Confirmation Criteria

- 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.

14.4.2. Response Criteria for GBM

This study employs response criteria from the Response Assessment in Neuro-Oncology (RANO) Working Group [Wen, 2010].

All measurable and non-measurable lesions should be assessed using the same techniques as at baseline. Ideally, subjects should be imaged on the same MRI scanner, or at least

with the same magnet strength, for the duration of the study to reduce difficulties in interpreting changes.

Measurable disease is defined as bidimensionally contrast enhancing lesions with clearly defined margins by CT or MRI scan, with two perpendicular diameters of at least 10 mm, visible on two or more axial slices that are preferably, at most, 5 mm apart with 0-mm skip. As with RECIST version 1.1, in the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be two times the slice thickness. In the event there are interslice gaps, this also needs to be considered in determining the size of measurable lesions at baseline. Measurement of tumor around a cyst or surgical cavity represents a particularly difficult challenge. In general, such lesions should be considered non-measurable unless there is a nodular component measuring ≥10 mm in diameter. The cystic or surgical cavity should not be measured in determining response.

Non-measurable disease is defined as either unidimensionally measurable lesions, masses with margins not clearly defined, or lesions with maximal perpendicular diameters less than 10 mm.

Radiographic response should be determined in comparison to the tumor measurements obtained at pretreatment baseline for determination of response, the smallest tumor measurements at either pretreatment baseline or after initiation of therapy should be used for determination of progression.

- Complete response (CR): Complete disappearance of all enhancing measurable and non-measurable disease on contrast enhanced MRI scan sustained for at least 4 weeks, no new lesions, and stable or improved nonenhancing (T2/FLAIR) lesions. In addition, subject must be off steroids or only on physiologic replacement doses. In the absence of a confirming scan 4 weeks later, this response will be considered only stable disease.
- Partial response (PR): Greater than or equal to a 50% reduction, compared to baseline, in the sum of products of the perpendicular diameters for all measurable lesions for at least 4 weeks, no progression of non-measurable disease, no new lesions, and stable or improved nonenhancing (T2/FLAIR) lesions. In addition, subject must be on a corticosteroid dose not greater than the dose at the time of baseline scan and be stable or improving clinically. In the absence of a confirming scan 4 weeks later, this response will be considered only stable disease.
- Progressive Disease (PD): Greater than or equal to a 25% increase in sum of the products of perpendicular diameters of enhancing lesions (compared with baseline if no decrease) on stable or increasing doses of corticosteroids, OR a significant increase in T2/FLAIR nonenhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not due to comorbid events, OR the appearance of any new lesions, OR clear progression of non-measurable lesions, OR definite clinical deterioration not attributable to other causes apart from tumor, or to decrease in corticosteroid dose. Failure to return for evaluation as a result of death or deteriorating condition should also be considered as progression.

- Stable disease (SD): If subject does not qualify for CR, PR, or PD and has stable nonenhancing (T2/FLAIR) lesions on same or lower doses of corticosteroids compared with baseline scan and clinically stable status. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging and subsequent follow-up imaging shows that this increase in corticosteroid dose was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

Increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumor, will not be used as a determinant of progression. Subjects with stable imaging studies whose corticosteroid dose was increased for reasons other than clinical deterioration related to tumor do not qualify for stable disease or progression. They should be observed closely. If their corticosteroid dose can be reduced back to baseline, they will be considered as having stable disease; if further clinical deterioration related to tumor becomes apparent, they will be considered to have progression. The date of progression should be the first time point at which corticosteroid increase was necessary.

The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decline in the Karnofsky Performance Status (KPS) from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration unless attributable to comorbid events or changes in corticosteroid dose. Similarly, a decline in the Eastern Cooperative Oncology Group and world health organization (WHO) performance scores from 0 or 1 to 2 or 2 to 3 would be considered neurologic deterioration.

Subjects with non-measurable enhancing disease whose lesions have significantly increased in size and become measurable (minimal bidirectional diameter of ≥ 10 mm and visible on at least two axial slices that are preferably, at most, 5 mm apart with 0-mm skip) will also be considered to have experienced progression. The transition from a non-measurable lesion to a measurable lesion resulting in progression can theoretically occur with relatively small increases in tumor size (e.g., a 9 X 9mm lesion [non-measurable] increasing to a 10 X 11mm lesion [measurable]). Ideally, the change should be significant (>5 mm increase in maximal diameter or ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions).

In general, if there is doubt about whether the lesion has progressed, continued treatment and close follow-up evaluation will help clarify whether there is true progression. If there is uncertainty regarding whether there is progression, the subject may continue on treatment and remain under close observation (e.g., evaluated at 4-week intervals). If subsequent evaluations suggest that the subject is in fact experiencing progression, then the date of progression should be the time point at which this issue was first raised.

14.4.3. Evaluation, Staging and Response Assessments for Non-Hodgkin's Lymphoma: The Lugano Classification (according to Cheson, 2014)

Evaluation, staging, and response criteria are summarized in 3 tables below.

Criteria for Involvement of Site

Tissue Site	Clinical	FDG Avidity	Test	Positive Finding
Lymph nodes	Palpable	FDG-avid histologies	PET-CT	Increased FDG uptake
		Non-avid disease	CT	Unexplained node enlargement
Spleen	Palpable	FDG-avid histologies	PET-CT	Diffuse uptake, solitary mass, miliary lesions, nodules
		Non-avid disease	CT	> 13 cm in vertical length, mass, nodules
Liver	Palpable	FDG-avid histologies	PET-CT	Diffuse uptake, mass
		Non-avid disease	CT	Nodules
CNS	Signs, symptoms		CT	Mass lesion(s)
			MRI	Leptomeningeal infiltration, mass lesions
			CSF assessment	Cytology, flow cytometry
Other (e.g., skin, lung, GI tract, bone, bone marrow)	Site dependent		PET-CT[a], biopsy	Lymphoma involvement

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.

a: PET-CT is adequate for determination of bone marrow involvement and can be considered highly suggestive for involvement of other extralymphatic sites. Biopsy confirmation of those sites can be considered if necessary.

Staging System for Primary Nodal Lymphomas

Stage	Involvement	Extranodal (E) Status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky[a]	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

NOTE. Extent of disease is determined by positron emission tomography–computed tomography for avid lymphomas and computed tomography for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

a: Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

Criteria for Response Assessment of Non- Hodgkin's Lymphoma

Response	Site	PET-CT-Based Response	CT-Based Response
Complete		Complete metabolic response (all of the following)	Complete radiologic response (all of the following)
	Lymph nodes and extralymphatic sites	Score 1, 2, or 3[a] with or without a residual mass on 5PS[2]	Target nodes/nodal masses must regress to ≤1.5 cm in LDi
		It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than	No extralymphatic sites of disease

Response	Site	PET-CT-Based Response	CT-Based Response
		normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	
	Non-measured lesion	Not applicable	Absent
	Organ enlargement	Not applicable	Regress to normal
	New lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if determinate, IHC negative
Partial		Partial metabolic response (all of the following)	Partial remission (all of the following)
	Lymph nodes and extralymphatic sites	Score 4 or 5[b] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of intervention, these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
	Non-measured lesion	Not applicable	Absent/normal, regressed, but no increase

Response	Site	PET-CT-Based Response	CT-Based Response
	Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
	New lesions	None	None
	Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease		No metabolic response	Stable disease
	Lymph nodes and extralymphatic sites	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of intervention	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
	Non-measured lesion	Not applicable	No increase consistent with progression
	Organ enlargement	Not applicable	No increase consistent with progression
	New lesions	None	None
	Bone marrow	No change from baseline	Not applicable
Progressive disease		Progressive metabolic disease	Progressive disease requires at least 1 of the following:
	Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:

Response	Site	PET-CT-Based Response	CT-Based Response
	Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-intervention assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir. 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
	Non-measured lesions	None	New or clear progression of preexisting non-measured lesions
	New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to

Response	Site	PET-CT-Based Response	CT-Based Response
			lymphoma Assessable disease of any size unequivocally attributable to lymphoma
	Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

a: A score of 3 in many patients indicates a good prognosis with standard intervention, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid underintervention). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

b: PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Algorithm for determining combined imaging response based on Lugano criteria

Anatomic/Radiologic Response	**Metabolic Response**	**Combined Imaging Response**
CR	CMR, NE, or missing	CR
PR	CMR	CR
CR	PMR	PR
CR	NMR	PR

PR	PMR	PR
PR	NMR	PR
SD	PMR	PR
PD	PMR	PD
SD	NMR	SD
CR, PR, SD or NE	PMD	PD
CR, PR, SD or NE	NE or missing	CR, PR, SD or NE (Anatomic Response)
PD	NMR	PD
PD	PMD	PD

14.4.4. iRECIST Guidelines

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used to assess tumor response and progression, and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed according to the rules described below. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. These data will be captured in the clinical database.

Clinical stability is defined as meeting all of the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed **clinically unstable** should be discontinued from study treatment at site-assessed radiologic evidence of PD. It is strongly preferred to obtain the repeat tumor imaging, when feasible, for confirmation of PD by iRECIST. The tumor assessment should be repeated at least 4 weeks and up to 8 weeks later to confirm PD by iRECIST. Images should continue to be sent in to the central imaging vendor for potential central review.

If repeat imaging does not confirm PD per iRECIST and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

If a participant has confirmed radiographic progression (iCPD) as defined below, study treatment should be discontinued; however, if the participant is achieving a clinically meaningful benefit, as assessed by the Investigator and confirmed by the Medical Monitor, continuation of study treatment may be considered upon agreement of all parties. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 8.1 and submitted to the central imaging vendor.

Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological PD by RECIST 1.1 the investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management (see Table 30 and Figure 14-1). This decision should be based on the participant's overall clinical condition (See discussion of clinical stability above).

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir
    - **Note:** the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

At the confirmatory imaging visit assessment, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR). Timing of confirmatory imaging is described in Section 8.1.

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
  - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
  - For new lesions, worsening is any of these:
    - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
    - Visible growth of new non-target lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND

- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset." This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, continuation of study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in the Time and Events Tables and submitted to the central imaging vendor.

Detection of Progression at Visits after Pseudo-Progression Resolves

After resolution of pseudo-progression (i.e., achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
    - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
    - If non-target lesions have never shown unequivocal progression, doing so for the first-time results in iUPD.
    - If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions.
- New lesions
    - New lesions appear for the first time
    - Additional new lesions appear

- Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
- Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication [Seymour, 2017].

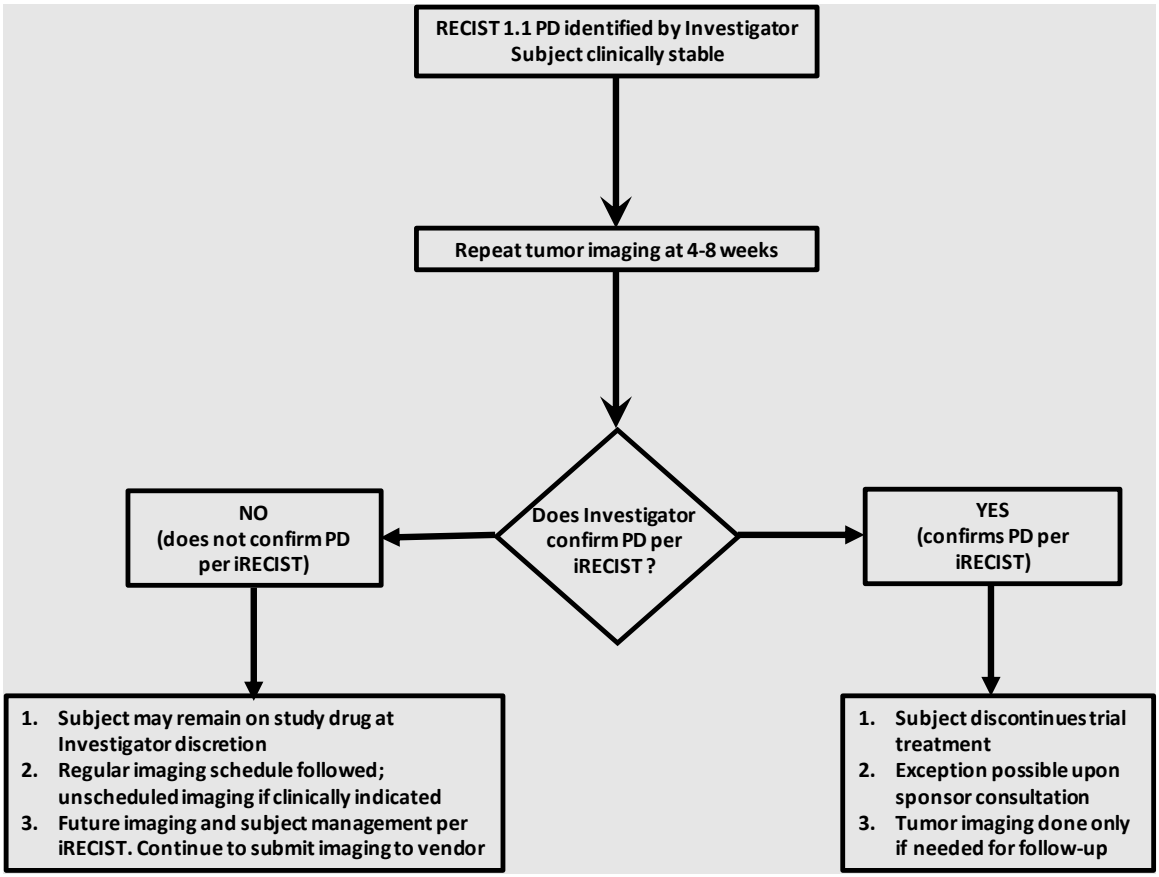
Table 30 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
Repeat tumor imaging confirms PD (iCPD) by iRECIST per investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.

iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1.

Figure 14-1 Imaging and Treatment for Clinically Stable Participants after First Radiologic Evidence of PD Assessed by the Investigator



14.5. Appendix 5: Estimated Glomerular Filtration Rate

CKD-Epi:

Females, serum creatinine >62 µmol/L: $144 \times (\text{serum creatinine} \times 0.0113/0.7)^{-1.209} \times 0.993^{\text{age}}$

Females, serum creatinine ≤62 µmol/L: $144 \times (\text{serum creatinine} \times 0.0113/0.7)^{-0.329} \times 0.993^{\text{age}}$

Males, serum creatinine >80 µmol/L: $141 \times (\text{serum creatinine} \times 0.0113/0.9)^{-1.209} \times 0.993^{\text{age}}$

Males, serum creatinine ≤80 µmol/L: $141 \times (\text{serum creatinine} \times 0.0113/0.9)^{-0.411} \times 0.993^{\text{age}}$

[Levey, 2009]

14.6. Appendix 6: Liver Safety Required Actions and Follow-up Assessments

Phase I/II liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance) [www.fda.gov, 2009].**Phase I/II liver chemistry stopping criteria and required follow up assessments**

Liver Chemistry Stopping Criteria – Liver Stopping Event **Subject with entry criteria ALT≤ 2.5 x ULN**	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN **and** cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Liver Chemistry Stopping Criteria – Liver Stopping Event **Including subjects with documented liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN**	
ALT-absolute	**Both** ALT ≥ 5xULN **and** ≥2x baseline value
ALT Increase	**Both** ALT ≥ 3xULN **and ≥** 1.5x baseline value that persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	**Both** ALT ≥ 3xULN **and ≥** 1.5x baseline value that cannot be monitored for 4 weeks
Symptomatic[3]	**Both** ALT ≥ 3xULN **and ≥** 1.5x baseline value associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study	• Viral hepatitis serology[4]

Liver Chemistry Stopping Criteria – Liver Stopping Event

Subject with entry criteria ALT≤ 2.5 x ULN

treatment

- Report the event to GSK **within 24 hours**
- Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
- Perform liver event follow up assessments
- Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below)
- **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to Appendix 7)
- If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments

MONITORING:

For bilirubin or INR criteria:

- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs**
- Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline
- A specialist or hepatology consultation is recommended

For All other criteria:

- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs**
- Monitor subjects weekly until liver chemistries resolve, stabilize or return
- Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5]
- Blood sample for pharmacokinetic (PK) analysis, obtained 2 days after last dose[6]
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin≥2xULN
- Obtain complete blood count with differential to assess eosinophilia
- Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
- Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications
- Record alcohol use on the liver event alcohol intake case report form (CRF)

For bilirubin or INR criteria:

- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).
- Serum acetaminophen adduct high-performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]).
- Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

Liver Chemistry Stopping Criteria – Liver Stopping Event **Subject <u>with</u> entry criteria ALT≤ 2.5 x ULN**	
to within baseline	

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase I/II Oncology liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
Subject <u>with</u> entry criteria ALT≤2.5x ULN ALT ≥3xULN **but** <5xULN **and** bilirubin <2xULN, **without** symptoms believed to be related to liver injury or hypersensitivity **and** who can be monitored weekly for 4 weeks **Subject <u>with documented</u> liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN** ALT ≥3x ULN and 1.5x baseline value **but** ALT <5x ULN and 2x baseline value **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury, or hypersensitivity **and** who can be monitored	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above **For subjects with entry criteria ALT≤2.5 x ULN** • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline. **For subjects with documented liver**

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
weekly for 4 weeks	**metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN** • If, after 4 weeks of monitoring, ALT <3xULN and <1.5x baseline value, and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline

14.7. Appendix 7: Liver Safety – Study Treatment Restart or Rechallenge Guidelines

Drug restart may be considered for a subject exhibiting compelling benefit for a critical medicine following drug-induced liver injury, if there is favorable benefit: risk ratio and no alternative medicine available.

If subject meets liver chemistry stopping criteria do not restart/rechallenge subject with study treatment unless:

- GSK Medical Governance approval **is granted** (as described below),
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

If GSK Medical Governance approval to restart/rechallenge subject with study treatment **is not granted**, then subject must permanently discontinue study treatment and may continue in the study for protocol-specified follow up assessments

Background Information on Drug Restart/Rechallenge

Rechallenge Following Liver Stopping Events that are Possibly Related to Study Treatment

Following drug-induced liver injury, **drug rechallenge is associated with a 13% mortality across all drugs in prospective studies** [Andrade, 2009]. Clinical outcomes vary by drug, with nearly 50% fatality with halothane re-administered within one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include:

- Hypersensitivity [Andrade, 2009] with initial liver injury (e.g. fever, rash, eosinophilia)
- jaundice or bilirubin >2xULN with initial liver injury (direct bilirubin >35% of total)
- subject currently exhibits severe liver injury defined by: ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total), or INR≥1.5
- serious adverse event or fatality has earlier been observed with drug rechallenges [Papay, 2009; Hunt, 2010]
- evidence of drug-related preclinical liability (e.g. reactive metabolites; mitochondrial impairment) [Hunt, 2010]

Rechallenge refers to resuming study treatment following drug induced liver injury (DILI). Because of the risks associated with rechallenge after DILI this should only be considered for a subject for whom there is compelling evidence of benefit from a critical or life-saving medicine, there is no alternative approved medicine available, and a benefit:risk assessment of rechallenge is considered to be favourable.

Approval by GSK for rechallenge with study treatment can be considered where:

- Investigator requests consideration of rechallenge with study treatment for a subject who is receiving compelling benefit with study treatment that exceeds risk, and no effective alternative therapy is available.
- Ethics Committee or Institutional Review Board approval for rechallenge with study treatment must be obtained, as required.
- If the rechallenge is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the rechallenge with study treatment. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for rechallenge with study treatment must return to the clinic twice a week for liver chemistry tests until stable liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If after study treatment rechallenge, subject meets protocol-defined liver chemistry stopping criteria, study treatment should be permanently discontinued.
- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment rechallenge.
- GSK to be notified of any adverse events, as per Section 9.

Restart Following Transient Resolving Liver Stopping Events NOT Related to Study Treatment

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with human leukocyte antigen (HLA) markers of liver injury.

Approval by GSK for study treatment restart can be considered where:

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
- Restart risk factors (e.g., fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis, possible study treatment-induced liver injury or study treatment has an HLA genetic marker associated with liver injury (e.g., lapatinib, abacavir, amoxicillin/clavulanate) are reviewed and excluded
- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.

- If restart of study treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.
- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment restart.
- GSK to be notified of any adverse events, as per Appendix 9.

14.8. Appendix 8: Genetic Research

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and response to medicine, including GSK3326595 or any concomitant medicines.

US Food and Drug Administration states that an *in vitro* companion diagnostic device (IVD) could be essential for the safe and effective use of a corresponding therapeutic product to:

- Identify subjects who are most likely to benefit from a particular therapeutic product;
- Identify subjects likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product;
- Monitor response to treatment for the purpose of adjusting treatment (e.g. schedule, dose, discontinuation) to achieve improved safety or effectiveness

Global regulatory requirements for IVD companion diagnostic tests are evolving. If a DNA-based IVD companion diagnostic device might be needed to identify subjects who are appropriate for the GSK medicinal product(s) under investigation in this protocol, then GSK should collect and retain DNA samples from subjects who carry the genetic variant of interest as well as DNA samples from subjects who do not carry the genetic variants of interest to validate the performance of the companion diagnostic. Any IVD companion diagnostic research objectives should be described in subject informed consent forms.

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in the RAP prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 ml blood sample will be taken for deoxyribonucleic acid (DNA) extraction. A Blood sample is collected at the baseline visit, after the subject has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or "coded") with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample

destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

14.9. Appendix 9: Definition of and Procedures for Recording, Evaluating, Follow-Up, and Reporting of Adverse Events

14.9.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. • The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events <u>NOT</u> meeting definition of an AE include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

14.9.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

g. Is associated with liver injury <u>and</u> impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

Refer to Appendix 3 for the required liver chemistry follow-up instructions

14.9.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina

- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

14.9.4. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- Post Protocol Amendment 8 implementation, SAEs, AESIs, AEs leading to treatment discontinuation and overdoses (as defined in Section 14.9.1) will be recorded via a paper process and provided to GSK (refer to SRM)
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.
- Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer.
- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

14.9.5. Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental Activities of Daily Living (ADL)[1]
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[2]
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

1. Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

2 Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up

information, amending the SAE data collection tool accordingly.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

14.9.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool. Post Protocol Amendment 8 implementation, SAEs will be collected via paper process and submitted to GSK (refer to SRM).
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and e-mail it to the Medical Monitor
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

14.10. Appendix 10: Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 9. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will discontinue study medication

For male study subjects:

- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- Post Protocol Amendment 8, pregnancy information will be collected up to 90 days after last dose of study treatment via paper process and submitted to GSK (refer to SRM).

14.11. Appendix 11: Details of Bayesian Hierarchical Model

Y_i is the response indicator for the ith subject, and $\pi_j = P(Y_i = 1 \mid j_i = j)$ is the true response rate for cohort j. In the logic scale, θ_j is the mean log odds treatment effect of response:

$$\theta_j = \log\left(\frac{\pi_j}{1-\pi_j}\right) - \log\left(\frac{\eta_j}{1-\eta_j}\right)$$

Basic Hierarchical Model

A basic hierarchical model structure is described here and is incorporated within the clustered hierarchical model framework used in this study. Borrowing occurs to the extent indicated by the data using a hierarchical normal model on the treatment effects:

$$\theta_j \sim N(\mu, \tau^2).$$

Were only this basic hierarchical model used for analysis, the prior distributions would be:

$$\mu \sim N(0, 1.82) \text{ and } \tau^2 \sim IG(0.5, 0.125),$$

where $IG(\alpha,\beta)$ is the inverse gamma distribution defined by:

$$f(x \mid \alpha, \beta) = \frac{\beta^{\alpha} e^{-\beta/x}}{x^{\alpha+1}\Gamma(\alpha)}$$

This distribution is non-informative in the sense that its parameters are analogous to having a single observation. The variance component τ is a key parameter that plays a role in the degree of borrowing among cohorts. Small values of τ result in a greater degree of borrowing while large values of τ correspond to less borrowing. The distribution of τ is based on the variability of the observations, and the observed between cohort variation is an important component of the model's performance. The effects of any particular prior distribution for τ can be assessed via simulations in evaluating a design's operating characteristics, type I error rate and statistical power.

Clustered Hierarchical Model

A clustered hierarchical model considers the possibility that "clusters" exist among the collection of histologies. A therapy may be effective for some histologies but not for others. Histologies within the same cluster have greater influence on each other than they do on histologies in other clusters. On the other hand, histologies in different clusters are conditionally independent given any particular configuration of clusters. There is borrowing at the cluster level and borrowing across histologies within a particular cluster. Borrowing across clusters depends only on similarities between clusters and not of individual histologies.

The number of clusters is unknown in advance but information will be gleaned from the data using Dirichlet Process Mixtures (DPM). The full prior is constructed in 2 stages. In the first stage, the histologies are assigned to particular clusters, with the number of clusters unspecified. Conditional on this particular clustering, the hierarchical model is fit within each cluster. A difference from the basic hierarchical model is in the parameter τ. Each cluster has its ownτ. And the prior distribution on τ is now different:

$$\tau^2 \sim IG(3,0.5).$$

Without the clustering, an informative prior on τ that places high probability on small values of τ could yield conclusions similar to simple pooling across histologies. This is not desirable. Instead its preferred to preserve the integrity of individual histologies to the extent that they give dissimilar results. With the clustering, a prior such as the one selected above meets this desideratum. When τ is small, as evinced by the data, histologies will only be placed in the same cluster if the data for those histologies are sufficiently similar to other histologies in the cluster. When τ is large, the histologies will be assigned to separate clusters and response rates estimated separately. This clustering approach provides further protection against borrowing between dissimilar histologies while enhancing the borrowing between similar histologies.

The prior distribution in a DPM is governed by the parameter α. When α is small, the prior favors large clusters. As α tends to zero, the prior tends to place all its mass on a single cluster containing all the histologies. As α increases, the prior places more mass on clustering with a large number of clusters. As α becomes large, the prior places all of its mass on having a separate cluster for each histology (thus, no borrowing across histologies). A value of $\alpha = 0$ corresponds to the usual hierarchical model with no clustering, while a very large αtreats all the histologies separately. Common values of α might be between 0.5 and 5. We have selected $\alpha = 2$ for the final model. This value has been used for the final algorithm and the operating characteristics including type I error and power.

The key aspect of the clustering portion of the prior involves which histologies are clustered together. This is accomplished by creating a sequence of bins (in theory there are infinitely many bins, but the number of bins actually used cannot exceed the number of histologies). Thus imagine a sequence of bins C1,C2,C3,… with associated probabilities p_{C1},p_{C2},p_{C3} and so forth. In the prior, each histology is placed in a bin according to the p_{Ck} probabilities. Thus, if one p_{Ck} is near 1, then all histologies will be likely to randomly fall in the same bin. If all the p_{Ck} values are small, it will be likely that all the histologies will randomly fall in separate bins. Histologies that fall within the same bin are defined as being in the same cluster. More details may be found in Escobar [Escobar, 1995] or Neal [Neal, 2000].

The p_{Ck} probabilities are determined through a stick breaking process [Sethuraman, 1994]. Let $p_{C1} \sim Beta(1,\alpha)$. This leaves $1-p_{C1}$ probability to be allocated to the remaining bins. Let p_{C2} be a $Beta(1,\alpha)$ proportion of that remaining mass, so $p_{C2} \sim Beta(1,\alpha)*[1-p_{C1}]$. There is now $1-p_{C1}-p_{C2}$ mass unallocated. Let p_{C3} be a $Beta(1,\alpha)$ proportion of the remaining mass, so $p_{C3} \sim Beta(1,\alpha)*[1-p_{C1}-p_{C2}]$ and so on for p_{C4}, p_{C5}, and so forth. This

process generates an infinite sequence of p_{Ck} values, but generally the first few contain most of the probability. In terms of the posterior distribution, only the bins which contain the histologies are of interest, and thus only 9 of the infinite bins will actually be used.

The role of α can be seen from this construction. If α is very small, then the Beta(1,α) proportions will tend to be close to 1. Thus, the first p_{C1} is quite likely to be near 1, and thus all the histologies will tend to lie in the first bin. If α is very large, all the Beta(1,α) values will tend to be small, and thus each p_{Ck} will tend to be small. This creates a situation where each histology is likely to be in a separate bin. Our proposed value of α=2 avoids these forced extremes and allows the data to drive the posterior distribution. After the histologies have been assigned to bins in the prior, histologies within the same bin will tend to have more similar data than histologies in separate bins. Thus, in the posterior distribution, histologies with similar data are viewed as more likely to be from the same bin (and hence the same cluster). Histologies with very different data, in contrast, will have high posterior probability of being in separate bins/clusters, and thus will be estimated separately.

The posterior distribution also can be thought of in 2 stages, the first being a posterior distribution on the clustering, and then conditional on the clustering the posterior distribution from the hierarchical model. Conditional on the clustering, borrowing happens within clusters, but not across clusters. In situations where the clustering is uncertain (always in practice), one will see a proportional amount of borrowing between histologies, proportional on the posterior probability of the histologies within the same cluster. The aim of the clustering is to identify situations where the drug generally works for some histologies and generally does not work for others, so that these two disparate effects are not averaged together through the borrowing.

14.12. Appendix 12: COVID-19 APPENDIX: RECOMMENDED MEASURES

Overall Rationale for this Appendix

COVID-19 pandemic may impact the conduct of clinical studies. Challenges may arise from quarantines, site closures, travel limitations interruptions to the supply chain for the investigational product or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing.

This protocol appendix outlines measures that may be applicable for any site impacted by the COVID-19 pandemic. The purpose of the appendix is to provide information on the measures to be taken to protect participants' safety, welfare and rights, and promote data integrity.
These measures will remain in place until the site is able to resume normal working activities.

Study Procedures During COVID-19 Pandemic

During the special circumstances caused by the current COVID-19 pandemic, you should consider specific public health guidance, the impact of any travel restrictions implemented by local/regional health authorities and local institutions, and individual benefit /risk when making enrollment and treatment decisions for trial participants.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention including follow up, however when not possible, for the duration of these special circumstances, the following measures may be implemented for enrolled participants where applicable country and local regulations and infrastructure allow.

- Clinical investigators should document in site files and in participant notes/Electronic Heath Records as appropriate how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes, and indicate which trial participants were impacted and how those trial participants were impacted (as per the current local COVID-19 related regulatory guidance).

- Missing protocol required data/visits due to COVID-19 must be noted in participant notes and recorded as a COVID-19-related protocol deviation.

Protocol Defined Procedures/Visits:

- Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include collection of blood and urine samples, measurement of vital signs and weight, and preparation and administration of study drug (at the discretion of the Investigator , based on safety and tolerability). It is the responsibility of the investigator to inform GSK or delegate when this occurs and to

document in source notes. The participant should be informed of the plan and any potential risks associated with this approach and sign a revised Informed Consent Form if required. IRB/Ethics committee should be informed and/or approve of this change in approach and the process documented in study files.

- Remote visits may be performed at the participant's home by qualified study personnel or at a local medical facility, unless the Investigator deems that a site visit is necessary.

- Additional unscheduled safety assessments such as routine blood sampling may be performed at the discretion of the Investigator including in the participant's home, if deemed necessary.

- Biological samples may be collected at a different location, other than the study site (e.g., at participant's home) by qualified study personnel or at a local medical facility according to standard operating procedures and applicable regulations. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.

- Where applicable country and local regulations for telemedicine allow: If visits to a site/home are not feasible, then the medical evaluation of the subject may take place by telemedicine which will use secure video conferences, phone calls, and a web portal and/or mobile application as a way of communicating with and monitoring the participant's progress.

- The study investigator is responsible for ensuring that the identification, management, and reporting of AEs and SAEs are completed in accordance with the protocol and applicable regulations. AEs are first reported by participants to the investigator/site staff or may be identified by the site staff during interactions with the participants via telemedicine encounters. In addition, mobile nurses may identify AEs as well and report them to the investigator for evaluation. Additionally, AEs may be identified from lab reports, imaging or ECG reports, and other records. As determined by the investigator, the appropriate medical intervention, therapeutic intervention, and/or support measures are instituted, as necessary.

- The participant should be informed of the plan and any potential risks associated with the virtual medium and sign a revised Informed Consent Form if required. IRB/Ethics committee should be informed and/or approve of this change in approach and the process documented in study files.

  Note: If the Investigator wishes to conduct a trial visit at a location that has not been previously assessed by GSK, it is the investigator's responsibility to identify an adequate alternate location and to notify GSK of the alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, is well-equipped to perform study procedures and covered by an adequate insurance. Furthermore, the investigator should have sufficient oversight to ensure that the staff

at the alternate location are trained to perform study procedures.

Study Intervention(s)

- If despite best efforts it is not possible to administer the dose of study intervention as defined in the protocol (see Section 6 Study Interventions and Concomitant Therapy), the subject may still continue in the trial at PI discretion – advice of the Medical Monitor may be sought as appropriate.

- If allowed by country regulation/ethics, then for patients on part 1 or part 2 GSK3326595 can be shipped direct-to-patient (DTP) from the investigational site to the participant's home address. The process for this shipment must be agreed with GSK who will provide the relevant documentation and links to courier sites required to ensure shipments are adequately temperature controlled (if required) throughout transportation.
  Any study subjects in part 3 who cannot attend a clinical site will not be able to receive Pembrolizumab at home and therefore may continue on GSK3326595 study medication sent to their home or withdraw from the study whichever the investigator and study subject decides. No special procedures for the safe handling of GSK3326595 study drug are required.

- The Principal Investigator assumes Good Clinical Practice (GCP) responsibilities for IMP handling and the medical control for dispensing to patients. Site Staff should document the dispensing in the Dispensing/Accountability Logs adding a comment that this was a DTP dispensing.

- Compliance with study intervention administration will be verified through observation by study staff or trained home healthcare professionals.

- In some cases, trial participants who no longer have access to investigational product or the investigational site may need additional safety monitoring (e.g., on withdrawal of an active investigational treatment).

Data Management/Monitoring:

- Diary cards may be transmitted from and to the investigator by secure electronic mail and or conventional mail. If copies/scans of completed diaries are sent to the investigator by electronic mail, the participant should be instructed to maintain the original documents and to return them to the site when a visit to the site will be allowed.

- PROs may be completed by a telephone interview between site staff and subject if the subject cannot attend the site to complete the questionnaires on the electronic tablet.

- If on-site monitoring is no longer permitted, GSK will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by the

clinical site/institution. Remote SDV/SDR will be proposed to study sites to meet a patient and/or critical quality need, e.g., to assess participant safety or to ensure data integrity. In case of remote SDV/SDR, GSK will work with the site to ensure subject privacy.

- eCRF/CRF Final or Interim Sign off Process: The Principal Investigator (PI) is responsible for ensuring that the data within the eCRF casebook and any other data sources utilized during the study for each study participant is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 4.9.2). The PI may sign/re-sign the eCRF from any computer/location by accessing InForm (or other eDC platform) using his/her unique eCRF log-in credentials. The PI may delegate this activity to another medically qualified and trained sub-investigator and this must be documented on the Delegation of Responsibilities (DoR) Log. It is recommended that the PI identifies a sub-investigator as a back-up for eCRF signatures. The sub-investigator must be appropriately trained on the protocol and eCRF requirements (with training documented), and the DoR log updated accordingly.

- Essential Document Sign Off Process: If an investigator is unable to print and sign essential documents such as Protocol /Amendment signature page then Email approval can be accepted by replying to the relevant email that is sent by GSK.

14.13. Appendix 13: Country Specific Amendment (France)

Rationale for amendment

As per Health Authority request in France dated 16 June 2021 relating to the inclusion of cardiac monitoring (encompassing echocardiogram (ECHO) and troponin levels measurements) in the Protocol for Study 204653, the Sponsor has included, via this Country Specific Protocol Amendment (CSPA), limited to France, the requested measures in order to allow continued access to the study drug, for the remaining active study subjects in France, which is one (1) subject. No more subjects will be enrolled in France until further notice.

Serial cardiac troponin levels and echocardiograms were originally included as safety assessments from the commencement of Study 204653 (until Protocol Amendment 5) to assess potential effects of GSK3326595 on myocardial tissue in response to pre-clinical findings observed in 4- and 13- week toxicology studies in rat animal models. For more information, see latest Investigator Brochure Version 5.0 data cut off 04 February 2021.

No clinically significant cardiotoxic events have been observed by the Sponsor with 270 subjects treated in Study 204653, as of the data cut-off date of 04 February 2021. The GSK Safety Review Team reviewed the serial cardiac troponin levels, echocardiograms and adverse event (AE) reports, and did not identify any events related to study drug and consistent with cardiomyopathy, cardiac valve abnormalities, or associated toxicities. The study data were also reviewed by the Sponsor Integrated Cardiac Safety Panel, which includes internal and external cardiologists, who endorsed discontinuing from Protocol Amendment 5 serial echocardiogram and troponin monitoring, this decision was reviewed and confirmed in July 2021.

Study Assessments and Procedures

Echocardiogram

For the ongoing subject on study drug, ECHOs will be performed at the next planned visit, and at the end of treatment visit. Additional ECHO assessments should be performed as clinically indicated. The ECHO assessment should include at a minimum evaluation of left ventricular ejection fraction (LVEF) and evaluation of both right and left-sided valvular function and morphology. Blood pressure and weight should be measured and recorded at the time (or as close to the time as clinically feasible) of the ECHO.

Refer to the Study Reference Manual (SRM) for details regarding the measurement of blood pressure.

Troponins

For the ongoing subject on study drug, troponin will be collected at the next planned visit, then every 8 weeks (±5 days) thereafter, and at the end of the treatment visit. Either troponin T or I may be assessed at a local laboratory. The same local laboratory test

(troponin I or troponin T) should be used consistently for an individual subject throughout the study.

Withdrawal and Stopping criteria

LVEF Stopping Criteria

Subjects with symptoms of left ventricular dysfunction during treatment with GSK3326595 should interrupt the investigational agent and have repeat echocardiogram performed.

Subjects with a >10% decrease (from baseline) in LVEF to below the institutional LLN should discontinue treatment with GSK3326595. Ejection fraction should be monitored every 4 weeks for a total of 16 weeks or until resolution. If recovery occurs (LVEF >institutional LLN and symptom resolution) within 4 weeks, treatment with GSK3326595 may be restarted at a reduced dose in consultation with the GSK Medical Monitor.

Subjects with symptoms of left ventricle (LV) systolic dysfunction without an accompanying decrease in LVEF by echocardiogram should have a full evaluation performed as appropriate (e.g., cardiology consult, additional workup for swelling/shortness of breath) and symptoms should resolve to <Grade 2 prior to discussion of restarting GSK3326595 at the same or reduced dose with the GSK Medical Monitor.

Copies of all echocardiograms may be required by GSK for review. Any cardiology consultations performed on subjects who experience a >10% decrease in LVEF from baseline and whose cardiac ejection fraction is <institution's LLN will be required by GSK for review.

Valvular Toxicity Stopping Criteria

Subjects who have a new asymptomatic, moderate regurgitation or stenosis by echocardiogram (Grade 2 mitral/tricuspid/aortic valvular toxicity per NCI-CTCAE v4) should temporarily discontinue GSK3326595 and have a repeat evaluation by ECHO within 1 week. ECHO should be repeated every 1 to 2 weeks for 4 weeks or until valve recovery to baseline.

- If the valve recovers to baseline any time during the next 4 weeks after consultation with and approval from the GSK Medical Monitor, the subject may be restarted on GSK3326595 at a reduced dose(s). For such subjects, monitoring of the valve via ECHO will then be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 16 weeks and then per protocol.

- If repeat ECHO does not reveal valve recovery to baseline within 4 weeks, then the subject should permanently discontinue GSK3326595. The valve should continue to be monitored via ECHO every 4 weeks for 16 weeks or until resolution.

Subjects with a Grade 3 or 4 (symptomatic, severe regurgitation/stenosis by imaging with symptoms controlled by medical intervention) valvular toxicity must discontinue GSK3326595. Valvular toxicity should continue to be monitored every 4 weeks for 16 weeks or until resolution. If recovery occurs (return to baseline via imaging AND symptom resolution) within 4 weeks, the subject may restart GSK3326595 at a reduced dose after consultation with and approval from the GSK Medical Monitor.

Signature Page for 204653 TMF-14123404 v2.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 20-Apr-2022 07:02:24 GMT+0000

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