TITLE PAGE

Protocol Title: A Phase I, Open-Label Study of GSK1795091 Administered in Combination with Immunotherapies in Participants with Advanced Solid Tumors

Protocol Number: 204686 Amendment 06

Short Title: Study of a combination of GSK1795091 and immunotherapies in participants with advanced solid tumors

Compound Numbers: GSK1795091

Sponsor Name and Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

GlaxoSmithKline
1250 South Collegeville Road
Collegeville, PA 19426, USA
Telephone: PPD

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline (GSK) 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

Medical Monitor contact information can be found in the Study Reference Manual (SRM)

Regulatory Agency Identifying Number(s):

Investigational New Drug (IND) number: IND136203

EudraCT number: 2017-003545-23

Approval Date: 08-SEP-2020

PPD

From: PPD
Sent: Thursday, September 10, 2020 7:29 PM
To: PPD
Cc: PPD
Subject: FW: Prot-Amend6-204686-sponsign

From: Hesham Abdullah PPD
Sent: Tuesday, September 08, 2020 3:04 PM
To: PPD
Cc: PPD
Subject: RE: Prot-Amend6-204686-sponsign

Dear PPD ,

As Chair of the Oncology PRF and Head of Oncology Clinical Development, I approve Amendment 6 to Protocol 204686.

Best,

Hesham

From: PPD
Sent: Tuesday, September 8, 2020 2:32 PM
To: Hesham Abdullah PPD
Subject: Prot-Amend6-204686-sponsign

Dear Sponsor,

To approve the clinical protocol indicated below, reply to this email and state your approval.

PROTOCOL NUMBER: 204686
DOCUMENT IDENTIFIER: 2017N327572_07
AMENDMENT NUMBER: 6PROTOCOL TITLE: A Phase I, Open-Label Study of GSK1795091 Administered in Combination with Immunotherapies in Participants with Advanced Solid Tumors

Name of Sponsor Signatory: Hesham Abdullah, MD, MSc, RAC

Title of Sponsor Signatory: SVP, Head Clinical Development, Oncology R&D

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 6	*08-SEP-2020*
Amendment 5	*02-MAR-2020*
Amendment 4	*12-AUG-2019*
Amendment 3	*14-SEP-2018*
Amendment 2	*25-JUL-2018*
Amendment 1 CAN-1	*06-MAR-2018*
Amendment 1	*08-DEC-2017*
Original Protocol	*28-SEP-2017*

Amendment 6: 08-SEP-2020

Overall Rationale for the Amendment: There will be no further enrolment and Part 2 of the study will not open as the development of GSK1795091 was discontinued by GSK. This decision was based on strategic prioritorization of the portfolio and is not due to the safety profile of GSK1795091.

Section # and Name	Description of Change	Brief Rationale
Section 1, Synopsis	• Language is added to close enrolment, discontinue efficacy follow-up and specify that one survival follow-up is required (if applicable). • Discontinue plans for Part 2 and deleted language regarding Part 2.	The development of GSK1795091 has been discontinued. This decision was based on strategic prioritization of the portfolio and is not due to the safety profile of GSK1795091.
Section 2, Schedule of Activities	• Updates made to reflect closed enrolment, discontinued efficacy follow-up and specify that one survival follow-up is required (if applicable). • Table 3 Part 2 is removed. • Table 4 Part 2 is removed.	As above.
Section 5 Study Design	• Language is added to close enrolment, discontinue efficacy follow-up and specify that one survival follow-up is required (if applicable). • Discontinue plans for Part 2 • Number of participants is updated to reflect removal of Part 2. • End of study language is updated to be defined as when the last subject has completed/discontinued study treatment, completed the Treatment Discontinuation Visit (TDV) assessments, and the OS FU visit is completed (as applicable). • Study Schematic is updated to reflect Part 2 removal.	As above.
Section 7 Treatments	• Language updated to reflect removal of Part 2.	As above.
Section 8 Discontinuation Criteria	• Language is added to close enrolment, discontinue efficacy follow-up and specify that one survival follow-up is required (if applicable).	As above.

Section # and Name	Description of Change	Brief Rationale
Section 9	• Time period for collection AE and SAE data is updated to reflect collection will be from the time a participant consents to participate in the study up to 90 days after the last dose of study treatment(s) or until the start of another anti-cancer therapy, whichever is first. • PK will no longer be collected; however, event driven collections will be performed. • Biomarkers will no longer be collected.	As above.
Section 10 Stats	• Language Updated to reflect removal of Part 2. • Definition of study populations updated to accomodate generation of screen failure summaries.	As above
Appendix 14 : COVID-19	• Appendix added.	This appendix has been added to outline the changes that have been made in response to the COVID-19 pandemic

TABLE OF CONTENTS

PAGE

1. SYNOPSIS

Protocol Title: A Phase I, Open-Label Study of GSK1795091 in Combination with Immunotherapies in Participants with Selected Advanced Solid Tumors

Short Title: Study of combinations of GSK1795091 and immunotherapies in participants with advanced solid tumors

Rationale: The combination of two or more immunotherapies holds promise in treating patients with cancer. One model of a "cancer-immune cycle" describes a series of feed-forward steps by which the immune system recognizes and kills tumor cells, a cycle which is counterbalanced by tumor and host derived factors which suppress anti-tumor immune activation. These steps include:

- Release of cancer cell antigens
- Cancer antigen presentation
- Priming and activation
- Trafficking of T-cells to tumors
- Infiltration of T-cells into tumors
- Recognition of cancer cells by T-cells
- Killing of cancer cells

Rational combination strategies, such as immunotherapies acting at different steps in the immune cycle, could produce meaningful and synergistic activity compared to monotherapies. Combining a TLR4 agonist with a checkpoint modulator targets two complementary steps in the cancer-immunity cycle; TLR engagement results in the production of various inflammatory cytokines/chemokines such as tumor necrosis factor (TNF)α, interleukin (IL) 6, granulocyte colony-stimulating factor (G-CSF), and type I interferons (i.e., IFNα, IFNβ) and enhanced uptake, processing, and presentation of antigens. Based on nonclinical data, the combinations of GSK1795091 (a TLR4 agonist) and GSK3174998 (an OX40 agonist), GSK3359609 (an ICOS agonist) or pembrolizumab (a PD-1 inhibitor) is anticipated to have antitumor activity greater than any of the monotherapies.

Objectives and Endpoints:

With the implementation of amendment 06, the study is closed to enrolment and Part 2 will not be opened.

Objectives	**Endpoints**
Primary	
• To evaluate the safety and tolerability of GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or pembrolizumab.	• Adverse events (AEs), serious adverse events, dose-limiting toxicities, withdrawals due to AEs, dose reductions or delays, and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters).

Objectives	Endpoints
Secondary	
• To evaluate the antitumor activity of GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or pembrolizumab	• Objective response rate (ORR) and disease control rate (DCR) (complete response [CR]+ partial response [PR]+ stable disease [SD] ≥12 weeks), time to response, duration of response, progression-free survival (PFS), and overall survival..
• To characterize the pharmacokinetics (PK) of GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or pembrolizumab.	• GSK1795091 concentrations in plasma and assessment of PK parameters (e.g., maximum observed concentration [C_{max}], $AUC_{(0-\tau)}$ and trough plasma concentration [C_{trough}]) if data permit.
• To evaluate the immunogenicity of GSK3174998, GSK3359609, or pembrolizumab when administered in combination with GSK1795091.	• Number and percentage of participants who develop detectable anti-drug antibodies against GSK3174998, GSK3359609, or pembrolizumab.
Exploratory	
• To evaluate the immunologic effects of GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or pembrolizumab.	• Assessments of OX40 or ICOS receptor expression and occupancy of GSK3174998 or GSK3359609 on immune cells in the peripheral blood. • Assessment of the phenotype, quantity, and activation state of T cells and other immune cells in peripheral blood. • Assessment of tumor biopsies by immunohistochemistry or related technologies which may include but is not limited to the numbers of tumor-infiltrating lymphocytes and other cells expressing key phenotypic markers.
• To explore the association between treatment with GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or pembrolizumab and measures of gene expression and immune function.	• Assessment of gene expression and immune function from study participants tumor tissue and/or blood samples may include but is not limited to immune related gene expression (RNA expression or RNAseq), gene signatures, and T-cell receptor DNA sequences. • Assessment of soluble factors from study participants blood samples and/or tumor may include but is not limited to cytokines and stress-related proteins, cell free DNA

Objectives	Endpoints
	(cfDNA), and exosomes.
• To explore the association between treatment with GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or pembrolizumab and biomarkers which may be associated with response. To explore the utility of these measures to enrich for clinical efficacy and/or development of a diagnostic test.	• Comparison between antitumor activity and baseline biomarker samples from study participants blood and/or tumor which may include but are not limited to DNA, gene expression (RNA), proteins, immune cell phenotypes, and immune response markers. • Analysis of the data to identify potential selection biomarkers for participant enrichment.
• To characterize the PK of GSK3174998, GSK3359609, or pembrolizumab when administered in combination with GSK1795091.	• GSK3174998, GSK3359609, or pembrolizumab concentrations in plasma/serum and assessment of PK parameters (e.g., maximum observed concentration [C_{max}], $AUC_{(0-\tau)}$ and trough concentration [C_{trough}]) if data permit.
• To explore PK-Pharmacodynamic relationships, such between PK parameters and antitumor activity, safety or pharmacodynamic markers after treatment with GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or pembrolizumab.	• Evaluation of the relationship of antitumor activity as assessed by ORR, DCR, safety and/or pharmacodynamic markers with PK parameters (e.g., C_{max}).

• Pharmacogenetics (PGx): To evaluate the association of genetic variations in the host DNA and response to therapy.	• Germline genetic evaluations may be conducted to test for association with:
	  • Response to treatment, including GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or pembrolizumab or any concomitant medicines.
	  • Disease susceptibility, severity, and progression and related conditions.

• To explore the gut microbiome composition and relationship to treatment response.	• Sequencing of the microbiome from stool samples. Analysis of the data to identify potential selection biomarkers for participant enrichment • Evaluation of the relationship between antibiotic/probiotic use prior to treatment and antitumor activity
• To evaluate disease- and treatment-related	• Qualitative telephone interview.

Objectives	Endpoints
symptoms and impact on function and health-related quality-of-life.	

Overall Design:

This is a Phase I, open-label, non-randomized, multicenter and multi-country study designed to evaluate the safety, tolerability, PK, pharmacodynamic, and preliminary clinical activity of GSK1795091 administered in combination with other immunotherapies to participants with advanced solid tumors.

In Part 1, the safety and tolerability of escalating doses of GSK1795091 and a single dose level of a monoclonal antibody (mAb) combination partner (GSK3174998, GSK3359609, or pembrolizumab) will be evaluated in separate cohorts of participants with advanced solid tumor cancers according to an Neuenschwander-Continual Reassessment Method (N-CRM) design to identify doses for evaluation in Part 2. Part 1 will include a GSK1795091 run-in period of 2 weeks (i.e., GSK1795091 administration on Days 1 and 8) prior to administration of the combination partner beginning at Day 15. Approximately 5 dose levels of GSK1795091 in combination with a single fixed dose level of the combination partner are planned to be evaluated in Part 1. Following protocol amendment, GSK1795091 may also be further evaluated by additional routes of administration.

With the implementation of amendment 06, the study is closed to further enrollement and Part 2 will not be opened.

PK/Pharmacodynamic cohorts for each combination will be opened to enrollment during Part 1 to obtain additional PK and pharmacodynamic data, with an emphasis to obtain insight on the potential impact of the combination treatments on the immune cells and status of the tumor microenvironment, in conjunction with PK and pharmacodynamic markers obtained from blood. Tumor biopsies are required for enrollment to the PK/Pharmacodynamic cohorts, whereas biopsies are strongly encouraged but not mandatory for Part 1 dose escalation cohorts. For each combination, participants in the PK/Pharmacodynamic cohorts may be enrolled to any dose level which has already been completed and supported by adequate safety and tolerability from dose escalation for that combination. Up to a maximum of 45 participants may be enrolled into the PK/Pharmacodynamic cohorts with approximately 6 per dose level for each combination.

Number of Participants:

Approximately 72 participants will be enrolled into Part 1 (dose-escalation) of the study. Additionally, for each combination, up to 6 participants in each dose cohort, and a maximum of approximately 45 participants in total, may be enrolled into the PK/Pharmacodynamic cohort of Part 1. Additional cohorts (up to a maximum of 12 total participants) may be enrolled in Part 1 to allow for evaluation of more dose levels.

Treatment Groups and Duration:

Participants will receive the combination of GSK1795091 with either GSK3174998, GSK3359609, or pembrolizumab. In Part 1, escalating doses of GSK1795091 will be evaluated as guided by the N-CRM approach.

The study includes a screening period, a treatment period, and a follow-up period. Participants will be screened for eligibility beginning 4 weeks before the start of treatment. The duration of study treatment is expected to be up to 2 years. With the implementation of amendment 06, participants who discontinue study treatment for any reason will no longer be followed for disease assessments. For the purpose of safety follow-up, one Survival FU visit will be performed 12wks after the last dose of study treatment or prior to the start of the next anti-cancer therapy, whichever occurs first. If a new anti-cancer therapy is started before the TDV, the OS visit is not required. The study will conclude when the last subject has completed/discontinued study treatment, completed the Treatment Discontinuation Visit (TDV) assessments, and the OS FU visit is completed (as applicable).

2. SCHEDULE OF ACTIVITIES (SOA)

- Two bullets below do not apply to those sites in Canada.
- The timing and number of planned study assessments, including safety, laboratory, imaging, tumor biopsy, pharmacokinetic (PK), and pharmacodynamic/biomarker assessments included in the tables below 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.
- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The Institutional Review Board (IRB)/ Independent Ethics Committees (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF).
- With the implementation of Amendments 5 and 6, specific assessments are not required. Please see Table 1 and Appendix 13 for further details.

Table 1 Part 1 Dose Escalation and PK/Pharmacodynamic Cohorts: Safety, Laboratory, Efficacy, Study Treatment Procedures[v] (Darker Gray denotes activities that are discontinued based on amendment 06)

	Scrn[a/b]	GSK1795091 Monotherapy			Combination Treatment: GSK1795091 + treatment mAb[a]													Follow-up	
Week[a]	**≤4**	**1**		**2**	**3**		**4**	**5**	**6**	**7**	**8**	**9**		**10**	**11**	**12**	**>12 - 105[c]**	**TDV[d]**	**PFS FU[e]**	**SFU[f]**
Day	**≤28**	**1**	**2[s]**	**8**	**15**	**16[s]**	**22**	**29**	**36**	**43**	**50**	**57**	**58[s]**	**64**	**71**	**78**	**>78-736**		**Q12W**	**Q12W**
Informed Consent	X																			
Record all antibiotics and probiotics taken 60 days prior to dosing	X																			
Inclusion/Exclusion	X	X																		
Demographics, Medical History, Prior Medications, Disease Characteristics	X																			
Concomitant Medications		Continuous: assess at each visit from first dose of study treatment																		
Participant Registration		X																		
Anti-Cancer Treatment																		X	X	X
Study Treatment (note: administer GSK1795091 at least 1 hour after the end of the treatment mAb infusion)																				
Administer mAb treatment[g] (GSK3174998, GSK3359609, or pembrolizumab)					X				X			X				X	Q3W			
Administer GSK1795091[g]		X		X	X		X	X	X	X	X	X		X	X	X	Q3W			
Safety																				
AE/SAE Assessment		Assess at each visit from first dose until the TDV visit for AEs and until 90 days after last dose for AESI and SAEs[d]																		
ECOG PS	X	X		X	X		X	X	X	X	X	X		X	X	X	Q6W	X		

	Scrn[a/b]	GSK1795091 Monotherapy			Combination Treatment: GSK1795091 + treatment mAb[a]														Follow-up	
Week[a]	**≤4**	**1**		**2**	**3**		**4**	**5**	**6**	**7**	**8**	**9**		**10**	**11**	**12**	**>12 - 105[c]**	**TDV[d]**	**PFS FU[e]**	**SFU[f]**
Day	**≤28**	**1**	**2[s]**	**8**	**15**	**16[s]**	**22**	**29**	**36**	**43**	**50**	**57**	**58[s]**	**64**	**71**	**78**	**>78-736**		**Q12W**	**Q12W**
Physical Examination [h]	X	X			X				X			X				X	Q6W	X		
Vital Signs[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Q3W	X		
12-lead ECG[l]	X	X	X	X	X				X			X				X	Q12W	X		
Echocardiogram[q]	X																			
Laboratory Assessments (Safety) – perform assessments pre-dose on each dosing day (-1 day window)																				
Hepatitis B and C	X																			
Pregnancy Test Serum β-hCG at screening[r]	≤3d	Monthly (urine or serum)																X		
Clinical Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Q3W 24 hr, Wk 15 only[s]	X		
Hematology	X	X		X	X		X	X	X	X	X	X		X	X	X	Q3W	X		
Thyroid function	X								X							X	Q6W	X		
Calculated CrCl	X	X			X				X			X				X	Q3W	X		
Urinalysis	X	X			X				X			X				X	Q3W	X		
Lipid panel[u]	X																			
Disease Assessments																				
Tumor imaging [j]	X											X[p]				X	Q12W		X	
Patient Reported Outcomes																				
Telephone Interview														X[m]				X[n]		
Telephone call for survival status[f]																				X

	Scrn[a/b]	GSK1795091 Monotherapy			Combination Treatment: GSK1795091 + treatment mAb[a]														Follow-up	
Week[a]	**≤4**	**1**		**2**	**3**		**4**	**5**	**6**	**7**	**8**	**9**		**10**	**11**	**12**	**>12 - 105[c]**	**TDV[d]**	**PFS FU[e]**	**SFU[f]**
Day	**≤28**	**1**	**2[s]**	**8**	**15**	**16[s]**	**22**	**29**	**36**	**43**	**50**	**57**	**58[s]**	**64**	**71**	**78**	**>78-736**		**Q12W**	**Q12W**
Tumor Biopsies																				
Archived tumor [k]	X																			
Fresh tissue sample[k]	X											X				X				
Progressive disease tissue sample[o]																		X		
Microbiome Specimen																				
Stool Sample[t]	X											X								

Abbreviations: AE = Adverse Event; AESI = Adverse Events of Special Interest; β-hCG = Beta-Human Chorionic Gonadotropin; CrCl = Creatinine Clearance; ECG = Electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; PFS FU = Progression-Free Survival Follow-up; Q3W = every 3 weeks; Q6W = every 6-weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; SAE = Serious Adverse Event; Scrn = Screen; SFU = Survival Follow-up; TDV = Treatment Discontinuation Visit

a. Visit Windows: With the exception of Screening/baseline and Day 1 visits and unless otherwise specified, assessments performed at ≤3-week intervals will have a ±3 day window and assessments performed at >3-week intervals will have a ±1-week window. For Screening/Baseline and Day 1 visits, all procedures must be completed before first dose. Laboratory assessments for Safety will have a -1 day window at all visits.

b. Screening assessments or procedures to be performed up to 4 weeks (28 days) before the first dose (unless otherwise specified, with the exception of the screening serum pregnancy test which must be performed within 3 days of the first dose of study treatment). Informed consent must be signed before any study specific assessments are performed.

c. The frequency of assessments collected at the intervals stated "beginning from Week 12 onwards" will be as follows (unless stated otherwise in the table):
   1. Every dosing day (pre-dose every 3 weeks): clinical chemistry, hematology, urinalysis, calculated CrCl, vital signs (predose and EOI+2h)
   2. Every 6 weeks: thyroid function tests, ECOG PS assessments, physical examination (including weight)
   3. Every 12 weeks: 12-lead ECG, tumor imaging.

d. The TDV must be completed within 30 days from the last dose of study treatment and must be completed prior to the start of subsequent anti-cancer therapy. The window for this visit is +10 days. All AEs and concurrent medications will be collected until at least 30 days after the last dose of study treatment or the start of a new anti-cancer therapy, whichever occurs first. All AESIs and SAEs and any concurrent medications relevant to the reported AESIs and SAEs will be collected until at least 90 days after the last dose of study treatment or until the start of new anticancer therapy, whichever occurs first. Any drug or study-related SAEs occurring after the 90-day window will be reported according to directions provided in Section 9.2.1.

e. With the implementation of amendment 06, Progression-free survival FU data will no longer be collected.

f. With the implementation of amendment 06, one Survival FU visit will be performed 12wks after the last dose of study treatment or prior to the start of the next anti-cancer therapy, whichever occurs first. If a new anti-cancer therapy is started before the TDV, the OS visit is not required. See Appendix 13 for amendment 05 changes. Particpants can opt out of the telephone interview.

g. As of amendment 05, dosing with GSK1795091 was suspended. Dosing of treatment mAb (GSK3174998, GSK3359609, or pembrolizumab) will be at every 3-week intervals. Dosing of GSK1795091 will be at every 1-week intervals (Q1W) from Week 1 through Week 12 including the 2-week monotherapy run in period (Week 1 and Week 2). Starting at Week 12, GSK1795091 will be administered at every 3-week intervals (Q3W) to coincide with treatment mAb dosing. Participants will be dosed for a maximum of 2 years.
   - Infusion/injection of one or both study treatments may be up to 3 days before or after the planned date for administrative reasons only (e.g., routine scheduling, scheduling an infusion around a holiday). However, such changes from the planned date should not result in consecutive doses of GSK1795091 being administered within 3 days.

h. Physical exam must be completed per the SoA. A complete physical examination (including height and weight) must be performed at screening and TDV per Section 9.4.1. A brief physical examination (including weight) may be performed at other visits.

i. Vital Sign Schedule: See Appendix 13 for amendment 05 updated schedule.
   - On Day 1, vital signs must be collected predose GSK1795091 and at the following times after the end of injection (EOI) of GSK1795091: EOI +30m, EOI +2h, EOI +4h, EOI +6h. Vital signs should be assessed (and recorded) at all timepoints later than EOI +6h as clinically indicated (optional EOI +8h, EOI +12h, EOI +16h) until changes in body temperature, heart rate, and/or blood pressure attributable to cytokine production are resolving.
   - On Day 15 and 36, vital signs must be collected at predose treatment mAb infusion (GSK3174998, GSK3359609, or pembrolizumab) predose GSK1795091, EOI GSK1795091+ 2h, +4h, and +6h. Vital signs should be assessed (and recorded) at timepoints later than EOI +6h as clinically indicated (optional EOI +8h, EOI +12h, EOI +16h).
   - On Days 2, 16, and 58, vital signs corresponding to approximately EOI +24h will be assessed.
   - On all other visits, vital signs must be collected predose treatment mAb infusion (GSK3174998, GSK3359609, or pembrolizumab) (when administered), predose GSK1795091 and EOI GSK1795091 + 2h. Additional timepoints should be collected as clinically indicated (optional EOI +4h, EOI +6h, EOI +8h, EOI +12h, EOI +16h). From week 12, these will be taken Q3W correspo nding to dosing days.

j. Tumor Imaging Schedule:
   - Screening tumor imaging must be obtained up to 4 weeks (28 days) before the first dose.
   - Tumor imaging will be performed every 12 weeks (±1 week) until disease progression has been confirmed by irRECIST; Participants whose disease progresses are encouraged to have a confirmatory scan performed at least 4 weeks after the date of assessment during which the first indication of PD was demonstrated. Immune-related RECIST may be used to determine treatment decisions for PD.
   - Participants in the PK/Pharmacodynamic Cohort have an additional tumor imaging assessment on Week 9
   - If a participant has achieved a complete response (CR) or partial response (PR) in the previous radiologic assessment, a repeat scan should be performed as a part of the confirmation of response, no less than 4 weeks (28 days) after the criteria for response are first met
   - At the TDV, tumor imaging is only required if the last disease assessment did not show PD and was performed ≥6 weeks before TDV.
   - With the implementation of Amendment 6 PFS assessment is no longer required. During the PFS FU visits (performed when a participant has permanently discontinued study treatment before disease progression has been documented), tumor imaging will be obtained every 12 weeks (±1 week) until PD, initiation of a new anticancer treatment, or death, whichever comes first.

k. Tumor Biopsies: With the implementation of amendment 06, tumor biopsies on treatment are no longer required.

- NOTE: Tumor lesions planned for biopsy must not be used as indicator lesions for assessment of disease, unless discussed and agreed with the GSK Medical Monitor.
- Archived tissue sample is required for all participants at the time of screening. If archival sample is not available, a fresh biopsy is required.
- For Part 1 (Dose Escalation), Screening and on-treatment fresh biopsies are strongly encouraged but otherwise optional for participants in Part 1.
- Part 1 PK/Pharmacodynamic Cohort: a fresh tumor biopsy is required at screening (before first dose) and Week 9 (±7 days). Tumor biopsy at Week 12 (±7 days) should be attempted if feasible but is not mandatory.
- If a biopsy sample collection is missed due to a treatment delay, it may be collected at the next possible study visit or timepoint.

l. See Appendix 13 for amendment 05 updated ECG assessments schedule: Day 1 ECG measurements will be performed in triplicate predose GSK1795091 and at the following times after the injection (EOI) of GSK1795091: EOI +10m, EOI +2h, EOI +4h, EOI +6hr, EOI +24h. All other ECG measurements are performed predose treatment mAb infusion (GSK3174998, GSK3359609, or pembrolizumab), predose GSK1795091, EOI GSK1795091 +2h, and at screening as single ECG measurements.

m. See Appendix 13 for amendment 05 changes. Particpants can opt out of the telephone interview. Qualitative Telephone Interview to be completed via telephone within 21 days following Day 64.

n. See Appendix 13 for amendment 05 changes. Participants can opt out of the telephone interview. Interview to be completed via telephone within 21 days following the treatment discontinuation visit. Participants who have the TDV within 30 days of the Day 64 interview are not required to repeat the interview

o. With the implementation of amendment 06, tumor biopsies are no longer required.

p. Tumor imaging at Week 9 is for participants in the PK/Pharmacodynamic Cohort only; and is timed to coincide with the on-treatment tumor biopsy at Week 9. The disease assessment must be performed **after** the tumor biopsy.

q. Multigated acquisition scan (MUGA) is acceptable if ECHO is not available. Assessments after Screening visit should be performed as clinically indicated.

r. Perform only in women of child-bearing potential (WOCBP). A serum pregnancy test must be performed at screening, and subsequent pregnancy tests may be either serum or urine.
Final pregnancy test (serum or urine) must be performed in WOCBP 120 days after last study treatment.

s. See 24hr sample collection on the Part 1 PK/Pharmacodynamic Table 2. 24 hour assessments for Vital Signs, Clinical Chemistry and ECG measurements will have a ±8 hour window. At Week 15 only, Clinical Chemistry assessment corresponding to EOI+24 hr will also be assessed

t. The stool sample can be collected at any time during the screening period either at the participants home or during clinic visits using the provided collection kit. The collection kit will also be provided at the Week 8 visit and the sample may be collected during the week leading up to the Week 9 visit

u. The lipid panel includes the following tests: Cholesterol(Total), Triglycerides, HDL Cholesterol, LDL-Cholesterol (calculated), Cholesterol/HDL Ratio (calculated), and Non-HDL Cholesterol (calculated)

v. See Appendix 13 for instructions on activities during mAb monotherapy.

Table 2 Part 1 Dose Escalation and PK/Pharmacodynamics Cohorts: Pharmacokinetic, Pharmacodynamic, Anti-drug Antibody, and Genetic Assessments[k] (Based on amendment 05 and Appendix 13 the assessments in this table and post treatment visits will no longer be collected)

Treatment	**GSK1795091 monotherapy**												**Post treatment**	
Week	**1**		**2**	**3**	**3**	**4**	**6**	**9**	**9**	**10**	**12**	**>12**		
Day	**1**	**2**	**8**	**15**	**16**	**22**	**36**	**57**	**58**	**64**	**78**	**>78**	**Within 30d after last dose[f]**	**12 WK after last dose[g]**
Pharmacodynamic / Immunogenicity Blood Specimens														
Whole blood (Receptor occupancy/Immune phenotyping)[a]	Pre091			Pre, 4h	24h			Pre 4h[d]	24h				X[b]	X[b]
PBMCs	Pre091			Pre			Pre	Pre			Pre	Pre (Wk15 only[j])	X[b]	X[b]
Plasma (cytokines/ chemokines)	Pre091, 2h, 4h, 6h	24h	Pre091, 2h, 4h[d]	Pre, 2h, 4h, 6h	24h		Pre, 2h, 4h, 6h	Pre, 2h, 4h[d]	24h		Pre, 2h, 4h[d]	Pre, 2h, 4h[d], 24h (Wk15 only)[j]	X[b]	X[b]
Plasma (biomarkers)	Pre091							Pre				Pre (Wk15 only)[j]	X[b]	
Serum (biomarkers)	Pre091							Pre				Pre (Wk15 only)[j]	X[b]	
Serum ADA (GSK3174998, GSK3359609, or pembrolizumab)[h,i]				Pre			Pre	Pre			Pre	Pre[e] (Q12W)	X	X
Pharmacokinetic Blood Specimens														
Treatment mAb PK (GSK3174998, GSK3359609, or pembrolizumab)				Pre, EOI, EOI+4h	EOI+24h	X	Pre	Pre, EOI, EOI+4h	EOI+24h	X	Pre	Pre[e] (Q12W)	X	X
GSK1795091 PK	Pre091,	24h	Pre091,	Pre,	24h	Pre091		Pre,	24h	Pre091,	10min	10min[e]		

Treatment	**GSK1795091 monotherapy**													
Week	**1**		**2**	**3**	**3**	**4**	**6**	**9**	**9**	**10**	**12**	**>12**		
Day	**1**	**2**	**8**	**15**	**16**	**22**	**36**	**57**	**58**	**64**	**78**	**>78**	**Within 30d after last dose[f]**	**12 WK after last dose[g]**
	10min, 2h, 4h, 6h		10min, 4h[d]	10min, 4h				10min, 4h[d]		10min		(Q12W)		
Genetics Research Blood Specimen														
Genetics sample[c]	X													

Abbreviations: Ab = antibody; ADA = anti-drug antibody**;** EOI = end of infusion; PBMC = peripheral blood mononuclear cell; PK = Pharmacokinetics.

Dark gray denotes discontinued activities based on Amendment 06.

Timepoint Definitions for assessments associated with treatment mAb (GSK3174998, GSK3359609, or pembrolizumab) dosing:
X = Anytime during visit (sampling date/time must be recorded)
Pre = within 60 minutes before the start of the GSK3174998, GSK3359609, or pembrolizumab infusion
EOI= within 5-30 minutes after the end of GSK3174998, GSK3359609, or pembrolizumab infusion
EOI+2h = within 2 hours ±30 minutes of the end of the GSK3174998, GSK3359609, or pembrolizumab infusion
EOI+4h = within 4 hours ±1 hour of the end of the GSK3174998, GSK3359609, or pembrolizumab infusion
EOI+6h = within 6 hours ±1 hour of the end of the GSK3174998, GSK3359609, or pembrolizumab infusion
EOI+24h = 24 hours ±8 hours after the end of the GSK3174998, GSK3359609, or pembrolizumab infusion

Timepoint Definitions for assessments associated with GSK1795091 dosing:
X = Anytime during visit (sampling date/time must be recorded)
Pre091 = within 60 minutes before the start of the GSK1795091 injection
10min = within 10 minutes of the end of the GSK1795091 injection
2h = within 2 hours ±30 minutes of the end of the GSK1795091 injection
4h = within 4 hours ±1 hour of the end of the GSK1795091 injection
6h = within 6 hours ±1 hour of the end of the GSK1795091 injection
24h = 24 hours ±8 hours after the end of the GSK1795091 injection (sample intended to be drawn at same time as the EOI+24h sample associated with GSK3174998, GSK3359609, or pembrolizumab)

a. Procedures for the blood sample collection, processing, storage, and shipping are described in the Study Reference Manual.
b. The whole blood sample, plasma, serum, and PBMCs must be collected prior to the start of subsequent anti-cancer therapy.
c. Informed consent for optional genetics research must be obtained before collecting a sample. It is recommended that the blood sample be taken at the first opportunity after a participant has met all eligibility requirements, and can be done up to 28 days before Day 1 or on Day 1. Appendix 6 describes requirements for genetic research.
d. Sample to be taken as clinically feasible within the protocol window (i.e., if participant has been discharged from the clinic prior to the allowed sample procurement window, this sample is *not* mandatory).
e. Week 12 and then every 12 weeks.
f. Procedures at this visit must be completed within 30 days from the last dose of study treatment and must be completed prior to the start of subsequent anti-cancer therapy. Procedures can be done ±7 days, unless otherwise indicated.
g. Procedures can be done ±7 days, unless otherwise indicated.
h. Serum samples are required to be collected prior to dosing (i.e., pre-dose) on each dosing day and at the indicated assessment visits following study treatment discontinuation, and one sample collected 12 weeks post last dose of study treatment. In addition to these scheduled immunogenicity assessments, "event-driven" testing will also be employed for those participants that experience anaphylaxis, serious hypersensitivity, or AEs related to study treatment administered that led to withdrawal from study treatment. See Section 10.3.2.3 for full details.
i. 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, serum samples should be taken from the participant for immunogenicity testing at the time of the event and again 30 days, 12 weeks, and 24 weeks after.
j. After week 12, PBMCs, Plasma (cytokines/chemokines), Plasma (biomarkers) and Serum taken at Week 15 only. At Week 15, a plasma (cytokines/chemokines) assessment corresponding to EOI+24 hr will also be collected.
k. See Appendix 13 for instructions on activities during mAb monotherapy.

3. INTRODUCTION

3.1. Study Rationale

The model of a "cancer-immune cycle" describes a series of feed-forward steps by which the immune system recognizes and kills tumor cells, a cycle which is counterbalanced by tumor and host derived factors which suppress anti-tumor immune activation [Chen, 2013; Chen, 2017]. The steps of tumor immune recognition and killing include release of cancer cell antigens, cancer antigen presentation, priming and activation, trafficking of T-cells to tumors, recognition of cancer cells by T-cells, and killing of cancer cells. Immune suppressive factors which may be operative in tumor microenvironment include checkpoint pathways (e.g., programmed death receptor-1 [PD-1], cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4]) and a range of immunosuppressive factors (e.g., IDO, TGF-β), as well as immune inhibitory cell populations including T regulatory (Treg) cells, myeloid derived suppressor cells, and immune suppressive macrophages (M2-macrophages). Thus, cancer persistence and growth results from aberrant cell replication together with a relative imbalance in favor of immune suppressive factors as compared to anti-tumor immune activating responses.

The therapeutic benefit of blocking the immuno-inhibitory checkpoint pathways PD-1 and CTLA-4 recently has been demonstrated across multiple tumor types, yielding durable responses in some patients. However, a majority of patients do not respond to monotherapy with checkpoint inhibitors, and strategies to increase their activity by combination approaches are being actively explored. It is also possible that immunotherapies acting at different steps in the cycle and on different cells and pathways could have improved therapeutic indices over currently available monotherapies. Furthermore, engaging novel pathways and combinations may provide therapeutic options for patients wherein the pre-existing host and tumor microenvironment factors do not favor response to PD-1 or CTLA-4.

Toll-like receptors (TLRs) are a family of 'sensor' proteins primarily expressed on certain immune and epithelial cells that function as activators of innate immunity in response to microbial-related molecules known as Pathogen-Associated Molecular Patterns (PAMPs). PAMPs include molecules such as nucleic acids, flagellar proteins, and lipopolysaccharide (LPS), the prototypical ligand for TLR4. Ligand-driven activation of TLRs results in the production of various inflammatory cytokines and chemokines such as tumor necrosis factor (TNF)α, IL-6, IL-8, IP-10, G-CSF, interferons (IFNs), and enhanced uptake, processing, and presentation of antigens by antigen presenting cells. Further effects of TLR4 agonism observed in animal models of cancer include reduction of Treg cells and promotion of macrophage phenotypic switching from an immunosuppressive M2 phenotype to an immune active M1 phenotype.

GSK1795091 is a synthetic TLR4 agonist that is being developed by GlaxoSmithKline as an immunological adjuvant to be administered in combination with other immune system modulators for the treatment of cancers. GSK1795091 is not being developed as a monotherapy given the lack of robust anti-tumor activity that has been reported for the drug class in participants with advanced malignancies [Guha, 2012; Weihrauch, 2015; Pashenkov, 2006]. Therefore, the first-time in human (FTIH) study of GSK1795091 was

performed in healthy participants to evaluate preliminary safety, PK, pharmacodynamics, and to identify a pharmacologically active starting dose to initiate studies in cancer patients [Refer to GSK Document Number 2015N236402_03, Study 204685].

The adverse event (AE) profile in the GSK1795091 FTIH study was characterized by cytokine-related effects such as flu-like symptoms and changes in temperature and heart rate (Section 3.2.1.2). One (1) study participant experienced an elevation in transaminases (Section 3.2.1.2.1). Overall, the clinical profile of GSK1795091 as evaluated in healthy participants was consistent with that anticipated by the repeat dose GLP toxicology studies in rats and monkeys and with the profiles of other TLR agonists reported in both healthy participants and cancer patients [Kanzler, 2007; Bahador, 2007; Schmoll, 2014; Northfelt, 2014; Isambert, 2013]. Data from the FTIH study was used to support the starting dose and dose rationale in the present study (Section 5.5).

Other attractive immunotherapy anticancer targets include costimulatory pathways that enhance T-cell function. OX40 is one such costimulatory receptor expressed primarily on activated CD4+ and CD8+ T-cells. OX40 agonists have been shown to increase antitumor immunity and improve tumor-free survival in non-clinical models, and OX40 agonist monoclonal antibodies (mAbs) are currently being evaluated in Phase I clinical trials. GSK3174998 is a humanized wild-type IgG1 anti-OX40 agonistic mAb being developed for the treatment of advanced malignancies.

ICOS is another costimulatory receptor that is highly induced on CD4+ and CD8+ T cells upon TCR engagement and activation [Paulos, 2010; Wakamatsu, 2013]. A growing body of literature supports the concept that activating ICOS on CD4+ and CD8+ T cells has antitumor potential, and multiple lines of nonclinical and clinical evidence have established the rationale for targeting ICOS in cancer. GSK3359609 is a modified humanized IgG4 anti-ICOS mAb currently under study in patients with advanced solid tumors.

Pembrolizumab is a humanized IgG4 kappa monoclonal antibody that blocks the interaction between the PD-1 receptor found on T cells and its ligands, PD-L1 and PD-L2. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab releases the PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. Pembrolizumab is in clinical development as an IV immunotherapy for advanced malignancies and indicated for the treatment of patients across a number of conditions. For more details on specific indications refer to pembrolizumab IB [KEYTRUDA SPC, 2019] and approved labelling.

This study will assess the safety, PK, pharmacodynamics, and preliminary clinical activity of GSK1795091 administered in combination with other immunotherapies to participants with advanced solid tumors. GSK3174998, GSK3359609, and pembrolizumab are well-suited for combination with GSK1795091 based on mechanisms of action targeting complementary nodes of the cancer-immunity cycle and compelling antitumor activity observed in preclinical models. Subsequent combination partners and/or additional routes of administration may be evaluated (following protocol

amendment/s) based on biologic rationale, nonclinical data, and/or emerging clinical data.

3.2. Brief Background

3.2.1. GSK1795091 Background

An overview of GSK1795091 is provided below. Detailed information concerning the biology, pharmacology, PK, and safety characteristics can be found in the Investigators' Brochure (IB) for GSK1795091 [GSK Document Number 2015N239078_04]. Clinical information is aligned to that available at the time of protocol development.

GSK1795091 was initially developed in the course of structure-activity studies on LPS (also known as 'endotoxin'), the naturally occurring ligand of TLR4. GSK1795091 is a monosaccharide from the aminoalkyl glucosaminide 4-phosphate class of compounds intended for use as a vaccine adjuvant or an immune modulator. GSK1795091 is an agonist of TLR4 that induces immunologic responses in vitro and in vivo. GSK1795091, as a single-agent, stimulates cytokine production (in vitro and in vivo), changes in immune cell populations (in vivo) and generates fever response (in vivo).

3.2.1.1. GSK1795091 Nonclinical Activity

GSK1795091 has shown immunomodulatory activity in multiple in vitro and in vivo models. GSK1795091 added to whole blood ex vivo induces cytokine production, and when administered to BALB/c mice, induces phenotypic trends in peripheral blood leukocytes including decreased regulatory T-cells (Tregs), increased T-cell activation, and expansion of myeloid cells and monocyte/macrophages. GSK1795091 administered to CT-26 tumor-bearing BALB/c mice resulted in an increase in survival compared to control groups.

The in vitro and in vivo pharmacology of GSK1795091 is consistent with other TLR agonists [Kanzler, 2007]. In vitro cytokine induction (IL-1β, IL-6, IP-10 and TNFα) by GSK1795091 is similar to that of LPS. In rabbits, a species used for assessing endotoxin contamination of parenteral formulations due to their high sensitivity, GSK1795091 produced a transient increase in body temperature similar to that which occurs following LPS administration. In the repeat dose intravenous toxicity studies in rats and monkeys, GSK1795091 was associated with the expected pro-inflammatory actions of a TLR4 agonist. The primary systemic effect seen with weekly dosing of GSK1795091 in rat (dosing up to 4 weeks) and monkey (dosing up to 6 weeks) studies was increased levels of specific cytokines; all other findings were transient and considered secondary to this primary response. Adverse findings were only noted in rat and include microscopic changes in the heart valves and lymphocytic inflammatory cell infiltrates in the liver.

The no-observed-adverse-effect-level (NOAEL) is 15 µg/kg/dose and 200 µg/kg/dose, in the rat and monkey, respectively. Based on the predicted human exposure at the highest planned clinical dose of 250 ng (predicted maximum concentration [C_{max}] is approximately 0.036 ng/mL, and predicted area under the plasma concentration-time curve [AUC] is approximately 1.21 ng·h/mL), the margin to the NOAEL dose in rat is

approximately 2061X for C_{max} and 214X for AUC and in monkey is approximately 40,000X for C_{max} and 24,132X for AUC.

3.2.1.2. GSK1795091 Development Plan and Clinical Experience

This protocol describes Study 204686, evaluating the combination of GSK1795091 with other immunotherapies. The study will be the second evaluation of GSK1795091 in humans and the first in participants with cancer.

GSK1795091 is not planned for development as a monotherapy in cancer participants given that the TLR agonist drug class has not produced robust monotherapy antitumor activity in multiple prior clinical trials of participants with advanced malignancies. However, the safety, PK, and pharmacodynamics results from the FTIH study support the design and conduct of a clinical trial in cancer participants where the benefits of GSK1795091 are more likely to be realized as an adjuvant in combination with other immune therapies with complementary modes of action. Should the combination(s) demonstrate robust anti-tumor activity and a favorable safety profile, monotherapy study arms could be added by future amendment to explore the relative contributions of the study treatments.

Like GSK1795091, other TLR agonists including the prototypical TLR4 agonist, LPS, have been evaluated in both healthy participants and cancer patients for experimental and therapeutic purposes. Administration causes dose-dependent increases in cytokines including TNFα, IL-6, and IL-8, which peak within 2 to 4 hours and return to normal within 24 hours. In cases where the same TLR agonist has been administered to both healthy participants and to cancer participants, the PK and pharmacodynamic profiles have been similar for the two populations [Schmidt, 2015; Dietsch, 2014]. Clinical safety data for the drug class is characterized by a predictable tolerability profile of transient fever and flu-like symptoms (e.g., chills, nausea, malaise, etc.) attributable to cytokine production [Bahador, 2007]. A review of studies comprising thousands of healthy participants that have been administered LPS notes that long-term toxicities have not been described [Bahador, 2007]. Although elderly participants have greater decreases in blood pressure as compared to young participants administered 2 ng/kg doses of LPS [Krabbe, 2001], the difference in sensitivity has not prevented administration of even higher doses (5 ng/kg) to cancer participants [Engelhardt, 1991]. At these doses, peak TNFα and IL-6 levels can exceed 5000 pg/ml, and further dose escalation has been limited by rising transaminase levels [Engelhardt, 1991]. In other trials of TLR4 agonists in participants with advanced malignancies, cytokine-associated SAEs such as bronchospasm and hypotension have been reported [Vosika, 1984; de Bono, 2000]. Overall, the cytokine-associated adverse events associated with TLR agonists overlaps minimally with the profiles of checkpoint modulators. Thus, the safety profile of TLR agonists is well suited for administration in combination with other immune therapies such as checkpoint modulators.

The FTIH study of GSK1795091 was a randomized, double-blind (sponsor unblinded), placebo-controlled, ascending dose and parallel group study in healthy participants (GSK Document Number 2015N236402_03, Study 204685). In Part 1, single IV bolus doses of placebo or GSK1795091 7, 21, 60, or 100 ng were administered (n=6 GSK1795091, n=2 placebo per dose level, except the 60 ng cohort which was repeated, i.e., n=12

GSK1795091, n=4 placebo). Dose escalation was stopped, per protocol, following the 100 ng cohort, in which 3 of 6 participants experienced AEs of moderate intensity. In Part 2, participants were to receive repeat doses of GSK1795091. However, Part 2 was not started following an elevation in transaminases on study day 30 for 1 participant in cohort 4 (60 ng) of Part 1 (Section 3.2.1.2.1).

Preliminary PK assessments of GSK1795091 were performed based on available data. No quantifiable concentrations were observed at the 7 ng dose (assay lower limit of quantification [LLOQ] = 2 pg/mL), and insufficient PK concentrations were above the LLOQ at the 21 ng dose to enable calculation of AUC. Median peak concentrations (C_{max}) at doses 21 (n=6), 60 (n=12) and 100 ng (n=6) doses were 3.90, 10.02 and 23.26 pg/mL, respectively. The C_{max} values from these three single doses were evaluated for dose-proportionality using the power model loge (PK parameter) = a + b * loge (dose) where "a" is the intercept and "b" is the slope and was fitted by restricted maximum likelihood using SAS Proc Mixed. An estimate of the slope with corresponding 90% confidence interval (CI) was obtained from the power model to assess the degree of dose-proportionality, wherein a slope equal to 1.0 is indicative of dose-proportionality. The 90% confidence interval for the slope was (0.84, 1.20) and (0.96, 1.24) with inclusion and without inclusion, respectively, of a participant from the 100 ng dose cohort who showed an approximately 3-fold lower C_{max} compared to other participants from this cohort. These intervals were contained within the interval (0.8, 1.25) indicating that slope is around unity implying that dose-proportionality is observed for C_{max} within this dose range. Half-life could not be reliably estimated for lower dose groups due to limited data above the assay LLOQ. The median half-life calculated from the 100 ng dose is ~72 h, which is in agreement with expectations based on extrapolation of preclinical data.

The safety profile of GSK1795091 in the FTIH study [GSK Document Number 2015N236402_03], included AEs consistent with cytokine production and was generally qualitatively similar to profiles of other TLR agonists. Based on preliminary, unblinded safety data, as of 7 days after completing dosing in the 100 ng cohort, the most common clinical findings were influenza-like illness (10 participants), body temperature increased (4 participants), abdominal pain, back pain, dizziness, headache, oropharyngeal pain, presyncope, (2 participants). No other AEs were observed in more than 1 participant. The frequency of safety observations increased with dose as described below.

- Following administration of 7 or 21 ng GSK1795091 (6 participants in each group), the reported AEs and changes in vital signs resembled the placebo group.
- Following administration of 60 ng GSK1795091 (12 participants), mild influenza-like symptoms or headache were reported for 7 participants. One (1) participant had moderate abdominal cramps considered possibly related to study treatment. One (1) participant experienced a 58 bpm increase in heart rate to a maximum of 125 bpm. One (1) participant experienced a 12-fold increase in alanine aminotransferase (ALT) (described Section 3.2.1.2.1).
- Following administration of 100 ng GSK1795091 (6 participants), influenza-like symptoms were reported for 5 participants. Three (3) participants experienced moderate AEs considered at least possibly related to study treatment by the

investigator, including orthostatic presyncope, muscle tremor, back pain, nausea, dizziness, influenza-like symptoms. Because 3 of 6 participants experienced AEs of moderate intensity dose escalation was stopped, per protocol.

3.2.1.2.1. *Hepatic adverse events*

In study 204685, 1 participant received a single 60 ng IV dose of GSK1795091 and experienced a 12-fold increase in ALT. The time course of the increase was notable in that the participant had a slightly elevated ALT immediately prior to dosing (53 U/L; upper limit of normal [ULN] = 50 U/L), and the value remained of low grade but trended upward to 89.6 U/L on day 7 post-dose and 122.5 U/L on day 21. On day 32, the ALT increased to 563.4 U/L, and it peaked on day 34 (626.7 U/L) before declining. Beginning with day 35, total bilirubin was elevated (29.9 μmol/L; ULN = 21 μmol/L). Day 35 aspartate aminotransferase (AST), indirect bilirubin, and direct bilirubin were 254.5 U/L (ULN = 50 U/L), 25.8 μmol/L (ULN = 17.6 μmol/L), and 4.1 μmol/L (ULN = 3.4 μmol/L), respectively. The participant experienced no other AEs on the trial and only had mild increases in body temperature (0.6^{o}C) and heart rate (14 bpm) relative to predose values. A thorough evaluation by a hepatologist including comprehensive laboratory studies and liver ultrasound provided no additional insight into the elevations in hepatic laboratory values. Of note, the participant had multiple elevations in transaminases and total bilirubin before or during other clinical trials at the investigative site, although all were of low grade (maximum ALT <4-fold ULN; maximum total bilirubin < 1.5-fold ULN).

The elevation in transaminases and total bilirubin was considered possibly related to GSK1795091 by the investigator. In addition, the sponsor, in consultation with external hepatologists, considered an undefined, underlying, low-grade hepatic pathology to possibly have contributed to the elevation in transaminases, given the participant's history. A potential role for GSK1795091 as contributing to the observed increases cannot be ruled out based on the available information.Transaminases were routinely measured in all participants in the study, and no other participant experienced an increase.

In study 204686, as of the cutoff date of June 25, 2019, 1 participant received study treatment (GSK1795091 150 ng and GSK3174998 24 mg) for 6 weeks and experienced a serious adverse event of hepatitis which met liver stopping criteria and dose-limiting toxicity criteria. A 40-year-old male with no previous history of liver disease or liver metastases developed elevations in ALT 11x ULN (peak ALT 461 IU/L, ULN ALT 41 IU/L), AST 11x ULN (peak AST 461 IU/L, ULN AST 40 IU/L) and ALP 7.7x ULN (peak ALP 994 IU/L, ULN ALP 129 IU/L). Total and direct bilirubin remained within normal limits. There was no nausea, vomiting, fever or abdominal pain. At the time of the hepatitis, the subject was also receiving antibiotic treatment (with ciprofloxacin and amoxycillin/clavulanate) for an intra-abdominal abscess. Viral serology, autoantibody panel and imaging did not reveal an alternative cause for the event. Study drugs were interrupted, the subject was treated with 1 mg/kg methylprednisolone and the transaminases were resolving (ALT 283, AST 68) three days after peak values. ALP remained elevated (865 IU/L). Disease progression was noted on the imaging and the subject elected to withdraw from the study. The investigator and sponsor considered the

event possibly related to GSK1795091 and GSK3174998. The sponsor, in consultation with external expert hepatologists also considered concomitant amoxycillin/clavulanate as a possible cause. A potential role for GSK1795019 and GSK3174998 cannot be ruled out based on available information.

3.2.2. GSK3174998 Background

An overview of GSK3174998 is provided below. Detailed information concerning the biology, pharmacology, PK, and safety characteristics can be found in the IB [GSK Document Number 2014N212091_05]. Clinical information is aligned to that available at the time of protocol development.

GSK3174998 is a humanized wild-type IgG1 anti-OX40 agonistic mAb. GSK3174998 demonstrated several mechanisms of action in vitro including promoting effector CD4+ T-cell proliferation, inhibiting the induction of IL-10-producing CD4+ Type 1 regulatory (Tr1) cells and blocking the suppressive function of natural Tregs (nTregs), and binding to the fragment crystallizable region (Fc) receptor (FcR), which is anticipated to augment OX40 signaling via cross-linking of the antibody via the Fc domain on FcR positive cells. Importantly, it has been shown that OX40 activation gives a costimulatory signal to T-cells, dependent on a T-cell receptor (TCR) engagement, suggesting that GSK3174998 is not a super agonist in the models tested which is supported by available clinical experience.

3.2.2.1. GSK3174998 Nonclinical Activity

GSK3174998 (and mouse surrogate antibodies) have shown activity in multiple in vitro and in vivo models. GSK3174998 demonstrated several mechanisms of action in vitro, including promoting effector CD4+ T-cell proliferation, inhibiting the induction of IL-10 producing CD4+ Tr1 cells and blocking the suppressive function of nTregs, and binding to FcR, which is anticipated to augment OX40 signaling via cross-linking of the antibody via the Fc domain on FcR positive cells. A surrogate mAb to murine OX40 (OX86) was administered to female BALB/c mice bearing CT26 mouse colon carcinoma tumors, and produced an increase in survival compared to control groups. Together, these data provide rationale for GSK3174998 to be used as an immunotherapy for the treatment of cancer.

The cynomolgus monkey was demonstrated to be an appropriate toxicology species due to human comparability with OX40 protein sequence identity, GSK3174998 binding and activity. GSK3174998 was well tolerated in monkey toxicology studies following weekly IV dosing for up to 4 weeks at doses up to 100 mg/kg/week with no adverse test article-related findings noted. Anti-GSK3174998 antidrug antibodies (ADAs) were detected in most monkeys given ≤10 mg/kg; however, the ability to determine toxicity in the terminal necropsy animals was not compromised by ADAs due to the fact that robust target engagement was observed. No infusion reactions were observed in monkeys, including those with ADA.

3.2.2.2. GSK3174998 Clinical Experience

Eighty-two (82) participants with advanced solid tumors have been treated in the ongoing FTIH study 201212 as of 13 August 2017 [GSK Document Number 2014N225045_02, Study 201212]. Of the 82 participants, 45 were treated with GSK3174998 monotherapy across 6 dose levels of (0.003 0.01, 0.3, 1, 3, and 10 mg/kg), and 39 participants were treated with the combination of GSK3174998 and pembrolizumab 200 mg, at GSK3174998 doses of 0.003 0.01, 0.3, 1 mg/kg. Two participants crossed over from monotherapy to combination therapy. To date, GSK3174998 was well tolerated in humans with no indication of dose-related increases in AEs based on current data.

In the GSK3174998 monotherapy study arm, no dose-limiting toxicities or treatment-related Grade 3, Grade 4, or Grade 5 toxicities were reported. A single event led to treatment discontinuation, Grade 3 aphasia due to Grade 5 stroke. The most common AEs were fatigue (11, 24%), back pain (9, 20%), diarrhea (9, 20%), nausea (8, 18%), asthenia (8, 18%), vomiting (8, 18%), anemia, (7, 16%), headache (5, 11%), dyspnoea (5, 11%), myalgia (4, 11%), pain in extremity (5, 11%), and pyrexia (5, 11%). The most common treatment related AEs included diarrhea (5, 11%) and fatigue (5, 11%).

In the GSK3174998 combination study arm, no treatment related Grade 4 or Grade 5 toxicities were reported. Two patients reported Grade 3 treatment-related AEs. One patient with head and neck cancer treated with 1 mg/kg GSK3174998 and 200 mg pembrolizumab reported treatment related Grade 3 AEs of asthenia and infusion reaction, both attributed to study treatment and occurring over one month apart from another. A second patient with triple-negative breast cancer (TNBC) treated with 3 mg/kg GSK3174998 reported Grade 3 lymphopenia attributed to study treatment. One dose limiting toxicity of Grade 2 pleural effusion was reported in a patient with TNBC. The

only AE leading to treatment discontinuation was Grade 3 fatigue. The most common AEs were pleural effusion (9, 23%), fatigue (6, 15%), decreased appetite, (5, 13%), pyrexia (5, 13%), arthralgia (4, 10%), and dyspnoea (4, 10%). The most common treatment related AEs included fatigue (5, 13%) and nausea (3, 8%).

Of note, there was no evidence for an acute cytokine release syndrome (CRS) associated with GSK3174998 administration at any dose tested, despite having a measured receptor occupancy >80% in peripheral blood in the immediately post-dose timeframe for all tested doses (see Figure 8 for additional information on GSK3174998 receptor occupancy). This is consistent with the mechanistic understanding of OX40 providing a costimulatory signal to T-cells dependent on a TCR engagement and not functioning as a super agonist. Overall, the safety profile of GSK3174998 does not appear to have overlapping toxicity with TLR agonists.

For further details on the safety of GSK3174998, please refer to the IB [GSK Document Number 2014N212091_05].

3.2.3. GSK3359609 Background

An overview of GSK3359609 is provided below. Detailed information concerning the biology, pharmacology, PK, and safety characteristics can be found in the IB [GSK Document Number 2017N319717_02]. Clinical information is aligned to that available at the time of protocol development.

GSK3359609 is a humanized IgG4 anti-ICOS agonistic mAb with specific, high-affinity binding to and agonist activity of ICOS, which is expressed on CD4+ and CD8+ T cells. The desired pharmacology of GSK3359609 is to expand the total number and increase the activity of tumor specific effector CD4+ and CD8+ T cell populations. Tumor specific T cells must be first primed through contact with cognate antigens and activated into effector cells in order for induction of ICOS expression to occur and GSK3359609 to bind and elicit an agonist effect. Therefore, it is expected that GSK3359609 will be most active in disease settings where an antitumor immune response is primed as an inherent feature of the tumor or by prior lines of therapy. Additionally, GSK3359609 is expected to be active in combination with agents which prime or modulate tumor immunity.

3.2.3.1. GSK3359609 Nonclinical Activity

GSK3359609 biophysical properties and pharmacology have been extensively characterized in a series of nonclinical experiments. In vitro binding and functional studies were performed with recombinant protein as well as cell lines or primary human immune cells cultured ex vivo. Because ICOS was weakly expressed on resting T cells yet upon TCR engagement and activation became highly induced on CD4+ and CD8+ T cells, all binding and functional studies performed were with anti-CD3 and/or anti-CD28 activated PBMCs from healthy human donors.

GSK3359609 bound to recombinant human ICOS with an affinity of 1.34 nM as determined by Biacore methodology. GSK3359609 bound in a concentration-dependent manner to pre-activated primary CD4+ and CD8+ T cells from healthy human donors. As expected, minimal binding of GSK3359609 to T cells was noted in the absence of activation.

The nonclinical toxicology program for GSK3359609 was conducted in cynomolgus monkeys which were shown to be an appropriate species since the mAb cross reacts equally well with human and cynomolgus monkey ICOS receptors. There was no binding of GSK3359609 with rodent ICOS receptors. Receptor occupancy (evidence of GSK3359609 binding and decreased free receptor) was demonstrated in vivo in monkeys on $CD3^+CD4^+CD14^-$ T cells in peripheral blood after administration of single and multiple doses of GSK3359609 and persisted throughout the dosing phase and off-dose period. Immunohistochemical assessment of ICOS distribution in normal human tissues showed positive membranous staining in specific cells or lymphoid cell aggregates considered likely to be T cells in the tissues examined including lymphoid tissues, gastrointestinal tract, liver, pancreas and testes.

A range of in vitro and in vivo studies have been conducted to investigate the primary pharmacology of GSK3359609. The pharmacokinetics of GSK3359609 were investigated in two repeat dose cynomolgus monkey IV toxicology studies. Systemic exposure generally increased proportionally as the dose increased. A decrease in plasma concentrations was observed after, typical of an immunogenicity response; all animals were confirmed to be positive for anti-drug antibody (ADA).

GSK3359609 is not a super-agonist; as the ICOS agonist function of GSK3359609 required TCR engagement. In the absence of anti-CD3 antibodies, there was minimal to no detectable increase in T cell activation or induction of pro-inflammatory cytokines with either the immobilized or soluble form of GSK3359609. Activated CD4+ T cells treated with GSK3359609 resulted in a greater magnitude of T cell proliferation, and cytokine induction when the antibody was immobilized as opposed to being added as a soluble protein to the supernatant of the T cell cultures. It is known that antibody cross linking is required for T cell stimulation through other costimulatory receptors [Wacholtz, 1989]. Therefore, the bound-format in vitro assays mimic the in vivo condition wherein an ICOS antibody forms cell-to-cell cross-links through FcγR binding.

3.2.3.2. GSK3359609 Clinical Experience

As of 16 March 2018, 63 subjects received at least one dose of GSK3359609 as a monotherapy and 42 subjects received at least one dose of GSK3359609 in combination with 200 mg pembrolizumab in the ongoing FTIH study 204691 [GSK Document Number 2015N238345_03]. These subjects are included in the safety analysis.

Subjects received GSK3359609 monotherapy in dose escalation and expansion phases at the following dose levels: 0.001 mg/kg (n=1), 0.003 mg/kg (n=1), 0.01 mg/kg (n=2), 0.03 mg/kg (n=8), 0.10 mg/kg (n=11), 0.30 mg/kg (n=12), 1 mg/kg (n=18), and 3 mg/kg (n=10). One subject enrolled in the 0.03 mg/kg dose level received at Cycle 1 a GSK3359609 dose that equated to 0.15 mg/kg.

Among the dose levels of GSK3359609 monotherapy investigated (from 0.001 mg/kg to 3 mg/kg), a dose limiting toxicity (DLT) was observed in 1 subject at the 3 mg/kg dose level. The subject that experienced the DLT following monotherapy GSK3359609, a 52-year-old female, enrolled in the PK/PD cohort, experienced AEs of Grade 4 increases in AST, ALT, and gamma-glutamyltransferase (GGT); Grade 3 increases in lipase and bilirubin; Grade 2 increase in alkaline phosphatase; and Grade 1 increase in amylase.

The first of these events (AST increased) occurred 24 days after the start of study treatment. An ultrasound of the liver showed marked dilation of the biliary tract and the presence of a liver lesion measuring 51 x 41 mm. As of the clinical cutoff date, no event was considered serious. All the events were ongoing, considered related to study treatment, and led to treatment discontinuation.

In the overall Part 1 population, 56 of 63 subjects (89%) experienced at least one AE regardless of causality; 46% of these AEs were Grade 1 or 2 in severity. Twenty-two subjects (35%) experienced at least one AE with a maximum severity Grade of 3 in dose levels with > 2 subjects enrolled. The percentage of subjects who experienced at least one Grade 3 AE is: 50% (4 of 8 subjects) at 0.03 mg/kg; 36% (4 of 11 subjects) at 0.1 mg/kg; 33% (4 of 12 subjects) at 0.3 mg/kg; 44% (8 of 18 subjects) at 1 mg/kg; 10% (1 of 10 subjects) at 3 mg/kg. Four Grade 4 events were reported in two subjects (1 event each of increased AST, increased ALT, and increased GGT occurred in the same subject treated at 3 mg/kg, and tumor perforation in another subject treated at 0.1 mg/kg). Three Grade 5 events of dyspnea, lower gastrointestinal hemorrhage, and sepsis were reported in 1 subject each at 3, 1, 0.03 mg/kg, respectively. SAEs reported in >1 subject each overall included abdominal pain, lung infection, pain, and urinary tract infection, all of which were reported in 2 subjects each. Three subjects had AEs leading to permanent discontinuation of study treatment.

Forty-two (42) subjects received at least one dose of GSK3359609 in combination with pembrolizumab 200mg; this includes the dose escalation and expansion phases at the following dose levels: GSK3359609 0.01 mg/kg (n=5), GSK3359609 0.03 mg/kg (n=5), GSK3359609 0.10 mg/kg (n=5), GSK3359609 0.30 mg/kg (n=20), and GSK3359609 1 mg/kg (n=7).

No DLTs were reported for any of the 5 dose levels of GSK 3359609 in combination with pembrolizumab 200 mg investigated thus far (from 0.010 mg/kg to 1 mg/kg).

Grade 1 and 2 AEs were experienced by 21 subjects (50%) that received GSK3359609 in combination with pembrolizumab 200 mg. Twelve subjects (29%) experienced AEs that were Grade 3 or 4 and none were Grade 5. Among these 12 subjects, Grade 3 or 4 AEs were also considered serious for 7 and 1 subject(s), respectively. A Grade 3 event of diarrhea in 1 subject was considered related to study treatment by the investigator. At least one SAE was reported for 14 subjects in Part 2, of which 1 event of diarrhea was considered treatment related. No SAEs were reported in >1 subject each overall. One subject had an AE leading to permanent discontinuation of study treatment in Part 2.

For further details on the safety of GSK3359609, please refer to the IB [GSK Document Number 2017N319717_02].

3.2.4. Pembrolizumab Background

Pembrolizumab, a humanized monoclonal antibody against the PD-1 protein, has been developed by Merck & Co for the treatment of patients with cancer and has been approved for treatment of patients with multiple advanced malignancies. Refer to the pembrolizumab approved labelling for detailed background information [KEYTRUDA SPC, 2019; KEYTRUDA PI, 2019].

3.2.4.1. Pembrolizumab Clinical Experience in Combination with other TLR Agonists

Clinical trials of TLR agonists at doses associated with systemic cytokine-related AEs have not demonstrated frequent, severe, or unexpected toxicities when administered in combination with pembrolizumab [Flowers, 2017; Leung, 2017; Milhem, 2018]. For example, the TLR4 agonist G100 was administered alone and in combination with pembrolizumab [Flowers, 2017]. The overall frequency of treatment-related AEs was 69% for G100 alone vs. 85% for G100 + pembrolizumab. One (1) of 13 subjects experienced Grade 3 adrenal insufficiency with colitis, hyponatremia, and hypocalcemia, attributable to pembrolizumab. No other Grade 3 or greater events were described. The authors concluded that all AEs considered possibly related to G100 were grade 1 or 2 and the addition of pembrolizumab did not result in unexpected or worsening toxicity [Flowers, 2017]. SD-101 administered by intratumoral injection with standard doses of pembrolizumab in subjects with metastatic melanoma experienced frequent AEs characteristic of TLR agonists, e.g. chills (17/22 subjects; 77.3%); headache (16/22 subjects; 72.7%); myalgia (15/22 subjects; 68.2%); nausea (7/22 subjects; 31.8%); pyrexia (7/22 subjects; 31.8%); and influenza-like illness (6/22 subjects; 27.3%). Grade ≥3 AEs were observed in 59.1% of patients (most common: myalgia 13.6% and injection site pain 13.6%). Immune-related AEs occurred in 2 patients. [Leung, 2017]. When SD-101 was administered to subjects with metastatic SCCHN in combination with pembrolizumab, potential irAEs were reported at a frequency of 3/22 subjects (14%) [Cohen, 2018]. The authors concluded that the combination neither exacerbated the adverse event profiles of the monotherapies nor resulted in a unique safety signal for the combination [Leung, 2017; Cohen, 2018]. In an ongoing phase Ib dose escalation trial evaluating intratumoral TLR9 agonist CMP-001 in combination with pembrolizumab in 63 subjects with advanced melanoma, 15 Grade 3/4 related AEs were reported, including hypotension (n=7), anemia (n=2), chills (n=2), hypertension (n=2) and fever (n=2) [Milhem, 2018]. No maximum tolerated dose was identified during the dose escalation phase of the study. While acknowledging the limitations of direct comparisons to these studies, these results demonstrate that other TLR agonists administered at doses associated with systemic, cytokine-associated AEs have been well-tolerated in combination with pembrolizumab by subjects with advanced malignancies.

3.2.5. GSK1795091 Combination Background

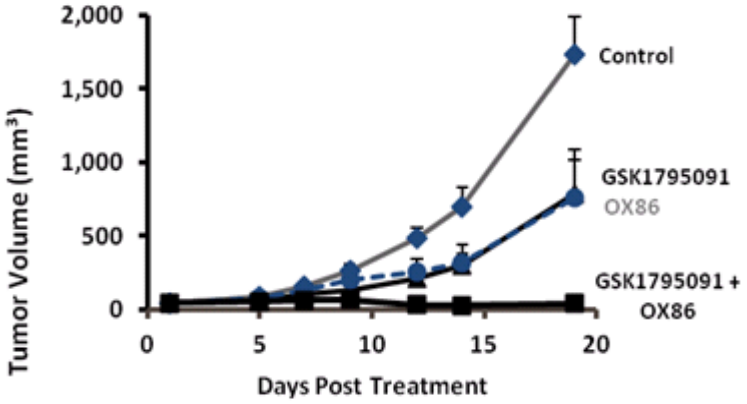
3.2.5.1. GSK1795091 In Vivo Studies

Efficacy Studies

Based on the potentially complementary mechanisms of action of GSK3174998 and GSK1795091, the combination was evaluated in BALB/c mice implanted with syngeneic CT-26 tumor xenografts. Four groups of 10 BALB/c mice with intact immune systems

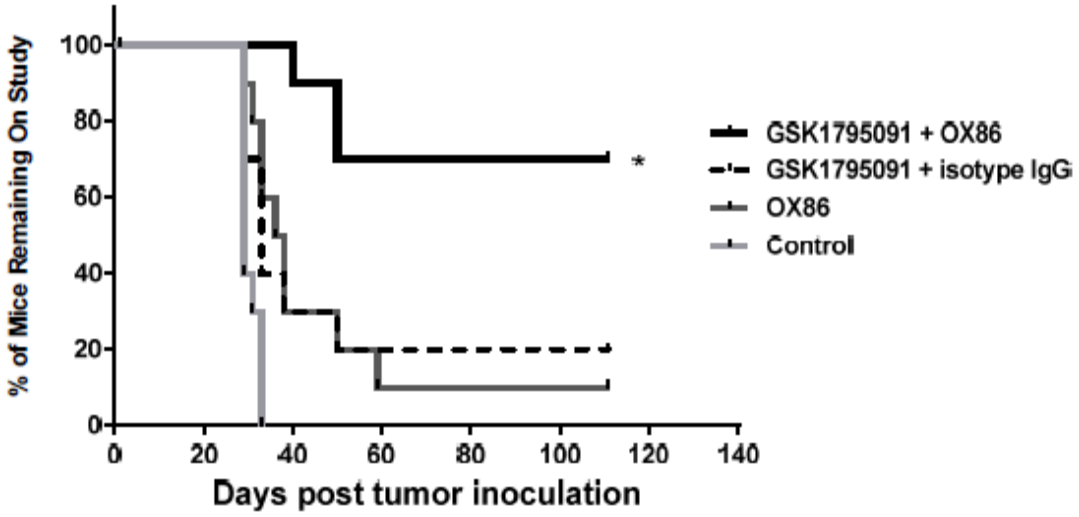
were implanted with CT-26 tumors. The mice received one of the following treatments: placebo, GSK1795091 (TLR4 agonist), OX86 agonist (mouse surrogate OX40 agonist antibody), or the combination of GSK1795091 and OX86 agonist. While the monotherapies had modest effects on tumor growth (Figure 1), the combination treatment of GSK1795091 and OX86 produced greater activity and durable responses.

Figure 1 CT-26 Tumor Growth in Balb/c Mice Treated with GSK1795091 (TLR4 agonist) and/or OX86 (mouse surrogate for OX40) agonist



The reduction in tumor volume translated to significant improvement in the survival of animals (Figure 2). Approximately 70% of animals that received the combination of GSK1795091 and OX86 survived more than 100 days. By contrast, 10-20% of the animals that received either monotherapy survived 100 days.

Figure 2 Survival of Balb/c Mice Implanted with CT-26 Tumors and Treated with GSK1795091 (TLR4 agonist) and/or OX86 agonist



GSK1795091 and GSK3359609 combination was evaluated in BALB/c mice implanted with syngeneic CT-26 tumors. Four groups of 10 BALB/c mice with intact immune systems were implanted with CT-26 tumors. The mice received one of the following treatments: placebo, GSK1795091 (TLR4 agonist), 7E.17G9 agonist (mouse surrogate ICOS agonist antibody), or the combination of GSK1795091 and 7E.17G9 agonist. While the monotherapies had very modest effects on tumor growth (Figure 3), the combination treatment of GSK1795091 and 7E.17G9 produced greater activity and durable responses. GSK1795091 and 7E.17G9 monotherapies resulted in 10% and 40% of mice that survived more than 100 days respectively, while the combination therapy resulted in 60% tumor free mice that survived more than 100 days (Figure 4).

Figure 3 **CT-26 Tumor Growth in Balb/c Mice Treated with GSK1795091 (TLR4 agonist) and/or ICOS agonist antibody (7E.17G9, mouse surrogate for GSK3359609)**

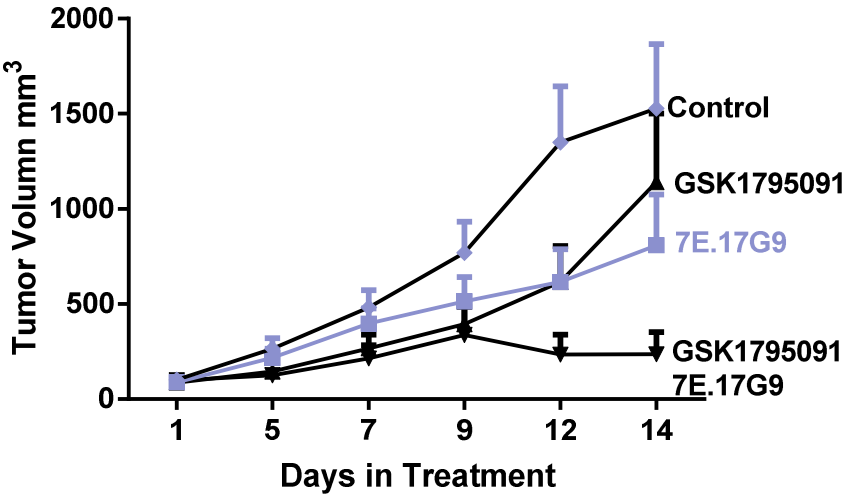


Figure 4 **Survival of Balb/c Mice Implanted with CT-26 Tumors and Treated with GSK1795091 (TLR4 agonist) and/or ICOS agonist antibody (7E.17G9, mouse surrogate for GSK3359609)**

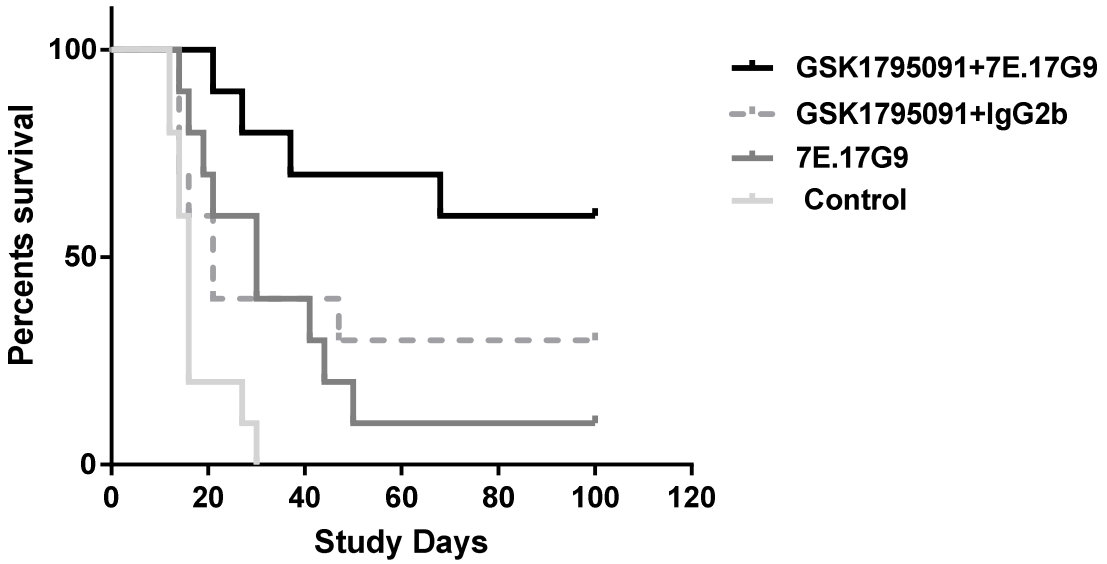


Figure 5 **EMT-6 Tumor Growth in Balb/c Mice Treated with GSK1795091 (TLR4 agonist) and/or PD-1 antibody (RMPI-14, mouse surrogate for pembrolizumab)**

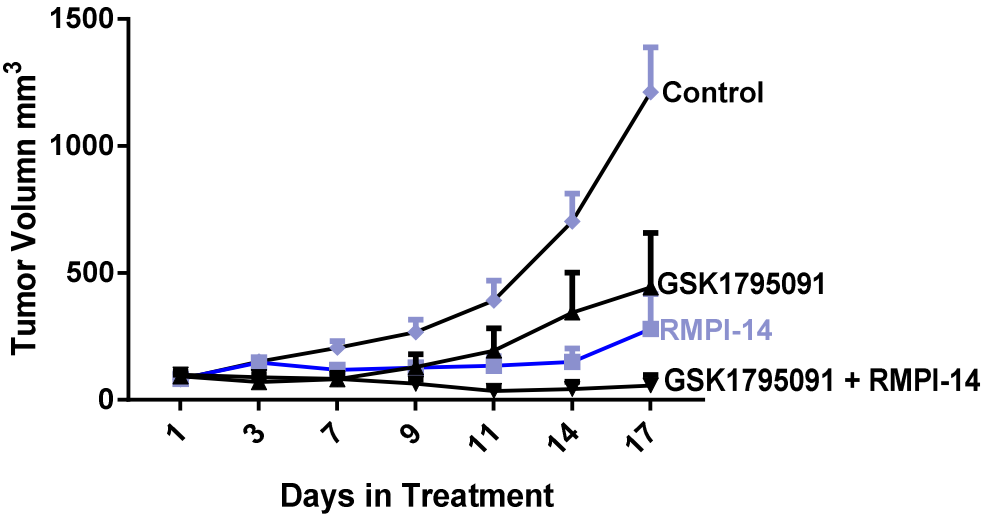
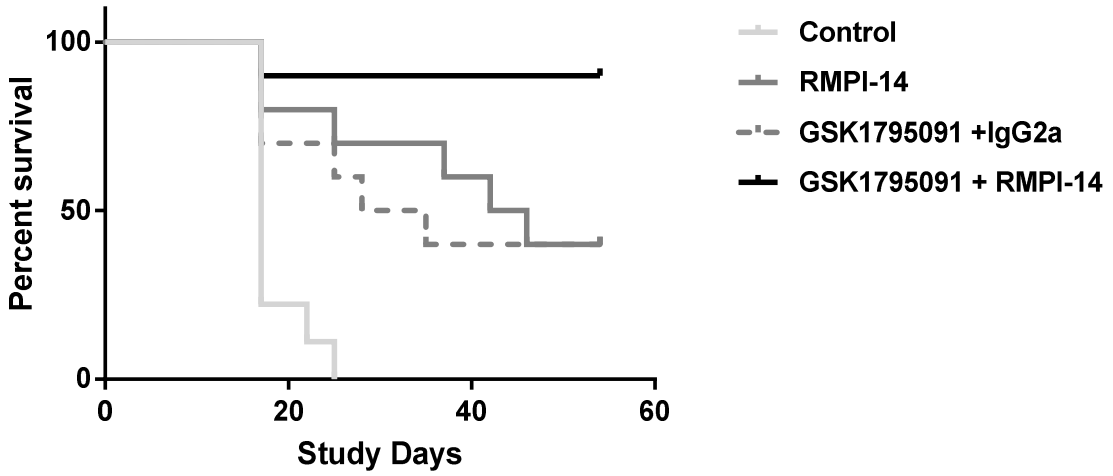


Figure 6 Survival of Balb/c Mice Implanted with EMT-6 Tumors and Treated with GSK1795091 (TLR4 agonist) and/or PD-1 antibody (RMPI-14, mouse surrogate for pembrolizumab)



GSK1795091 and a PD-1 antibody in combination were evaluated in BALB/c mice implanted with syngeneic EMT-6 tumors. Four groups of 10 BALB/c mice with intact immune systems were implanted with EMT-6 tumors. The mice received one of the following treatments: placebo, GSK1795091 (TLR4 agonist), RMP1-14 (mouse surrogate PD-1 antibody), or the combination of GSK1795091 and RMP1-14. While the monotherapies exhibited tumor growth inhibition (Figure 5), the combination treatment of GSK1795091 and RMPI-14 resulted in greater tumor growth inhibition. GSK1795091 and RMPI-14 monotherapies resulted in 40% tumor free mice that survived 60 to 80 days, while the combination therapy resulted in 90% tumor free mice that survived 60 to 80 days (Figure 6).

These preclinical efficacy results for GSK1795091 have been reproducible across a range of studies (e.g., testing of different doses, dose frequencies, and routes of administration), and together with in vitro and in vivo pharmacologic data, provide rationale for evaluating the combination of GSK1795091 with either GSK3174998, GSK3359609, or pembrolizumab in a clinical trial for the treatment of cancer.

Safety Studies

In a Safety PK/Pharmacodynamic study, groups of 3 cynomolgus monkeys were administered GSK1795091 (2 µg/kg) monotherapy or GSK1795091 in combination with GSK3174998 (10 mg/kg). Changes in IL-6, IL-8, IL-10, MCP-1, and IP-10 were observed, with peak cytokine values at 2 hours post-dose of test articles. Minimal changes from baseline were observed for TNFα, IFNγ, IL-2, and IL-1β. The ratios (combination:monotherapy) of median values (from lowest to highest) at 2 hours post-dose were 0.59, 0.77, 1.4, 1.6, and 2.5 for MCP-1, IL-8, IP-10, IL-6, and IL-10, respectively. Overall, cytokine values were variable and the distributions were generally overlapping when comparing the monotherapy and combination arms. There were no changes in hematology or clinical pathology parameters.

A review of the nonclinical toxicology findings with both GSK1795091 and GSK3174998 given as single agents indicate that additional combination toxicology studies in monkeys would not likely provide additional relevant clinical risk assessment data.

A review of the data from the nonclinical combination efficacy studies of GSK1795091 and anti-ICOS as well as the nonclinical toxicology findings for both GSK1795091 and GSK3359609 used as single agents was conducted and adequately provide support for their use in combination in the target patient population. Additionally, the nonclinical toxicology findings for both GSK1795091 and GSK3359609 given as single agents indicate that a combination toxicology study in monkeys would not likely provide additional relevant clinical risk assessment data.

A review of the data from the nonclinical combination efficacy studies of GSK1795091 and anti-PD1 as well as the nonclinical toxicology findings and clinical (pembrolizumab only) safety information for both GSK1795091 and pembrolizumab used as single agents was conducted and adequately provide support for their use in combination in the target patient population. Additionally, the nonclinical toxicology findings for both GSK1795091 and pembrolizumab given as single agents indicate that a combination toxicology study in monkeys would not likely provide additional relevant clinical risk assessment data.

3.2.5.2. GSK1795091 In Vitro Studies

The potential of GSK1795091 alone and in combination with GSK3174998, GSK3359609, or pembrolizumab to induce cytokine release in vitro was evaluated in PBMCs isolated from 10 healthy human donors (5 males and 5 females) under conditions of no anti-CD3 stimulation (resting) and with anti-CD3 stimulation (pre-stimulation), which was previously shown to upregulate OX40 surface expression on T-cells. Cytokines (IL-2, IL-6, IL-10, IFNγ, and TNFα) were measured following 24 hours incubation with GSK1795091 (10, 100 or 1000 pg/mL) and either GSK3174998, GSK3359609, or pembrolizumab mAbs (0. 01, 0.1, 1 or 10 μg/mL). Anti-CD28 and human IgG1 or IgG4 (as appropriate) isotype control antibodies were included as positive and negative controls, respectively. Positive cytokine induction by GSK1795091 and GSK3174998, GSK3359609, or pembrolizumab combination was defined as ≥3-fold increase above that of GSK1795091 alone.

3.2.5.2.1. *GSK1795091 and GSK3174998*

No effects on cytokine responses in resting or pre-stimulated PBMCs were detected at 10 pg/mL GSK1795091 in combination with any concentration of GSK3174998. For concentrations ≥100 pg/mL GSK1795091, addition of 1 μg/mL GSK3174998 to resting PBMCs produced minimal to mild increases (approx. 2-4 fold) in IL-6, IL-10, and/or TNFα in 2/10 donors, and in 1/10 donors in pre-stimulated PBMCs incubated with 1000 pg/mL GSK1795091 in combination with ≥1 μg/mL GSK3174998. There was high donor-to-donor variability in cytokine responses, and individual donors had inconsistent concentration-response curves amongst the various test conditions. These results suggest that the potential for enhanced cytokine release when these agents are administered in

combination in patients appears to be low, but cannot be eliminated due to the high amount of data variability.

3.2.5.2.2. *GSK1795091 and GSK3359609*

No increases greater than 3-fold over single treatment arm in IL-2, IL-6, IL-10, IFN-γ, or TNF-α were detected in PBMCs treated with GSK1795091 in combination with GSK3359609 (at concentrations up to 1000 pg/mL and 10 μg/mL, respectively) compared to GSK1795091 alone, either in the presence or absence of anti-CD3 stimulation. These results suggest that the potential for enhanced cytokine release when these agents are administered in combination in patients appears to be low.

3.2.5.2.3. *GSK1795091 and pembrolizumab*

When pembrolizumab (≥0.1 μg/mL) was combined with GSK1795091 (10, 100 or 1000 pg/mL) in rested PBMCs, there was an increase in the anti-inflammatory cytokine IL-10 [median increase 3.1-fold (range 0.01- to 119-fold)] in up to 5 of 10 donors compared to the respective concentrations of GSK1795091 plus human IgG4 isotype control. Enhanced responses were also observed in rested PBMCs of one to three donors (out of 10) for at least one inflammatory cytokine: IL-2 [1.5-fold (0.01- to 4.5-fold)], IL-6 [1.8-fold (1.1- to 8.2-fold)], or TNF-α [1.7-fold (0.2- to 7.8-fold)]. There was high donor-to-donor variability in cytokine responses, and individual donors had inconsistent concentration-response curves amongst the various test conditions. Given that a subset of the donors had increases in one or more pro-inflammatory cytokines, IL-2, IL-6, and TNF-α, the potential for enhanced cytokine release when GSK1795091 and pembrolizumab are administered in combination in patients cannot be eliminated (see the Investigator's Brochure, GSK Document Number 2015N239078_04).

3.2.5.3. Clinical Combinations of GSK1795091 and GSK3174998

As of 13 August 2018, preliminary clinical data were available for 4 subjects that received GSK1795091 50 ng and in combination with GSK3174998 24 mg. Three (3) participants completed the 6-week DLT evaluation period. One (1) participant received the first doses of GSK1795091 and GSK3174998 in combination and remained on study without adverse events. One (1) subject experienced a SAE (constipation), considered unrelated to study treatment by the investigator. One (1) subject, with a history of hypertension, experienced Grade 3 hypertension that resolved with administration of Demerol 25 mg. Based on preliminary data, no adverse events considered related to GSK1795091 during the monotherapy run-in period, increased in severity when administered in combination with GSK3174998.

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of GSK1795091, GSK3174998, and GSK3359609 may be found in the respective IBs [GSK Document Number 2015N239078_04 , GSK Document Number 2014N212091_05, and GSK Document Number 2017N319717_02]. Information for pembrolizumab is found in the KEYTRUDA Prescribing Information. The following section outlines the risk assessment and mitigation strategy for this protocol.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Products [GSK1795091, GSK3174998, GSK3359609, and pembrolizumab]		
Cytokine release syndrome (CRS) and/or cytokine-associated symptoms (flu-like symptoms, fever, tachycardia, hypotension, etc.).	TLR agonists are known to increase serum cytokine levels based upon extensive preclinical and clinical data [Kanzler, 2007; Astiz, 1995; Dillingh, 2014; Isambert, 2013].	• GSK1795091 starting dose selected as a minimally active dose based on clinical and pharmacodynamic data from the GSK1795091 FTIH study [GSK Document Number 2015N236402_03]. No further modification appears indicated given available in vivo and in vitro combination data for GSK1795091 and clinical data for the mAbs. • The first 3 participants at each dose level receive study treatment at least 3 days apart • Evaluation of GSK1795091 tolerability during a 2-week run-in period before administration as a combination. • Conservative and progressively smaller relative dose increases of GSK1795091 between cohorts (Section 5.1.1) • Adverse event management with supportive care and paracetamol. In the event of unexpectedly severe cases, AE management with fluids, oxygen, vasopressor support, etc. Refer to Section 7.2.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Vagal reactions	Rare cases of severe vagal reactions, bradycardia and asystole have been described in healthy participants receiving LPS. Risks for these events may include prior history of syncope and inadequate hydration [van Eijk, 2004].	• Hydration of participants before and after study product administration. • Frequent vital sign and electrocardiogram (ECG) measurements in the immediate post-dose time frame. • Adverse event management with fluids and, if necessary, vasopressor support (Section 7.2.1).
Infusion reactions and hypersensitivity	Risk for infusion reactions and hypersensitivity is inherent to many mAbs [Brennan, 2010].	• Exclusion of participants with history of severe hypersensitivity to another mAb. Refer to Section 6.2 for exclusions. • GSK3174998, GSK3359609, and pembrolizumab administration to be completed with no residual infusion-associated events before GSK1795091 administration. Refer to Section 7.2.1 for management of infusion reactions.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Immune-related AEs	Monoclonal antibodies which affect the adaptive immune-system and promote the killing of tumor cells (e.g., ipilimumab, pembrolizumab and nivolumab) have been associated with inflammatory AEs such as diarrhea/colitis, pneumonitis, nephritis, hypophysitis, adrenalitis, thyroiditis, severe skin reactions, uveitis, myocarditis and hepatotoxicity. These are well established after treatment with checkpoint modulators, and are consistent with the immune-stimulatory mechanism of action of these agents. Data are insufficient at this time to fully appreciate the characteristics of GSK3174998 or GSK3359609 in this regard; however, surveillance for events of this nature is warranted. Risks of irAEs are well-described for pembrolizumab [KEYTRUDA PI, 2019].	• Exclusion of participants with: • Toxicity (≥Grade 3) related to prior immunotherapy leading to study treatment discontinuation Refer to Section 6.2.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Liver toxicity	One (1) participant with a history of transaminase and bilirubin elevations experienced a mild increase in ALT at study day 7 (>1.5-fold) and a significant increase in ALT (12-fold ULN), AST (5-fold ULN) and total bilirubin (1.4-fold ULN) 35 days following a single dose of GSK1795091.	• Exclusion of participants with ALT or bilirubin 1.5-times ULN or greater at screening. • Administration of GSK1795091 monotherapy during a 2-week run-in period. Participants with an increase in ALT 1.5x baseline and 1.5x ULN not attributable to another cause during the run-in will discontinue study treatment and not receive GSK1795091 and mAbs in combination. • Criteria for stopping dosing, monitoring and managing transaminase elevations, and rechallenging participants that experience a transaminase elevation (Appendix 7).
Embryofetal harm	Based on the mechanism of action, pembrolizumab can cause fetal harm [KEYTRUDA PI, 2019]. The risks of GSK1795091, GSK3174998 and GSK3359609 are unknown. Based on the therapeutic targets for GSK1795091, GSK3359609, and GSK3174998, they have the potential to modulate maternal tolerance to the fetus and can therefore cause fetal harm. (Riella, 2013; Clark, 2004; Heikkinen, 2004).	• Exclude pregnant woman from participation in the study and require highly effective contraceptive measures for WOCBP.
Immune complex disease	Immune complex formation and deposition were findings in nonclinical safety studies for GSK3359609 (refer to the GSK3359609 IB)	• Clinical laboratory safety assessments and immunogenicity testing

3.3.2. Overall Benefit: Risk Conclusion

This is an open-label, dose escalation study and the first study of the combination of GSK1795091 with GSK3174998, GSK3359609, or pembrolizumab conducted in humans; this study will enroll participants with advanced solid tumors. There is biologic rationale to study these combinations for the treatment of cancer based on complementary modes of action on the immune system, and antitumor activity of the combinations that exceeds activity of the monotherapies in preclinical models. However, it is unknown if the combinations will have clinical activity for patients with cancer.

Based on nonclinical in vivo and ex vivo combination evaluations and clinical experience to date, and the conservative starting dose of GSK1795091, the safety profiles of the combinations are not expected to exceed that of the monotherapies at the starting doses. In contrast to experience to date with GSK3174998 and GSK3359609, it is expected that increasing the dose of GSK1795091 past a certain threshold will be associated with DLTs given the TLR4 agonist mechanism of action and experience with other TLR agonists including LPS. As a checkpoint inhibitor, rather than a direct immune-stimulator, pembrolizumab is not expected to substantially increase the potential for DLTs with GSK1795091, but the potential for specific synergies cannot be excluded a priori.

Consistent with other Phase 1 trials for the treatment of cancer, a target DLT frequency has been set as 16-33%, and a Bayesian adaptive dose escalation design for GSK1795091 is employed to efficiently determine the dose(s) associated with this DLT frequency. In addition, it is possible that infrequent events unrelated to GSK1795091 dose, such as increases in hepatic laboratory values, might be observed. This risk will, in part, be mitigated by a run-in period for GSK1795091 prior to the initiation of combination study treatment. The run-in provides an evaluation of monotherapy GSK1795091 safety and tolerability in participants with cancer and prevents the administration of combination therapy to participants that experience, with GSK1795091 alone, a DLT, unacceptable tolerability, or an increase in ALT to 1.5x ULN and 1.5x baseline. Overall, the benefit: risk is typical of a Phase I study of participants with advanced cancer.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or pembrolizumab.	• AEs, SAEs, DLTs, withdrawals due to AEs, dose reductions or delays, and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters).
Secondary	
• To evaluate the antitumor activity of GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or pembrolizumab	• Objective response rate (ORR) and disease control rate (DCR) (complete response [CR]+ partial response [PR]+ stable disease [SD] ≥12 weeks), time to response, duration of response, progression-free survival (PFS), and overall survival (OS).
• To characterize the pharmacokinetics (PK) of GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or pembrolizumab.	• GSK1795091, concentrations in plasma and assessment of PK parameters (e.g., Cmax, AUC(0-τ) and Ctrough) if data permit.
• To evaluate the immunogenicity of GSK3174998, GSK3359609, and pembrolizumab when administered in combination with GSK1795091.	• Number and percentage of participants who develop detectable ADA against GSK3174998, GSK3359609, or pembrolizumab.
Exploratory	
• To evaluate the immunologic effects of GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or pembrolizumab.	• Assessments of OX40 or ICOS receptor expression and occupancy of GSK3174998 or GSK3359609 on immune cells in the peripheral blood. • Assessment of the phenotype, quantity, and activation state of T cells and other immune cells in peripheral blood. • Assessment of tumor biopsies by immunohistochemistry or related technologies which may include but is not limited to the numbers of tumor-infiltrating lymphocytes and other cells expressing key phenotypic markers.
• To explore the association between treatment with GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or pembrolizumab and measures of gene expression and immune function.	• Assessment of gene expression and immune function from study participants tumor tissue and/or blood samples may include but is not limited to immune related gene expression (RNA expression or RNAseq), gene signatures, and T-cell receptor DNA sequences. • Assessment of soluble factors from study participants blood samples and/or tumor may include but is not limited to cytokines and stress-related proteins, cell free DNA (cfDNA), and exosomes.

Objectives	Endpoints
• To explore the association between treatment with GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or pembrolizumab and biomarkers which may be associated with response. To explore the utility of these measures to enrich for clinical efficacy and/or development of a diagnostic test.	• Comparison between antitumor activity and baseline biomarker samples from study participants blood and/or tumor which may include but are not limited to DNA, gene expression (RNA), proteins, immune cell phenotypes, and immune response markers. • Analysis of the data to identify potential selection biomarkers for participant enrichment.
• To characterize the PK of GSK3174998, GSK3359609, or pembrolizumab when administered in combination with GSK1795091.	• GSK3174998, GSK3359609, or pembrolizumab concentrations in plasma/serum and assessment of PK parameters (e.g., maximum observed concentration [C_{max}], $AUC_{(0-T)}$ and trough concentration [C_{trough}]) if data permit.
• To explore PK-Pharmacodynamic relationships, such between PK parameters and antitumor activity, safety or pharmacodynamic markers after treatment with GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or pembrolizumab.	• Evaluation of the relationship of antitumor activity as assessed by ORR, DCR, safety and/or pharmacodynamic markers with PK parameters (e.g., C_{max}).
• Pharmacogenetics (PGx): To evaluate the association of genetic variations in the host DNA and response to therapy.	• Germline genetic evaluations may be conducted to test for association with: • Response to treatment, including GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or pembrolizumab. • Disease susceptibility, severity, and progression and related conditions.
• To explore the gut microbiome composition and relationship to treatment response.	• Sequencing of the microbiome from stool samples. Analysis of the data to identify potential selection biomarkers for participant enrichment • Evaluation of the relationship between antibiotic/probiotic use prior to treatment and antitumor activity
• To evaluate disease and treatment related symptoms and impact on function and health-related quality-of-life.	• Qualitative telephone interview.

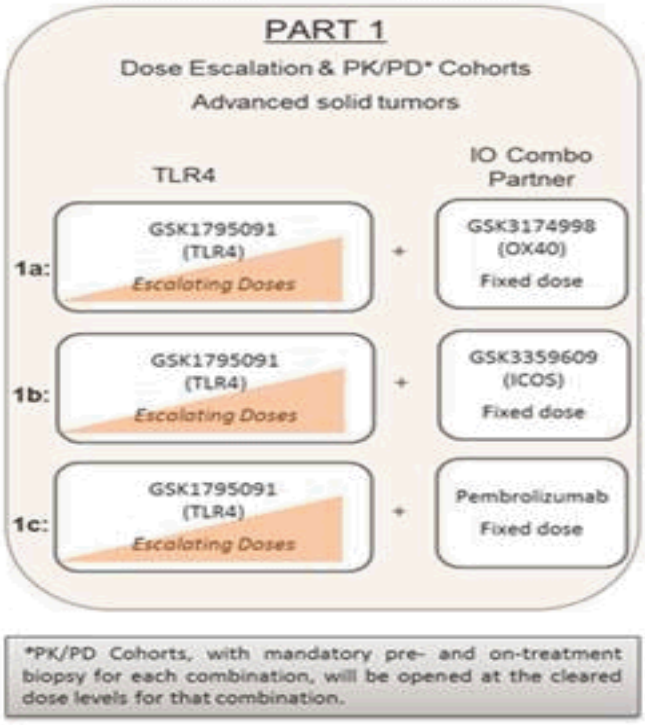
5. STUDY DESIGN

5.1. Overall Design

This is a Phase I, open-label, non-randomized, multicentre, multi-country study designed to evaluate the safety, tolerability, PK, pharmacodynamic, and preliminary clinical activity of GSK1795091 administered in combination with other immunotherapies to participants with advanced solid tumors.

With the implementation of amendment 06, the study is closed to enrolment and Part 2 will not be opened.

Figure 7 Study Design



Part 1 is divided into 3 treatment arms based on the GSK1795091 combination partner; Part 1a, Part 1b, or Part 1c. Each of the three treatment arms may have up to 5 dose escalation cohorts to investigate the safety and tolerability of escalating doses of GSK1795091with a single dose level of the combination partner. GSK1795091 combination partners are:

- GSK3174998 24 mg (Part 1a)
- GSK3359609 80 mg (Part 1b)
- Pembrolizumab 200 mg (Part 1c)

Part 1 will include a GSK1795091 run-in period of 2 weeks (i.e., GSK1795091 administration on days 1 and 8) prior to administration of the combinations beginning on day 15 (Week 3). Following protocol amendment, GSK1795091 may also be evaluated by additional routes of administration. Safety data will be evaluated according to a Neuenschwander-Continual Reassessment Method (N-CRM) design [Neuenschwander, 2008].

With the implemention of amendment 06, enrolment into the study is now closed and Part 2 of the study will not open.

For each combination of GSK1795091 in Part 1, PK/Pharmacodynamic cohorts will be opened at cleared dose levels for that combination (i.e. the most recent investigated dose level that supported dose escalation) to explore the potential relationships between dose, biological effects in the tumor microenvironment, and tumor response. A particular emphasis in the PK/Pharmacodynamic cohort is placed on evaluating the possible effects of the combination on the immune cells and immune status within the tumor microenvironment. Thus, to be eligible for the PK/Pharmacodynamic cohort, participants must consent to mandatory fresh biopsy collection at baseline and on treatment (see Section 2, SoA). An additional radiographic disease assessment (see Section 2, SoA) will support exploratory investigation of tumor growth kinetics in this cohort. Note that while consent to fresh tumor biopsy is not required for participation in the dose escalation cohorts in Part 1, it is strongly encouraged. Up to 6 participants per dose level may be enrolled into the PK/Pharmacodynamic cohort for each combination and a maximum of approximately 45 participants in total.

The study includes a screening period, a treatment period, and a follow-up period. Participants will be screened for eligibility beginning 4 weeks before the start of treatment. The duration of study treatment will be up to 2 years. .

With the implementation of amendment 06, participants who discontinue study treatment for any reason will no longer be followed for disease assessments. One Survival FU visit will be performed 12wks after the last dose of study treatment or prior to the start of the next anti-cancer therapy, whichever occurs first. If a new anti-cancer therapy is started before the TDV, the OS visit is not required. The study will conclude when the last subject has completed/discontinued study treatment, completed the Treatment Discontinuation Visit (TDV) assessments, and the OS FU visit is completed (as applicable). Following protocol amendment(s), additional participants may be enrolled to evaluate additional routes of study treatment administration (e.g., intratumoral administration), additional agents to be used in combination with GSK1795091, or additional indications, based on emerging nonclinical and/or clinical data.

5.1.1. Part 1: Dose Escalation of GSK1795091 administered in combination with either GSK3174998, GSK3359609, or pembrolizumab

In Part 1, dose escalation will be performed to identify combination dose levels comprising GSK1795091 with either 24 mg GSK3174998 (Part 1a), 80 mg GSK3359609 (Part 1b), or 200 mg pembrolizumab (Part 1c). One (1) dose level of GSK3174998, GSK3359609, or pembrolizumab with up to 5 dose levels of GSK1795091 are planned for evaluation, pending emerging safety and tolerability information as dose escalation proceeds.

Part 1 will include a run-in period of 2 weeks in which GSK1795091 is administered once-weekly [i.e., administration on day 1 (Week 1) and day 8 (Week 2)] prior to initiation of combination treatment with either GSK3174998, GSK3359609, or pembrolizumab beginning on day 15 (Week 3). During the run-in period, participants that experience a DLT, unacceptable toxicity, or an increase in ALT (1.5x ULN and 1.5x baseline) and not attributable to another cause will be discontinued from the study and will not receive GSK1795091 in combination. (See Section 5.1.3).

Guidance for the management of toxicity, including dose modification algorithms, is provided in Section 7.2.

The starting schedule for GSK1795091 will be at every 1-week intervals (Q1W) from Week 1 through Week 12 including the 2-week monotherapy run in period (Week 1 and Week 2) (see SoA Table 1). Subsequently, GSK1795091 will be administered at every 3-week intervals (Q3W) to coincide with GSK3174998, GSK3359609, or pembrolizumab dosing. Thus, beginning with Week 12 for Part 1 and Week 13 for Part 2, both GSK1795091 and combination partners will be administered on the same study day at a frequency of Q3W.

Cohorts will be opened beginning with 50 ng GSK1795091 administered in combination with either 24 mg GSK3174998, 80 mg GSK3359609, or 200 mg pembrolizumab. Three (3) or more participants will be enrolled in each cohort. The total number of participants enrolled into each cohort and dose assignments will be guided by safety information (Section 5.1.3) from participants receiving the study treatment combinations according to N-CRM modelling (Section 5.1.1.1, [Neuenschwander, 2008]).

Sequential groups of 3-4 participants will be enrolled and dose escalation (or de-escalation) will proceed guided by an N-CRM design. Dose escalation for each cohort will proceed independently of the other cohorts, e.g. dose escalation for Part 1a is not required prior to dose escalation for Part 1b or Part 1c. The first 3 participants at each dose level will receive study treatment at least 3 days apart (e.g., if the participant in a cohort were dosed on Monday, the earliest the next participant could be dosed is Thursday). Once the 6-week DLT evaluation period has been completed for at least 3 subjects in each group (Section 5.1.3), N-CRM analysis will be performed to guide the dose level to which the next 3-4 participants will be assigned based on DLT frequency (Section 5.1.1.1). The number of participants allocated to any cohort is an estimate; participants may also be allocated to PK/Pharmacodynamic cohorts at a previous dose level that supported dose escalation.

Dose levels -1 are available for GSK3174998 (8 mg +50 ng GSK1795091) and GSK3359609 (24 mg + 50 ng GSK1795091) if the target toxicity level is exceeded in Cohort 1 and a dose reduction is needed below planned doses. No dose reductions for pembrolizumab will be implemented.

5.1.1.1. Description of the Continual Reassessment Method

The N-CRM model-based design is a Bayesian adaptive dose escalation scheme that assumes a 2-parameter logistic model for the toxicity rate as a function of dose. It is a modified version of the original Continual Reassessment Method proposed by [O'Quigley, 1990]. The N-CRM method is fully adaptive and makes use of all DLT information, therefore is expected to locate the target dose level efficiently. In this case, the model will be applied to the dose escalation decision for GSK1795091, which will be performed independently for each combination.

Dose escalation decisions will be held after participants within any given cohort have been observed for at least 6 weeks after starting the study treatment (per Section 5.1.3). At the time of each dose escalation decision, the Fixed and Adaptive Clinical Trial Simulator (FACTS [Tessella, Abington, United Kingdom]) will be used to obtain the posterior probabilities for the DLT rate. The N-CRM estimates for each potential dose will provide the posterior probabilities that the DLT rate lies in each of four toxicity ranges:

- [0%, 16%] Underdosing
- [16%, 33%] Target toxicity
- [33%, 60%] Excessive toxicity
- [60%, 100%] Unacceptable toxicity

The recommended dose for dose escalation, based on the N-CRM model, will be the dose with the highest posterior probability of lying in the target toxicity interval with the additional requirement that the sum of the posterior probabilities of the DLT rate lying in the excessive toxicity or unacceptable toxicity range is less than 25%. An updated estimate of the toxicity curve will be provided at the time of each dose escalation meeting. Note that de-escalation as well as escalation is possible using this method. Dose escalation will continue until conditions for either scenario (i) or (ii) are met:

i) Six participants have been treated at the current target dose

   AND

   For the current dose level, the posterior probabilities of the DLT rate lying within the excessive toxicity interval or within the unacceptable toxicity interval sum to less than 25%

   AND

   For the next higher dose, the posterior probabilities of the DLT rate lying within the excessive toxicity interval or within the unacceptable toxicity interval sum to greater than 25%.

ii) No doses are usable (i.e., for all doses, the posterior probabilities of the DLT rate lying within the excessive toxicity interval or within the unacceptable toxicity interval sum to more than 25%)

AND

At least 2 DLTs have been observed.

Dose recommendations based on the N-CRM analysis will be used as guidance. To ensure safety of participants, additional participants may be enrolled at a current dose level at the discretion of the study investigators and sponsor, even though a higher dose is recommended by N-CRM analysis.

5.1.1.2. Logistic Model for N-CRM

A two-parameter logistic model will be used for N-CRM analysis for dose level selection during the dose escalation phase. This model will estimate the probability of observing a DLT at each dose level in the study as DLT information becomes available.

The logistic model that used for describing the dose-toxicity relationship is:

$$ln\left(p_d/(1-p_d)\right) = \alpha + \beta * ln\left(d/d_m\right),$$

where p_d is the probability of DLT at dose d, and d_m is a reference dose, and α and β are Bayesian priors.

5.1.2. PK/Pharmacodynamic Cohort(s)

Characterizing the effects of treatment on the tumor microenvironment is essential to the understanding the mechanism of action of GSK1795091 and its combination partners at the site of action. Thus, for each combination of GSK1795091 in Part 1, PK/Pharmacodynamic cohorts will be opened to characterize the biological effects in the tumor microenvironment and explore the potential relationships between dose and tumor response. PK/Pharmacodynamic cohorts, with up to 6 participants per dose level, will be opened for GSK1795091 dose levels previously cleared for dose escalation.

Pre- and on-treatment tumor biopsies are required for enrollment to this cohort. PK, pharmacodynamic markers, and safety samples will be drawn according to Section 2 to obtain additional PK and pharmacodynamic data. Following the selection of a recommended combination dose for Part 2, participants in the Part 1 PK/Pharmacodynamic cohort may have the dose escalated to a higher completed dose level (not exceeding the target toxicity level) after Week 9 once the necessary PK/Pharmacodynamic procedures and tissue biopsies have been completed. See Section 5.1.7 for further instructions on intra-participant dose escalation.

5.1.3. Dose-Limiting Toxicity

All toxicities will be graded using National Cancer Institute - Common Toxicity Criteria for AEs (NCI-CTCAE), version 4.0.

An AE is considered to be a DLT if it is considered by the investigator to be clinically relevant and attributed (definitely, probably, or possibly) to the study treatment and meets

at least 1 of the criteria listed in Table 3. If an AE is considered related to the underlying disease, it is not a DLT.

Table 3 Dose-Limiting Toxicity Criteria

Toxicity	DLT Definition
Hematologic	• Grade 4 neutropenia of >7 days' duration or febrile neutropenia • Grade 4 anemia • Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding
Non-hematologic	• Grade 4 toxicity • Grade 3 toxicity that does not resolve to ≤Grade 1 or baseline within 14 days despite optimal supportive care • Immune-related toxicity requiring >10 mg prednisone (or equivalent) per day after 12 weeks from the last dose of study treatment • Cardiopulmonary or hemodynamic toxicity starting within 24 hours of study treatment injection that requires >40% fraction inspired oxygen (FiO2), vasopressor administration, antiarrhythmic agent or other significant medical intervention. • ECG changes showing asystole or bradycardia that is symptomatic and requires medical intervention. • Liver toxicity (see Appendix 7) including o ALT ≥ 5xULN o ALT ≥ 3xULN persists for ≥4 weeks o ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) o ALT ≥ 3xULN and INR >1.5, if INR measured o ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity • Following events are **not** considered DLTs o Changes in leukocyte parameters within 48 hours of GSK1795091 administration o Grade 1 changes in ALT o ≥ Grade 3 electrolyte abnormalities that are corrected within 24 hours without clinical sequelae o Grade 3 tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor) o Grade 3 fatigue
Other (not addressed above)	• Toxicity that results in permanent discontinuation or dose reduction of GSK1795091 during the first 6 weeks of treatment • Any other event which in the judgment of the investigator and GSK Medical Monitor is considered to be a DLT

For participants to be considered evaluable for dose escalation decisions, missed study treatments must be limited during the first 6 weeks of dosing. Participants may not miss any study treatment administered Q3W and may not miss more than 1 study treatment administered Q1W.

Participants who withdraw from study treatment before completing 6 weeks of treatment for reasons other than DLT or who are not evaluable for dose escalation decisions may be replaced. If a participant experiences a DLT during this period, the participant will be discontinued from the study.

Guidance for the management of toxicity, including dose modification algorithms, is provided in Section 7.2.

5.1.4. Part 2: Expansion Cohort

With the implementation of amendment 06, the study is closed to enrolment and Part 2 will not be opened.

5.1.5. Oversight

The active study investigators, GSK medical monitor, GSK pharmacovigilance physician, GSK statistician, GSK physician(s) independent of the study team and contract organization physicians will be responsible for decisions to escalate doses. Prior to the dose escalation decision, the attendees will review critical safety information defined in Section 5.1.3, and in the Dose Escalation Plan. Decisions will be based on safety information and other available data from ongoing and prior cohorts.

The dose-determination 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 study master file.

Although the N-CRM will be used to recommend the next dosing level, clinical judgment by the study investigators and GSK study team can override this recommendation or halt enrollment into any cohorts as deemed appropriate at any time during the trial.

5.1.6. Tumor Types Enrolled During Parts 1

In Part 1, participants with advanced solid tumors will be enrolled.

5.1.7. Intra-Participant Dose Escalation

Intra-participant dose escalation will be considered on a case-by-case basis provided the participant has completed at least 6 weeks of study treatment without the occurrence of a SAE or ≥Grade 2 drug-related toxicity. Approval by the Sponsor is required for intra-participant dose escalation.

5.1.8. Study Treatment

Study Part	Study Treatment: GSK1795091 in combination with GSK3174998, GSK3359609, or pembrolizumab
Part 1: Dose Escalation	
1a	GSK3174998 24 mg IV and GSK1795091 IV
1b	GSK3359609 80 mg IV and GSK1795091 IV
1c	pembrolizumab 200 mg IV and GSK1795091 IV

5.2. Number of Participants

Approximately 72 participants will be enrolled into Part 1 (dose-escalation) of the study with approximately 24 participants in each combination. .

Additionally, for each combination, up to 6 participants in each dose cohort and a maximum of approximately 45 participants in total may be enrolled into the PK/Pharmacodynamic cohorts of Part 1. Additional cohorts (up to a maximum of 12 total participants) may be enrolled in Part 1 to allow for evaluation of additional dose levels of GSK1795091.

In Part 1, if a participant prematurely discontinues before the completion of 6-weeks treatment for reasons other than DLT, a replacement participant may be enrolled at the discretion of the Sponsor in consultation with the investigator.

5.3. Participant and Study Completion

In Part 1, participants will be considered to have completed the study if they complete screening assessments and receive at least 1 study treatment and experience a DLT or complete the 6-week DLT observation period, and the treatment discontinuation visit (TDV).

Cause of death must be documented in the case report form (CRF)/electronic CRF (eCRF). A participant will be considered to have withdrawn from the study if the participant has not died and is lost to follow-up, has withdrawn consent, at the investigator's discretion is no longer being followed or if the study is closed/terminated.

Disease progression and AEs, are not by themselves reasons for withdrawal from the study. The end of the study is defined as the last participant has completed/discontinued study treatment and completed the TDV assessments, and the OS follow-up visit is completed (as applicable). See SoA (Section 2) .

5.4. Scientific Rationale for Study Design

The combination of GSK1795091 with either GSK3174998, GSK3359069, or pembrolizumab was selected based on complementary mechanisms of action and robust antitumor activity in preclinical models.

Eligibility criteria require that participants have progressed after standard therapies or are otherwise unsuitable for standard therapies, and the criteria are intended to minimize the risk of adverse reactions to treatment with immunotherapies.

In Part 1, dose escalation of GSK1795091, with a fixed dose of the combination partners, will be performed using an N-CRM model to optimize the allocation of participants to dose levels with a 16-33% DLT frequency. The DLT criteria are based on typical oncology rules with additional modifications for toxicities expected for the study treatments.

In Part 1, a 2-week run-in period for GSK1795091 precedes the administration of the combination therapy. The run-in provides an evaluation of monotherapy GSK1795091 safety and tolerability in participants with cancer and prevents the administration of combination therapy to participants that experience, with GSK1795091 alone, a DLT, unacceptable tolerability, or an increase in ALT to 1.5x ULN and 1.5x baseline.

5.5. Dose Justification

5.5.1. Overview

GSK1795091, GSK3174998, and GSK3359609 have been previously administered as monotherapies in studies 204685 (GSK Document Number 2015N236402_03), 201212 (GSK Document Number 2014N225045_02), and 204691 (GSK Document Number 2015N238345_03), respectively.

The selection of starting combination doses has taken into consideration all available data, including the safety, tolerability, and pharmacology data of monotherapy GSK1795091, monotherapy GSK3174998, and monotherapy GSK3359609 observed in the respective FTIH studies [GSK Document Number 2015N236402_03, GSK Document Number 2014N225045_02, and GSK Document Number 2015N238345_03] and for pembrolizumab as summarized in the Prescribing Information [KEYTRUDA PI, 2019], together with pharmacology and safety data from animal models and human ex vivo (peripheral blood mononuclear cell [PBMC]) assays, conducted under monotherapy and combination conditions.

5.5.1.1. Starting dose for TLR4 agonist GSK1795091

The starting dose of GSK1795091 is 50 ng administered once-weekly IV. Previously GSK1795091 was administered at doses up to 100 ng IV to healthy participants in the FTIH Study (204685). Based on data from the FTIH study, the starting dose in the current study (50 ng) is expected to produce low level pharmacological effects consistent with TLR4 agonism based on data from the FTIH study (Section 3.2.1.2).

Because robust TLR receptor saturation assays are not available, target engagement by GSK1795091 in the FTIH study (204685) was monitored using representative inflammatory cytokine biomarkers. Based on review of available preliminary data (dose levels up to 100 ng), post-dose elevations of cytokines following administration of GSK1795091 in the FTIH study were of a low magnitude compared to historical clinical studies of TLR agonists administered to cancer patients. For example, the peak levels of inflammatory cytokines at 2h, such as TNFα (median:12 pg/ml; min: 6 pg/ml; max: 23 pg/ml) and IL-6 (median: 132 pg/ml; min: 81 pg/ml; max: 184 pg/ml pg/ml, respectively), associated with administration of 100 ng GSK1795091 are below levels reported in previous studies of TLR agonists in cancer patients (>1000 pg/ml) [Chow, 2017; Engelhardt, 1991]. These differences are likely not a function of differences in study populations, given that prior comparisons of TLR agonists in healthy participants and cancer participants have shown similar cytokine responses between populations [Schmidt, 2015; Dietsch, 2014]. Even acknowledging possible differences in pharmacodynamic assay performance, the greater than 10–100 fold margin between

cytokine concentrations associated with 100 ng doses of GSK1795091 versus concentrations reported in other studies of cancer patients provides reassurance that a significant margin separates the starting dose of GSK1795091 and maximum tolerated dose of other TLR agonists.

Consistent with the mechanism of action of GSK1795091, body temperature and heart rate increased with dose in Study 204685 (GSK Document Number 2015N236402_03). Mean maximum change with 95% CI in body temperature in the participants that received placebo was 0.4 ± 0.2ºC. For GSK1795091 dose levels, 7 ng, 21 ng, 60 ng, and 100 ng, mean maximum change with 95% CI in body temperature was 0.5 ± 0.3, 0.6 ± 0.4, 0.8±.5, and 1.3 ± 0.3 ºC, respectively. Mean maximum change with 95% CI in heart rate in the participants that received placebo was 6 ± 5 beats per minute. For GSK1795091 dose levels, 7 ng, 21 ng, 60 ng, and 100 ng, mean maximum change with 95% CI in heart rate was 8 ± 9, 10 ± 18, 18 ± 15, 21 ± 5 beats per minute, respectively. Thus, a 50 ng starting dose is expected to be associated with modest changes in body temperature and heart rate.

Based on preliminary, unblinded safety data (described in Section 3.2.1.2), the most common clinical findings were influenza-like symptoms and increased body temperature. Predominantly mild AEs were reported when doses up to 60 ng were administered. Three (3) participants experienced moderate AEs following administration of 100 ng GSK1795091.

In addition to the aforementioned dose-related AEs, 1 out of the 12 participants that received a 60 ng dose of GSK1795091 experienced a 12-fold ULN increase in ALT, 5-fold ULN increase in AST, and 1.4-fold ULN increase in total bilirubin on day 35. As only 1 event was observed and the dose administered was below the maximum administered, 100 ng, the data are too limited to relate elevations in hepatic laboratories to dose. Because of the possible risk of infrequent or idiosyncratic transaminase elevations, a 2-week GSK1795091 run-in period will be performed in Part 1, including monitoring and study treatment discontinuation criteria for ALT elevations, before GSK1795091 and combination partners are administered.

In summary, at the GSK1795091 starting dose of 50 ng, minimal pharmacodynamic effects and dose-related cytokine-associated clinical effects are expected. The risk of infrequent events of uncertain relationship to GSK1795091 dose will be mitigated by a 2-week monotherapy run-in period.

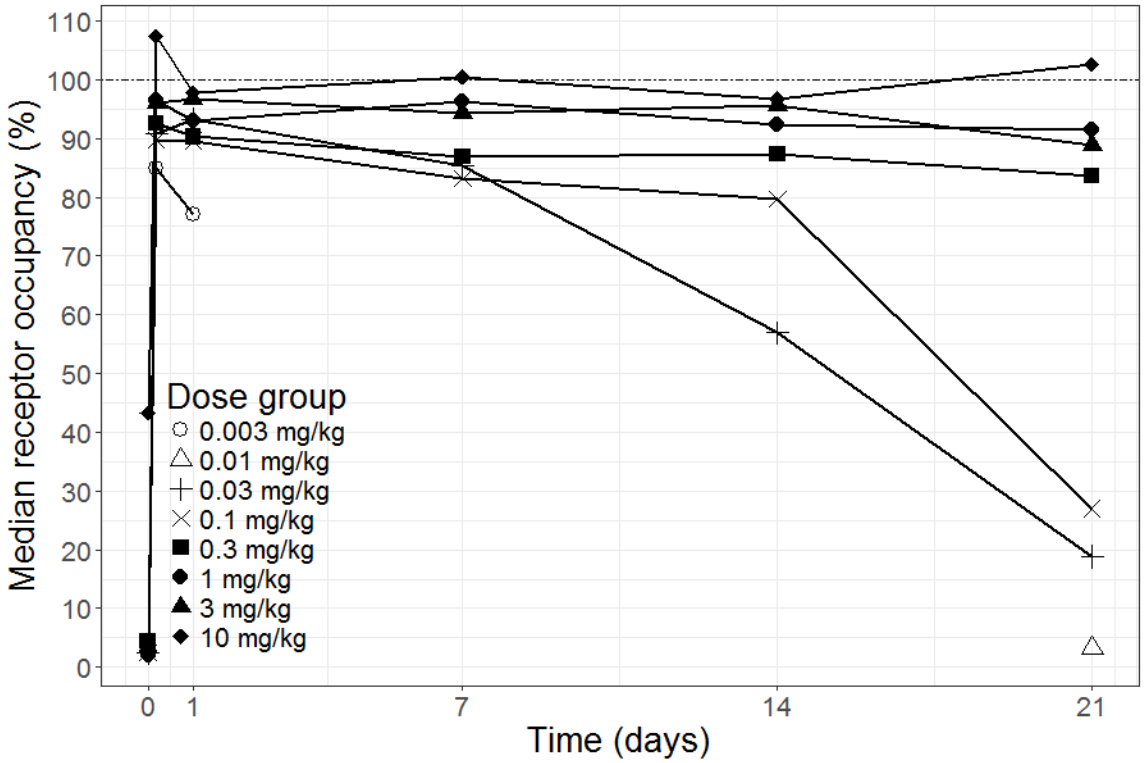
5.5.1.2. Dose for OX-40 agonist GSK3174998

The starting dose of GSK3174998 is 24 mg (~0.3 mg/kg) IV administered every 3 weeks (Q3W). No DLTs were observed over a range from 0.003 mg/kg (~0.24 mg) to 10 mg/kg (~800 mg) in cancer patients receiving GSK3174998 monotherapy in GSK Document Number 2014N225045_02, Study 201212. Thus, the starting dose of 24 mg is 1/33 of the top dose of GSK3174998 that was evaluated and produced no DLTs in Study 201212.

OX40 receptor occupancy (RO) in the central circulation is expected to be near maximal over the whole 3-week dosing interval with 24 mg GSK3174998 based on measured RO

in Study 201212 (see the 0.3 mg/kg dose level in Figure 8). Efficacy responses to OX40 agonism have been observed at widely varying dose levels, including 0.3 mg/kg.

Figure 8 Median Receptor Occupancy Profiles for Varying Doses of GSK3174998



Preliminary measured RO data from Study 201212 (GSK Document Number 2014N225045_02) Part 1A (GSK3174998 monotherapy).

Based on the totality of available data, including receptor occupancy, efficacy and safety, a 24 mg dose level was selected for GSK3174998. Based on emerging safety, exposure and/or pharmacodynamic data, the dose for GSK3174998 may be adjusted lower, to 8 mg, if agreed by the study investigators and GSK study team.

5.5.1.3. Dose for ICOS agonist GSK3359609

The starting dose of GSK3359609 is 80 mg (~1 mg/kg) IV administered Q3W. In the FTIH study (Study 204691) of GSK3359609, doses up to 3mg/kg (~240 mg) Q3W were evaluated as monotherapy or in combination with pembrolizumab 200 mg Q3W. Based on the available clinical exposure and safety data from Study 204691 as listed in the IB [GSK Document Number 2017N319717_02], GSK3359609 can be dosed up to 3 mg/kg (~240 mg). One DLT was reported in one out of 10 participants treated at this dose (see Section 3.2.3.2). The planned dose of GSK3359609 for evaluation in the present study is 80 mg, or approximately 1/3 the top dose studied to date.

GSK3359609 systemic concentrations at different dose levels have been simulated with a population pharmacokinetic model developed with available clinical data.

ICOS receptor occupancy (RO) in the central circulation has been estimated based on predicted GSK3359609 systemic exposures and potency values for the functional effects of GSK3359609 characterized from *in vitro* binding/activation assays. Potency values generated from three different binding/activation assays (Kd, T-cell binding, IFN-γ release) were in the range of 0.09 to 4.14 µg/mL. The corresponding ICOS RO levels with predicted GSK3359609 systemic exposures at different dose levels are listed in Table 4. The predicted RO demonstrates that the 80 mg dose (~1 mg/kg) provides adequate level of target engagement across all three approaches. The currently planned 80mg GSK3359609 dose may be adjusted lower to 24mg based on emerging safety, exposure and/or pharmacodynamic data if agreed by the study investigators and GSK study team.

Table 4 Projected CD4+ receptor occupancy in central circulation from population PK predicted median steady-state peak and trough exposures of GSK3359609 (Q3W regimen) based on in vitro potency estimates

Dose (mg)	C_{max} (µg/mL)	Cτ (µg/mL)	RO based on K_d [0.09 µg/mL] (%)		RO based on T-cell binding [0.989 µg/mL] (%)		RO based on IFNγ release (bound) [4.14 µg/mL] (%)	
			At C_{max}	At Cτ	At C_{max}	At Cτ	At C_{max}	At Cτ
8	3.47	0.919	97.5	91.1	77.8	48.2	45.6	18.2
24	10.3	2.73	99.1	96.8	91.3	73.4	71.4	39.8
80	***34.7***	***9.23***	***99.7***	***99.0***	***97.2***	***90.3***	***89.3***	***69.0***
240	103.6	27.3	99.9	99.7	99.1	96.5	96.2	86.8

Note: 8 (~0.01mg/kg) to 240mg (~3mg/kg) Q3W regimen evaluated as monotherapy and in combination with pembrolizumab 200mg Q3W in Clinical study 206491

5.5.1.4. Pembrolizumab dose

The dose regimen for pembrolizumab, 200 mg IV Q3W, is the approved dosing scheme as described in the Prescribing Information [KEYTRUDA PI, 2019]. No reduction in dose is planned given that pembrolizumab has been administered in combination with other TLR agonists to subjects with advanced cancers without causing a notable change in the safety and tolerability profile [Flowers, 2017; Leung, 2017; Milhem, 2018]. Moreover, the safety and efficacy profile of the approved dose regimen for pembrolizumab is well established, whereas the efficacy of lower doses is not fully characterized.

5.5.1.5. Combination considerations

At the 50 ng starting dose of GSK1795091, only minimal clinical and pharmacodynamic effects are expected. Therefore, at the starting dose, GSK1795091 is not expected to significantly alter the safety and tolerability profile of GSK3174998, GSK3359609, or pembrolizumab. Conversely, these mAb combination partners are not expected to significantly alter the safety and tolerability profile of GSK1795091 based on available in vitro data, in vivo data, clinical data for GSK1795091, and reported clinical data for other TLR agonists.

5.5.1.5.1. *Combination of GSK1795091 and GSK3174998*

Collectively, in vitro, in vivo, and preliminary clinical data suggest that GSK3174998 is unlikely to significantly alter the safety profile of GSK1795091.

In vitro studies of GSK1795091 and GSK3174998 in PBMCs produced increases in IL-6, IL-10 or TNF-α for 6 of 10 healthy donors treated with GSK3174998 (≥0.1 pg/mL) in combination with GSK1795091 (≥100 pg/mL) compared to either GSK3174998 or GSK1795091 alone. No effect of GSK3174998 at concentrations up to 10 pg/mL was observed on cytokine responses at 10 pg/mL GSK1795091. There was high donor-to-donor variability in cytokine responses, and individual donors had inconsistent concentration-responses of the various test conditions. Therefore, the potential for enhanced cytokine release when these agents are administered in combination in patients cannot be eliminated due to the high amount of data variability.

GSK3174998 did not enhance cytokine induction by GSK1795091 in cynomolgus monkeys. Overall, when GSK1795091 was evaluated alone or in combination with GSK3174998, cytokine values were variable and the distributions were generally overlapping. Based on these nonclinical data, GSK3174998 is not expected to significantly alter the safety and tolerability profile of GSK1795091.

As of the cut-off date of 13 August 2018, 4 study participants have received GSK1795091 and GSK3174998, in combination. The tolerability for the combination was not diminished as compared to the monotherapies. Specifically, no exacerbation of acute, cytokine-related events was observed.

In summary, in vitro data and preliminary clinical data for GSK1795091 and GSK3174998 support the ongoing combination of these agents. On average, GSK3174998 has a modest effect on GSK1795091-induced cytokines in vitro. However, variability in response is significant and the potential for enhanced cytokine release when these agents are administered in combination in patients cannot be eliminated. This risk is mitigated by the 2-week GSK1795091 monotherapy run-in period that prevents administration of combination therapy to participants that do not tolerate GSK1795091 monotherapy (See Section 5.1.3). Preliminary clinical data reaffirm that the combination of GSK1795091 with GSK3174998 is tolerated at the starting doses.

5.5.1.5.2. *Combination of GSK1795091 and GSK3359609*

Collectively, in vitro and in vivo data suggest that GSK3359609 is unlikely to significantly alter the safety profile of GSK1795091.

In vitro studies of GSK1795091 and GSK3359609 in PBMCs were performed. No increases in IL-2, IL-6, IL-10, IFN-γ, or TNF-α were detected in PBMCs treated with GSK3359609 in combination with GSK1795091 (at concentrations up to 1000 pg/mL and 10 pg/mL, respectively) compared to GSK3359609 alone, either in the presence or absence of sub-optimal anti-CD3 stimulation.

In vivo, the anti-ICOS 7E.17G9 clone was evaluated in the CT26 murine syngeneic tumor model in combination with the TLR4 agonist GSK1795091 in two separate in vivo studies. Female BALB/c mice bearing CT26 mouse colon carcinoma tumors

(n=10/group) were given twice weekly IP doses of 7E.17G9 at 10 or 100 µg/mouse for 3 weeks alone and in combination with GSK1795091 at 5, 10 or 25 µg/mouse. The treatments were well-tolerated with no significant loss of body weight.

Overall, the nonclinical data for GSK1795091 and GSK3359609 administered as monotherapies support the starting combination of low doses of GSK1795091 and GSK3359609.

5.5.1.5.3. *Combination of GSK1795091 and pembrolizumab*

Collectively, in vitro, in vivo, and clinical data reported for TLR agonists and pembrolizumab suggest that pembrolizumab is unlikely to significantly alter the safety profile of GSK1795091.

In vitro, when pembrolizumab (≥0.1 µg/mL) was combined with GSK1795091 (10, 100 or 1000 pg/mL) in rested PBMCs, there was an increase in the anti-inflammatory cytokine, IL-10 [median increase 3.1-fold (range 0.01- to 119-fold)], in up to 5 of 10 donors compared to the respective concentrations of GSK1795091 plus human IgG4 isotype control. Enhanced responses were also observed in rested PBMCs of one to three donors (out of 10) for inflammatory cytokines IL-2 [1.5-fold (0.01- to 4.5-fold)], IL-6 [1.8-fold (1.1- to 8.2-fold)], or TNF-α [1.7-fold (0.2- to 7.8-fold)]. There was high donor-to-donor variability in cytokine responses, and individual donors had inconsistent concentration-response curves amongst the various test conditions. Given that a subset of the donors had increases in one or more of the pro-inflammatory cytokines, IL-2, IL-6, and TNF-α, the potential for enhanced cytokine release when GSK1795091 and pembrolizumab are administered in combination in patients cannot be eliminated.

The anti-PD-1 RMP1-14 clone was evaluated in the EMT6 murine syngeneic tumor model in combination with GSK1795091. BALB/c mice were given twice weekly IP doses of RMP1-14 at 200 µg/mouse for 3 weeks alone and in combination with GSK1795091 at 2.5 or 25 µg/mouse. The treatments were well-tolerated with no significant loss of body weight.

Clinical trials of other TLR agonists at doses associated with systemic cytokine-related AEs have not demonstrated unexpected toxicities when administered in combination with pembrolizumab [Flowers, 2017; Leung, 2017; Milhem, 2018]. Flowers et al. evaluated the AE profile of G100, a TLR4 agonist, alone and in combination with pembrolizumab and reported that all AEs considered possibly related to G100 were grade 1 or 2 and the addition of pembrolizumab did not result in unexpected or worsening toxicity. Leung et al., similarly concluded that the combination did not exacerbate adverse events associated with the monotherapies. Conversely, the authors of these reports have concluded that the combination the TLR agonists, at doses associated with systemic cytokine-related effects, did not result in a diminished safety profile for pembrolizumab [KEYTRUDA PI, 2019]. See Section 3.2.4.1 for further details.

In summary, in vitro data for GSK1795091 and pembrolizumab along with clinical data for other TLR agonists and pembrolizumab support the combination of these agents. On average, pembrolizumab has a minimal effect on GSK1795091-induced inflammatory

cytokines in vitro, with high donor-to-donor variability noted. However, the potential for enhanced cytokine release when these agents are administered in combination in patients cannot be eliminated. This risk is mitigated by the 2-week GSK1795091 monotherapy run-in period that prevents administration of combination therapy to participants that do not tolerate GSK1795091 monotherapy (See Section 5.1.3). Clinical reports for multiple TLR agonists administered at doses associated with systemic cytokine related AEs do not indicate a heightened risk of combining with pembrolizumab (Section 3.2.4.1). In general, the nonclinical data for GSK1795091 and pembrolizumab and clinical data reported for other TLR agonists with pembrolizumab support the starting combination of low doses of GSK1795091 with pembrolizumab.

Overall, the clinical and nonclinical data for GSK1795091, GSK3174998, GSK3359609, and pembrolizumab administered as monotherapies and in combination support the starting combination of low doses of GSK1795091 with either GSK3174998, GSK3359609, or pembrolizumab.

5.5.2. Dose Escalation and Top Dose

Based on available clinical data, the tolerability of GSK1795091 approximates that of LPS. Therefore, the top dose of GSK1795091 for study participants with cancer is expected to be similar to doses of LPS studied in similar populations, namely 2 to 4 ng/kg (i.e., 160 to 320 ng). The top dose of GSK1795091 will not exceed approximately 250 ng, which would represent a less than 3-fold escalation beyond the 100 ng dose which has been studied in the FTIH healthy volunteer study. The dose escalation step size of 50 ng increments results in a dose escalation scheme with progressively more conservative relative increases (e.g., 50 ng to 100 ng = 100% increase; 100 to 150 ng = 50% increase; 150 ng to 200 ng = 33% increase; 200 ng to 250 ng = 25% increase).

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the GSK investigational product or other study treatment that may impact participant eligibility is provided in the IBs/IB supplements. Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or participant safety. Therefore, adherence to the criteria as specified in the protocol is essential.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be ≥18 years of at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Histological documentation of advanced solid tumor.
3. Archival tumor tissue obtained at any time from the initial diagnosis to study entry. Although a fresh biopsy obtained during screening is preferred, archival tumor specimen is acceptable if it is not feasible to obtain a fresh biopsy.

   Note: Participants enrolled in a PK/Pharmacodynamic Cohort must provide a fresh biopsy of a tumour lesion not previously irradiated during the screening period and must agree to provide at least one additional on-treatment biopsy.
4. Disease that has progressed after standard therapies or for which standard therapy is otherwise unsuitable (e.g., intolerance).
5. Measurable disease, i.e., presenting with at least 1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). See Appendix 9 for definition of a measurable lesion.
6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1.
7. Life expectancy of at least 12 weeks.
8. Adequate organ function (see Table 5):
9. In France, a participant will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

Table 5 Organ Function

System	Laboratory Values
Hematologic	
ANC	≥1.5x10^9/L
Hemoglobin[a]	≥9 g/dL
Platelets[a]	≥100x10^9/L
PT/INR and PTT (unless participant is receiving anticoagulant)	<1.5xULN
Hepatic	
Total bilirubin *For participants with Gilbert's Syndrome (only if direct bilirubin ≤35%)*	≤1.5xULN *≤3.0xULN*
ALT	≤1.5xULN
Renal	
Calculated CrCl[b]	> 50 mL/min
Endocrine	
TSH[c]	WNL
Cardiac	
Ejection fraction	≥ 50% by echocardiogram [d]

ANC = Absolute neutrophil count; ALT = alanine aminotransferase; CrCl = creatinine clearance; INR = International Normalized Ratio; TSH = thyroid-stimulating hormone; ULN = upper limit of normal; WNL = within normal limits; PT = prothrombin time; PTT = partial thromboplastin time

a. Participants must maintain hemoglobin and/or platelet values for at least 2 weeks without transfusion or growth factor support.
b. Estimated CrCl should be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (see Appendix 10)
c. If TSH is not within normal limits at baseline, the participant may still be eligible if total T3 or free T3 and free T4 are within the normal limits
d. Multigated acquisition scan (MUGA) is acceptable if echocardiography is not available

Sex

10. Male or female

a. Female participants:

A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least 1 of the following conditions applies:

i. Not a woman of childbearing potential (WOCBP) as defined in Appendix 5

OR

ii. A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 120 days after the last dose of study treatment.

Informed Consent

11. Capable of giving signed informed consent as described in Appendix 3 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Additional Inclusion Criteria for Participants in Part 2a (GSK3174998 expansion) and Part 2b (GSK3359609 expansion)

12. Histological or cytological documentation of SCCHN (oral cavity, oropharynx, hypopharynx, or larynx) that is recurrent, locally advanced, or metastatic and is not amenable to curative treatment options, surgery or definitive chemoradiation therapy.
13. Received, ineligible for, or otherwise unsuitable for platinum-based therapy and anti-PD-1/PD-L1 therapy.
14. Received no more than 3 prior lines of systemic therapy for metastatic disease.

Additional Inclusion Criteria for Participants in Part 2c (pembrolizumab expansion)

15. Histological or cytological documentation of SCCHN (oral cavity, oropharynx, hypopharynx, or larynx) that is recurrent, locally advanced, or metastatic and is not amenable to curative treatment options, surgery or definitive chemoradiation therapy.
16. Received no more than 2 prior lines of systemic therapy for metastatic disease.

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Malignancy other than disease under study with the exception of those from which the participant has been disease-free for more than 2 years and not expected to affect the safety of the participant or the endpoints of the trial.
2. Symptomatic central nervous system (CNS) metastases or asymptomatic CNS metastases that have required steroids within 2 weeks prior to first dose of study treatment.
3. Active autoimmune disease that has required systemic disease modifying or immunosuppressive treatment within the last 2 years.

   Note: Replacement therapy (e.g., thyroxine or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is permitted.
4. Concurrent medical condition requiring the use of systemic immunosuppressive treatment within 28 days before the first dose of study treatment.
5. Known human immunodeficiency virus infection.
6. Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice, or cirrhosis.

   NOTE: Stable chronic liver disease (including Gilbert's syndrome or asymptomatic gallstones) or hepatobiliary involvement of malignancy is acceptable if participant otherwise meets entry criteria.

7. Presence of Hepatitis B surface antigen (HBsAg) at screening or within 3 months prior to first dose of study treatment

8. Positive Hepatitis C test result at screening or within 3 months prior to first dose of study treatment.

   NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained. Participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing

9. QTcF >450 msec or QTcF >480 msec for participants with bundle branch block

   The QTcF is the QT interval corrected for heart rate according to Fridericia's formula, machine-read or manually over-read.

10. Recent history (within the past 6 months) of acute diverticulitis, inflammatory bowel disease, intra-abdominal abscess, or gastrointestinal obstruction.

11. Recent history of allergen desensitization therapy within 4 weeks of starting study treatment.

12. History of severe hypersensitivity to mAbs.

13. History or evidence of cardiovascular (CV) risk including any of the following:

    - Recent (within the past 6 months) history of serious uncontrolled cardiac arrhythmia or clinically significant ECG abnormalities including second degree (Type II) or third degree atrioventricular block.
    - Cardiomyopathy, myocardial infarction, acute coronary syndromes (including unstable angina pectoris), coronary angioplasty, stenting, or bypass grafting within the past 6 months before enrollment.
    - Congestive heart failure (Class II, III, or IV) as defined by the New York Heart Association functional classification system [NYHA, 1994].
    - Recent (within the past 6 months) history of symptomatic pericarditis.

14. History of idiopathic pulmonary fibrosis, pneumonitis, interstitial lung disease, or organizing pneumonia, or evidence of active, non-infectious pneumonitis. Note: post-radiation changes in the lung related to prior radiotherapy and/or asymptomatic radiation-induced pneumonitis not requiring treatment may be permitted if agreed by the investigator and Sponsor.

15. Recent history (within 6 months) of uncontrolled symptomatic ascites or pleural effusions.

16. Any serious and/or unstable pre-existing medical, psychiatric disorder, or other condition that could interfere with the participant's safety, obtaining informed consent, or compliance to the study procedures.

17. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial, unless prospective Institutional Review Board (IRB) approval (by chair or designee) is given allowing exception to this criterion for a specific participant.

Prior/Concomitant Therapy

18. Prior treatment with the following agents:
    - OX40, ICOS agonist at any time.
    - Prior systemic or intratumoral therapy with TLR agonist.
    - Anticancer therapy or investigational therapy within 30 days or 5 half-lives of the drug, whichever is shorter.
    - Prior radiation therapy: permissible if at least 1 non-irradiated measurable lesion is available for assessment according to RECIST version 1.1 or if a solitary measurable lesion was irradiated, objective progression is documented. A wash out of at least 14 days before start of study treatment for radiation of any intended use to the extremities for bone metastases and 28 days for radiation to the chest, brain, or visceral organs is required.
19. Prior allogeneic or autologous bone marrow transplantation or another solid organ transplantation.
20. Toxicity from previous treatment including:
    - Toxicity Grade ≥3 related to prior immunotherapy and that lead to study treatment discontinuation.
    - Toxicity related to prior treatment has not resolved to Grade ≤1 (except alopecia, or endocrinopathy managed with replacement therapy).
21. Received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, granulocyte-macrophage colony-stimulating factor, and recombinant erythropoietin) within 2 weeks before the first dose of study treatment.

Other Exclusions

22. Major surgery ≤4 weeks before the first dose of study treatment. Participants must have also fully recovered from any surgery (major or minor) and/or its complications before initiating study treatment.
23. Known drug or alcohol abuse.
24. Receipt of any live vaccine within 4 weeks.

Additional Exclusion Criteria for Participants in Part 2c

25. Received prior anti-PD-1/PD-L1 therapy.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

No dietary restrictions are required. Note that participants should be well-hydrated before receiving study treatment (see Section 7.1)

6.3.2. Caffeine, Alcohol, and Tobacco

Participants who use products containing caffeine, alcohol, or tobacco are not required to change their habits of using these products during the study treatment.

6.3.3. Activity

Participants may experience orthostatic dizziness following administration of GSK1795091. Precautions should be taken to avoid falls after rising from a lying or seated position for several hours after administration of study treatment. In addition, participants will abstain from strenuous exercise for 8 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. This includes retesting specific vital sign measurements, laboratory assessments, etc. that may not have met eligibility criteria.

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. The term ‘study treatment’ is used throughout the protocol to describe any combination of products received by the participant as per the protocol design.

7.1. Treatments Administered

Participants receiving study treatment should be well-hydrated (TLR agonists have rarely been associated with severe bradycardia or asystole in clinical trials, attributed to poor hydration and/or history of syncope) [van Eijk, 2004]. Oral hydration should be encouraged in the days prior to study treatment and/or IV fluids (e.g., 1 L or as clinically indicated) administered before GSK1795091. Participants with a history of syncope

and/or uncertain compliance with hydration recommendations should receive additional pre-dose and/or post-dose fluids at the discretion of the investigator.

Treatment with GSK1795091 was suspended as of Protocol amendment 05. Participants may continue to receive either GSK3174998, GSK3359609 or pembrolizumab as monotherapy.

Following administration of GSK1795091, assessments must be performed as noted in the SoA. Cytokine-related AEs including changes in vital signs commonly begin within several hours of administration of GSK1795091. Participants must be monitored for 6 hours after administration of the first dose of GSK1795091 or longer as clinically indicated. Similarly, participants must be monitored for 6 hours after administration of the first 2 study treatments of GSK1795091 and combination partners. Participants that tolerate GSK1795091 without adverse changes in heart rate or blood pressure may have the duration of observation with subsequent study treatment reduced to 2 hours, provided the dose and schedule has not been changed. Guidelines for monitoring cytokine-related AEs are summarized in Section 7.2.1.1.

GSK1795091 and mAb combination partners GSK3174998, GSK3359609, or pembrolizumab will be administered to participants at each study site under medical supervision of an investigator or designee. GSK3174998, GSK3359609, or pembrolizumab will be administered first, and GSK1795091 will be administered at least 1 hour after the completion of the mAb infusion. The date and time of administration will be recorded in the source documents and reported in the eCRF.

If a participant experiences an infusion reaction with the administration of the mAb combination partner, associated AEs should resolve before GSK1795091 is administered. If AEs associated with the mAb are slow to resolve, it is acceptable to administer GSK1795091 on the following day. Should further delay be required, the participant will be discontinued from study treatment. Any participant who experiences an infusion reaction attributable to the mAb may receive GSK1795091 on the following day for all subsequent study treatments.

The specific time of study treatment administration (e.g., time of the week for first administration; time of the day for each administration) should take into consideration PK sampling time points and study visit procedures. See Section 2 for dosing timepoints and visit windows and Section 7.9 for additional details regarding dosing delays.

The Study Reference Manual (SRM) contains specific instructions for the preparation of GSK1795091, GSK3174998, GSK3359609, and pembrolizumab and the unit dose strength of each formulation.

Table 6 Investigational Product Dosage/Administration

Study Treatment Name:	GSK1795091	GSK3174998	GSK3359609	Pembrolizumab
Dosage formulation:	Solution for injection	Lyophilized powder for solution (reconstitution) for infusion	Solution for infusion	Solution for infusion or lyophilized powder for reconstitution[b]
Dosage level(s):	Dose Level: 50-250 ng	Dose level: 24mg	Dose Level: 80 mg	Dose Level: 200 mg every 3 weeks
Route of Administration:	IV injection	IV infusion – 30 min[a]	IV infusion - 30 min[a]	IV infusion - 30 min[a]
Packaging and Labeling	Study Treatment will be provided in container. Each container will be labeled as required per country requirement.	Study Treatment will be provided in container. Each container will be labeled as required per country requirement.	Study Treatment will be provided in container. Each container will be labeled as required per country requirement.	Commercial Supply Labeled as required per country requirement
Manufacturer:	GSK	GSK	GSK	Merck

Note: Refer to the SRM for detailed information on the investigational products

a. Infusions may be prolonged in the event of an infusion reaction. If multiple participants experience clinically significant infusion reactions, the infusion rate may be slowed for all future administrations of study treatment(s) for all participants. Should this global change in infusion rate be required, it will be communicated to the sites in writing.

b. The dosage form of pembrolizumab will be either solution or lyophilized powder for all subjects/doses. This will be dependent on country or site formulary requirements.

7.2. Dose Modification

Safety management guidelines, including dose modification algorithms, are provided below. Please note, in cases where the investigator is directed to permanently discontinue study treatment, these instructions are mandatory as described in Section 7 and Section 8.

An overview of the dose modification guidelines is presented in Table 7.

All AEs are to be graded according to NCI-CTCAE, version 4.0 (http://ctep.cancer.gov) and unless otherwise specified (e.g., Section 7.2.1.1). All dose modifications and the reason(s) for the dose modification must be documented in the eCRF.

The major classes of toxicity described in Section 7 include "cytokine-related AEs and infusion reactions" (Section 7.2.1) and "immune-related AEs" (irAE) (Section 7.2.2). Even though both cytokine production and immune activity play roles in both categories of events, the nomenclature is intended to describe distinct classes of AEs, as described below.

Investigators should refer to the IBs for GSK1795091 [GSK Document Number 2015N239078_04], GSK3174998 [GSK Document Number 2014N212091_05], and GSK3359609 [GSK Document Number 2017N319717_02] for additional information regarding the background of each drug and the management of other AEs or potential safety-related issues. Refer to the approved labelling for pembrolizumab-related background information and management of AEs [KEYTRUDA SPC, 2019; KEYTRUDA PI, 2019].

In case a dose reduction is necessary, the dose level of GSK1795091, the mAb or both may be changed as determined by the investigator and sponsor. If either study treatment is deemed intolerable and requires discontinuation despite optimal management, as described below, the participant must be discontinued from both study treatments. If one study treatment is not continued for reasons beside safety or tolerability, the other study treatment may be continued following approval by the sponsor and investigator. Refer to Appendix 13 and SOA (Section 2) for instructions regarding participant activity if only mAb monotherapy is administered.

GSK1795091 may be restarted at the next lower dose level, and/or the mAb (GSK3174998 or GSK3359609) at the next lower dose level described in Section 5.1.1. Pembrolizumab must always be administered at the fixed 200 mg dose level.

Table 7 General Dose Modification and Management Guidelines for Drug-Related Non-Hematologic Adverse Events Not Otherwise Specified

Severity	Management	Follow-up
Grade 1	• Administer symptomatic treatment as appropriate • Continue study treatment	*Symptoms resolve to baseline within 7 days:* • Provide close follow-up to evaluate for increased severity *Symptoms ongoing >7 days*: • Consider following algorithm for Grade 2 events
Grade 2	• Administer symptomatic treatment • Investigate etiology • Consider consulting subspecialist, biopsy, and/or diagnostic procedure • Discuss with Sponsor/Medical Monitor	*Symptoms ongoing >7 days or worsening* • Consider interruption of study treatment o Resume study treatment at the same dose if symptoms have improved to Grade 1 and steroid dose is 10 mg prednisone/day or less • For immune-related events, consider starting moderate dose systemic corticosteroids (e.g., 0.5 mg/kg/day of prednisone or equivalent) o Continue steroids until improvement to Grade 1 or resolution; taper steroids as medically appropriate • If symptoms continue or worsen to Grade 3-4, follow algorithm for Grade 3-4 events
Grade 3-4	• Interrupt or discontinue study treatment • Consult subspecialist • For possible immune-related events, administer 1-2 mg/kg/day IV methylprednisolone • Discuss with Sponsor/Medical Monitor	*Symptoms improve to Grade ≤2:* • For possible immune-related events, continue steroids until improvement to Grade ≤1 or baseline; taper steroids over at least 1 month, then if symptoms have improved to Grade 1 and steroid dose is 10 mg prednisone/day or less, consider resumption of study treatment at the next lower dose level of GSK1795091 and/or mAb *Symptoms ongoing:* • Discuss further management with consultant and Sponsor/Medical Monitor • Consider alternative immunosuppressive therapy

7.2.1. General Guidelines for Cytokine-Related Adverse Events and Infusion Reactions

Cytokine-related AEs and infusion reactions are toxicities with sometimes similar underlying pathology. However, for the purposes of this protocol, the 2 terms should not be used interchangeably. “Cytokine-related AEs” describe the common and expected spectrum of flu-like symptoms that are associated with administration of TLR agonists, such as GSK1795091, and are attributable to cytokine induction. The AEs may be related to the dose level of study treatments. “Cytokine release syndrome” describes a severe form of a cytokine-related AE. “Infusion reactions” describe the less common and typically idiosyncratic reactions to mAbs and other proteins that can occur by several mechanisms including, in some circumstances, IgE. The AEs are not necessarily related to the dose level of study treatments. The verbatim terms used to report “cytokine-related

AEs" or "infusion reactions" should describe the specific clinical signs or symptoms experienced by the study participant (e.g. chills, hypotension, rash, etc.) rather than non-descriptive, high-level terms (e.g. cytokine release syndrome, infusion reaction, etc.). The management recommendations for both cytokine-related AEs and for infusion reactions are summarized below.

7.2.1.1. Management of Cytokine Related Adverse Events and Cytokine Release Syndrome

The TLR agonists (including TLR4 agonists) are known to increase serum cytokine levels based upon evaluations in laboratory animals, healthy participants and patients [Kanzler, 2007; Astiz, 1995; Dillingh, 2014; Isambert, 2013]. Drugs in this class have generally caused mild to moderate toxicities associated with systemic cytokine production such as flu-like symptoms, fever, tachycardia, headache, nausea, and vomiting. The severity of cytokine-related AEs associated with TLR agonists generally peaks within several hours and subsides within a day. In a case report of a participant that self-administered a very high dose (1 mg) of LPS, supportive care was provided in an Intensive Care Unit (ICU). Reported treatment included fluids and vasopressors to maintain hemodynamic stability and diuresis for pulmonary edema [Taveira da Silva, 1993].

Recent experiences of CRS with cell therapies may or may not be relevant to managing CRS associated with other immunotherapies. Guidelines for managing CRS associated with cell therapies have been published [Lee, 2014]. Patients with mild or moderate AEs have been managed with supportive care, including fluids, vasopressors, and/or oxygen. Patients with high grade CRS have been managed in an intensive care unit and received immunosuppressive treatment. Anecdotally, tocilizumab (anti-IL-6 receptor antibody) has produced rapid and complete correction of CRS associated with cellular therapies [Maude, 2014]. Tocilizumab was recently approved by the FDA for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (8 mg/kg given as a 60-minute intravenous infusion for patients at or above 30 kg, with doses not to exceed 800 mg per infusion).

The attribution of signs and symptoms to cytokine production should be influenced by the timing with respect to administration of study treatment. The grading of cytokine-related AEs according to NCI-CTCAE criteria and according to Lee et al [Lee, 2014] is based on the requirement for intervention and the responsiveness to treatment. Recommendations for managing AEs are provided in Table 8.

Table 8 Cytokine Related Adverse Event Dose Modification and Treatment Guidelines

	Treatment	Premedication at Subsequent Dosing
Grades 1 or 2 Mild reaction; intervention may be indicated Grade 1: e.g., fever, constitutional symptoms Grade 2: e.g., hypotension responsive to fluids, hypoxia responsive to <40% FiO2 or other cytokine-related AEs responsive to intervention.	• Monitor vital signs until any changes in body temperature, heart rate, and blood pressure attributable to cytokine production are resolving. In some circumstances, monitoring overnight may be required. • Provide symptomatic/supportive care, including paracetamol, fluids, supplemental oxygen, etc., as required.	Premedication may be considered with subsequent study treatment. Participants that tolerate initial study treatment may have the duration of observation with subsequent study treatments reduced at the discretion of the investigator
Grades 3 or 4 Grade 3: AEs requiring aggressive intervention such as vasopressor administration, > 40% FiO2 or other cytokine-related AEs unresponsive to intervention. Grade 4: life threatening symptoms or severe organ toxicities with interventions including mechanical ventilation	• Monitor vital signs until any changes in body temperature, heart rate, and blood pressure attributable to cytokine production are resolving. In some circumstances, monitoring overnight may be required. • Perform ECG and/or echocardiographic monitoring as indicated based on medical history and cardiac function. • Provide symptomatic/supportive care, including paracetamol, fluids, supplemental oxygen, vasopressor administration, diuresis etc. as indicated. • Consider tocilizumab if conventional supportive measures are inadequate to control a declining clinical course or potentially life-threatening toxicities. • Obtain serum for C-reactive protein (CRP), tryptase, ferritin, and plasma for the cytokine panel (see Table 9 and SRM) within 3 hours of the event.	Should the cytokine-related event be attributed to GSK1795091 and further study treatment administered, the dose of GSK1795091 will be reduced to the next lower dose level.

	Treatment	Premedication at Subsequent Dosing
	• Do not administer further study treatment, unless approved by Sponsor/Medical Monitor.	
Appropriate resuscitation equipment and a physician should be readily available during the period of drug administration.		

Table 9 Biomarker Panel

Biomarker	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]
Plasma cytokine panel[b] (IFN-γ*^, TNF-α*^, IL-2*, IL-4, IL-5*, IL-6*^, IL-8*, IL-10*, IL-12p70, IL-1β, IL-1Ra, GCSF, IP-10, MCP-1, RANTES)	* Reported to be elevated in CRS [Lee, 2014] ^ consistently reported as elevated in CRS [Lee, 2014]

CRP=C-reactive protein; CRS= Cytokine release syndrome; IFN-γ = Interferon gamma; TNF-α = Tumor necrosis factor alpha; IL = Interleukin.

a. Performed by PI designated local laboratory
b. Performed by GSK designated laboratory

Note: Serum and plasma to be drawn within 3 hours of a Grade 3 or 4 cytokine related AE, as per Table 8

7.2.1.2. Management of Infusion Reactions

Infusion reactions are a well-documented AE associated with the administration of mAbs and other therapeutic proteins. The incidence of infusion reactions varies by mAb agent, and there are multiple mechanisms known to lead to infusion-related reactions including both IgE-dependant anaphylactic and non-IgE dependent anaphylactoid hypersensitivities.

Clinically infusion reaction may present as flushing, itching, urticaria, and/or angioedema, repetitive 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.

Should any of these symptoms or signs be observed with administration of GSK3174998, GSK3359609, or pembrolizumab, all must resolve before the administration of GSK1795091. Administration of GSK1795091 may be delayed until the following day. Should further delay be required for symptoms of the infusion reaction to resolve, the participant will be discontinued from study treatment. If a participant experienced an infusion reaction attributable to GSK3174998, GSK3359609, or pembrolizumab with prior administration, it is acceptable to administer GSK1795091 on the following day.

Guidelines for the management of infusion reactions are provided in Table 10.

Table 10 Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; requires infusion rate to be decreased; intervention may be indicated	• Decrease the rate of the mAb infusion to 25% or less of the original infusion rate until recovery from symptoms. • The participant must be closely monitored until resolution of symptoms. • Diphenhydramine 50 mg may be administered at the discretion of the treating physician. • When symptoms resolve, resume the infusion at 50% of the original infusion rate; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. • GSK1795091 may be administered following complete resolution of symptoms. • The amount of mAb infused must be recorded.	Diphenhydramine 50 mg (or equivalent) and/or paracetamol (acetaminophen) 325 mg to 1000 mg should be administered at least 30 minutes before additional study treatment administration. Study treatments may continue to be administered on the same day.
Grade 2 Moderate reaction such as generalized pruritus, flushing, rash, dyspnea, or hypotension with systolic blood pressure > 80 mmHg	**Stop Infusion.** • Begin an IV infusion of normal saline. • Administer diphenhydramine 50 mg IV (or equivalent) and/or paracetamol (acetaminophen) 325 mg to 1000 mg. • The participant must be closely monitored until resolution of symptoms. Corticosteroid therapy may be administered at the discretion of the treating physician. • When symptoms resolve, restart the infusion at 50% of the original infusion rate; if no	Diphenhydramine 50 mg (or equivalent) and/or paracetamol (acetaminophen) 325 mg to 1000 mg should be administered at least 30 minutes before additional study treatment administration. GSK1795091 may be administered the following day.

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
	further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. • Monitor participant closely. If symptoms recur, immediately discontinue the infusion; no further study treatment will be administered at that visit. Administer diphenhydramine 50 mg IV and continue to monitor the participant closely until resolution of symptoms. • Participants who develop Grade 2 toxicity despite adequate premedication must be permanently discontinued from further study treatment administration. • The amount of mAb infused must be recorded.	
Grades 3 or 4 Severe reaction [e.g., bronchospasm, generalized urticaria, systolic blood pressure < 80 mm Hg, hypoxemia, or angioedema] **Grade 3**: prolonged [i.e., requiring 6 or more hours to respond to symptomatic medication and/or discontinuation of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]. **Grade 4**: life-threatening; pressor or ventilatory support indicated	• **Immediately discontinue the mAb infusion**. No further study treatment will be administered, unless approved by Sponsor/Medical Monitor (criteria for rechallenge include but are not limited to participants who are receiving compelling benefit with study treatment that exceeds risk, and no effective alternative therapy is available). • The amount of mAb infused must be recorded on the eCRF. • Investigators should follow their institutional guidelines for the treatment of anaphylaxis (e.g., epinephrine 0.2 mg to 1.0 mg of a 1: 1,000 solution for subcutaneous administration or 0.1 mg to 0.25 mg of a 1: 10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed.) • Consider additional intervention in consultation with the Sponsor (e.g.,	Diphenhydramine 50 mg (or equivalent) and/or paracetamol (acetaminophen) 325 mg to 1000 mg should be administered at least 30 minutes before additional study treatment administration. GSK1795091 may be administered the following day.

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
	tocilizumab). • Obtain serum for CRP, tryptase, ferritin, and plasma for the cytokine panel (see Table 9 and SRM) within 3 hours of the event. • The participant must be closely monitored until resolution of symptoms.	
Appropriate resuscitation equipment and a physician should be readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

7.2.2. General Guidelines for Immune-Related Adverse Events

An "immune-related AE" (irAE) is defined as a clinically significant AE of any organ that is associated with study treatment exposure, is of unknown etiology, and is consistent with an immune-related mechanism. The classification refers to the traditional spectrum of AEs associated with checkpoint modulators (e.g., colitis, pneumonitis, etc.) The term is not intended to describe the acute cytokine-related AEs or infusion reactions described in Section 7.2.1. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

Early recognition of irAEs and initiation of treatment are critical to reduce the risk of complications, since the majority of irAEs are reversible with the use of steroids and other immune suppressants [Pardoll, 2012; Weber, 2012]. If an irAE is suspected, the participant must return to the study site as soon as possible instead of waiting for his/her next scheduled visit. Participants who experience a new or worsening irAE must be contacted and/or evaluated at the study site more frequently.

If an irAE is suspected, a thorough evaluation must be conducted in an effort to possibly rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes before diagnosing an irAE. Serological, immunological, and histological (biopsy) data should be considered to support the diagnosis of an immune-related toxicity. Consultation with the appropriate medical specialist should be considered when investigating a possible irAE.

Organs most frequently affected by irAEs include the skin and the colon due to their rapid regeneration rate. Less frequently affected tissues are lung, liver, and the pituitary and thyroid glands. Mild irAEs are usually treated symptomatically and do not require dosing delays or discontinuation. Higher grade and persistent lower grade irAEs typically necessitate interrupting or discontinuing treatment and administration of systemic steroids or other immunosuppressive agents (such as TNF blockers) when systemic steroids are not effective.

7.2.2.1. General Principles of Immune-Related Adverse Events Identification and Evaluation

Before administration of study treatment, investigators are to review a participant's AEs, concomitant medications, and clinical evaluation results e.g., vital signs, lab results, ECGs, ECOG PS, physical exam findings, responses, etc. as outlined in the Schedule of Activities (SoA) (Section 2)to monitor for new or worsening irAEs and ensure continued dosing is appropriate.

Adverse events of special interest (AESIs) are defined as events of potential immunologic etiology. Such events reported after treatment with other immune modulatory therapy include Grade ≥2 colitis, uveitis, hepatitis, pneumonitis, Grade ≥3 diarrhea, endocrine disorders, and specific cutaneous toxicities, as well as other events that may be immune mediated, including but not limited to demyelinating polyneuropathy, myasthenia gravis-like syndrome, non-infectious myocarditis, or non-infectious pericarditis [see Appendix 11 for a listing of AESIs].

For participants who experience signs or symptoms that may be consistent with an AESI, sites must notify the Sponsor of the event within 24 hours via email and/or phone. Documentation of events potentially qualifying for AESI must occur after discussion between the investigator and the Sponsor.

7.2.2.2. General Guidelines for Clinically Significant Toxicities Not Otherwise Specified

While specific guidance is provided for AESI, it is possible that other clinically significant drug-related toxicities that are not specifically described may occur and warrant dose modification. Table 7 provides general guidance for the management of clinically significant toxicities that are not otherwise specifically described in this section.

Investigators must contact the Sponsor within 24 hours of being notified of the event for all Grade ≥3 clinically significant non-hematological drug-related toxicities where interruption or permanent discontinuation of study treatment may be warranted according to the guidelines provided. Otherwise, investigators are encouraged to contact the Sponsor as needed to discuss any case that warrants separate discussion outside of the scope of current guidelines.

For events that do not resolve to less than or equal to Grade 1 within 12 weeks after the last infusion/injection, study treatment must be permanently discontinued after consultation with the Sponsor. With investigator and Sponsor agreement, participants with a laboratory AE still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled.

For participants who experience a recurrence of the same AE(s) at the same grade or greater with rechallenge of study treatment, a consultation between the Sponsor and investigator will occur to determine whether the participant should continue in the study. Recurrence of an SAE at the same grade or greater with rechallenge of study treatment must result in permanent discontinuation of the study treatment.

7.2.2.3. Management of Hepatotoxicity

In the event of treatment-emergent hepatotoxicity, potential contributing factors such as concomitant medications, viral hepatitis and other infectious causes, choledocholithiasis, and hepatic metastases, and myositis should be investigated. Concomitant medications known to be hepatotoxic which may be contributing to liver dysfunction should be discontinued or replaced with alternative medications to allow for recovery of liver function. As generally understood, AST or ALT >3x ULN and concomitant bilirubin ≥2.0x ULN (>35% direct bilirubin), in the absence of elevated alkaline phosphatase or biliary injury, suggests significant liver injury. Record alcohol use on the liver event alcohol intake form in the eCRF. Liver dysfunction must be fully evaluated even if clinical signs and symptoms indicate progression of liver tumor lesions. Imaging studies must be obtained to document potential progression of malignancy. Guidelines for management of emergent hepatotoxicity are shown in Section 8.1.1 and Appendix 7.

Report hepatotoxicity events to GSK within 24 hours. Complete liver event eCRF forms and SAE forms if the event also meets the criteria for SAE reporting.

If treatment is held or discontinued do not restart/rechallenge the participant with study treatment unless all of the requirements described in Section 8.1.1.1 have been met. Liver chemistry stopping criteria are provided in Section 8.1.1.

In Canada, if liver chemistry stopping criteria are met, participants will not be allowed to restart study drugs or be rechallenged.

7.2.2.4. Management of Gastrointestinal Events (Diarrhea or Colitis)

Signs/symptoms may include, but are not limited to: diarrhea, constipation, abdominal pain, cramping and/or bloating, nausea and/or vomiting, blood and/or mucus in stool with or without fever, rectal bleeding, peritoneal signs consistent with bowel perforation, and ileus.

Differential diagnosis: All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a *Clostridium difficile* titer. Dose modification guidelines for gastrointestinal events are provided in Table 11.

Table 11 Guidelines for Dose Modification and Management of Gastrointestinal Events (Diarrhea or Colitis)

Severity	Management	Follow-up
Grade 1	• Administer anti-diarrheal and symptomatic treatment as appropriate	*Symptoms resolve to baseline within 7 days:* • Provide close follow-up to evaluate for increased severity. *Symptoms ongoing >7 days*: • Consider following algorithm for Grade 2 events
Grade 2	• Interrupt study treatment • Administer antidiarrheal and symptomatic treatment • Discuss with Sponsor/Medical Monitor	*Symptoms resolve to Grade ≤1 or baseline within 3 days*: • resume study treatment *Symptoms ongoing >3 days, blood or mucus in stool, or ulceration/bleeding on endoscopy*: • consider GI consultation and endoscopy to confirm or rule out colitis • Start systemic corticosteroids (e.g., 0.5 mg/kg/day of prednisone or equivalent) • Continue steroids until improvement to Grade 1 or resolution; taper steroids as medically appropriate • Resume study treatment if symptoms have improved to Grade 1 and steroid dose is 10 mg prednisone/day or less • If symptoms continue or worsen to Grade 3-4, follow algorithm for Grade 3-4 events
Grade 3	• Interrupt study treatment • Assess for bowel perforation; do not administer corticosteroids if present • Consult gastrointestinal (GI) service, perform endoscopy with biopsy • Administer 1-2 mg/kg/day IV methylprednisolone • Discuss with Sponsor/Medical Monitor	• When symptoms improve to Grade ≤1, taper steroids over at least 1 month. • If corticosteroid therapy does not reduce initial symptoms within 48 to 72 hours, treat with additional anti-inflammatory measures. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45-60 days. • If symptoms worsen during steroid taper, retaper starting at a higher dose followed by a more prolonged taper. • Resume study treatment(s) if toxicity has resolved to Grade 1 and steroid dose is ≤10 mg prednisone or equivalent per day within 12 weeks of last dose. If the last dose was administered >12 weeks, study treatment(s) must be permanently discontinued. **Recurrence after rechallenge:** • **Discontinue** study treatment permanently unless otherwise agreed upon by the Sponsor/Medical Monitor and Investigators
Grade 4	• Permanently discontinue study treatment • Immediately inform Sponsor/Medical Monitor	• Management as per Grade 3

7.2.2.5. Management of Skin Toxicity

Differential diagnosis: All attempts should be made to rule out other causes such as metastatic disease, infection, or allergic dermatitis. Dose modification guidelines for skin toxicity are provided in Table 12.

Table 12 Guidelines for Dose Modification and Management of Skin Toxicity

Severity	Management	Follow-up
Grade 1	• Symptomatic management	Provide close follow-up
Grade 2	• Interrupt study treatment • Discuss with Sponsor/Medical Monitor • Consider dermatology consultation and biopsy	*Symptoms resolve to baseline within 7 days*: • resume study treatment *Symptoms ongoing > 7 days*: • Start topical or systemic corticosteroids (e.g., 0.5-1 mg/kg/day of prednisone or equivalent) • Continue steroids until improvement to Grade 1 or resolution; taper steroids as medically appropriate • Resume study treatment if symptoms have improved to Grade 1 and steroid dose is 10 mg prednisone/day or less • If symptoms continue or worsen, follow algorithm for Grade ≤3 events
Grade 3 or greater or Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations	• Permanently discontinue study treatment • Administer 1-2 mg/kg/day IV methylprednisolone • Discuss with Sponsor/Medical Monitor • Consider dermatology consultation and biopsy	• When dermatitis is controlled, taper steroids over at least 1 month

IV = Intravenous

7.2.2.6. Management of Endocrine Events

Signs/symptoms may include, but are not limited to: fatigue, weakness, headache, mental status and/or behavior changes, fever, vision disturbances, cold intolerance, abdominal pain, unusual bowel habits, loss of appetite, nausea and/or vomiting, and hypotension. Endocrine events may include the following AE terms: adrenal insufficiency, hyperthyroidism, hypophysitis, hypopituitarism, hypothyroidism, thyroid disorder, and thyroiditis. Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and/or electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes an adrenal crisis and must be considered a medical emergency.

Dose modification guidelines for endocrine events are provided in Table 13.

Table 13 Guidelines for Dose Modification and Management of Endocrine Events

Severity	Management	Follow-up
Grade 1 or 2 • Signs and/or symptoms of dysfunction • Endocrinopathies requiring hormone replacement or medical intervention	• Consider interruption of study treatment if symptomatic • Assess endocrine function • Consider pituitary imaging • Administer up to 1-2 mg/kg/day IV methylprednisolone if clinically indicated • Initiate appropriate hormone-replacement therapy • Consider consultation with endocrinology • Discuss with Sponsor/Medical Monitor	*Consider resuming study agent(s) when:* • Participant is stable (on hormone-replacement therapy if indicated) and symptoms have resolved or return to baseline • Participant is receiving ≤10 mg prednisone or equivalent per day
Grade 3 or greater • Adrenal crisis or other adverse reactions requiring hospitalization, urgent medical intervention.	• Consider interruption of study treatment • Discuss with Sponsor/Medical Monitor • Consider immediate initiation of 1-2 mg/kg/day IV methylprednisolone • Consult endocrinology • Other management as above	*Consider resuming study agent(s) when:* • Participant is stable (on hormone-replacement therapy if indicated) and symptoms have resolved or return to baseline • Participant is receiving ≤10 mg prednisone or equivalent per day

7.2.2.7. Management of Pneumonitis

Signs/symptoms may include, but are not limited to: dyspnea, dry cough, hemoptysis, fever, chest pain and/or tightness, abnormal breath sounds, and fatigue. If symptoms indicate possible new or worsening cardiac abnormalities additional testing and/or a cardiology consultation should be considered. Pneumonitis events may include the following AE terms: pneumonitis, interstitial lung disease, and acute interstitial pneumonitis.

If symptoms indicate possible new or worsening cardiac abnormalities additional testing and/or a cardiology consultation should be considered.

Differential diagnosis: All attempts should be made to rule out other causes such as metastatic disease, and bacterial or viral infection. It is important that participants with a suspected diagnosis of pneumonitis be managed as per the guidance below until treatment-related pneumonitis is excluded. Treatment of both a potential infectious etiology and pneumonitis in parallel may be warranted. Management of the treatment of

suspected pneumonitis with steroid treatment should not be delayed for a therapeutic trial of antibiotics. If an alternative diagnosis is established, the participant does not require management as below; however, the AE should be reported regardless of etiology. Dose modification guidelines for pneumonitis are provided in Table 14.

Table 14 Guidelines for Dose Modification and Management of Pneumonitis

Severity	Management	Follow-up
Grade 1 (asymptomatic with radiographic findings only)	• Discuss continued treatment with study treatment with Sponsor/Medical Monitor • Consider pulmonary consultation and/or bronchoscopy if clinically indicated	• Serial imaging
Grade 2	*First episode*: • Interrupt study treatment • Consider pulmonary consultation with bronchoscopy and bronchoalveolar lavage (BAL) • Administer 1-2 mg/kg/day IV methylprednisolone • Discuss with Sponsor/Medical Monitor *Second episode*: • Permanently discontinue study treatment	• When symptoms improve to ≤ Grade 1, taper steroids over at least 1 month. Permanently discontinue study treatment if unable to reduce corticosteroid dose to ≤10 mg prednisone or equivalent daily. • Rechallenge with study treatment at the same dose(s) may be considered if a first event improves to Grade 1 or resolves within 12 weeks of onset. Repeat chest imaging monthly as clinically indicated.
Grade 3 and 4	• Permanently discontinue study treatment • Bronchoscopy with biopsy and BAL is recommended • Administer 1-2 mg/kg/day IV methylprednisolone • Discuss with Sponsor/Medical Monitor	• When symptoms improve to ≤Grade 1, taper steroids over at least 1 month. • If corticosteroid therapy does not reduce initial symptoms within 48 to 72 hours, treat with additional anti-inflammatory measures. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45-60 days. • If symptoms worsen during steroid taper, retaper starting at a higher dose followed by a more prolonged taper. • Add anti-infective prophylaxis as appropriate.

7.2.2.8. Management of Hematologic Events

Dose modification guidelines for hematologic events are provided in Table 15.

Table 15 Guidelines for Dose Modification and Management of Hematologic Events

Severity	Management	Follow-up
Grade 1-2	• As clinically indicated	• Provide close follow-up to evaluate for increased severity
Grade 3	• Consider interruption of study treatment • Discuss with Medical Monitor • Obtain flow cytometry study of T and B lymphocytes • Consult hematology • Further management as clinically indicated	• As clinically indicated
Grade 4	• Consider discontinuation of study treatment for any severe or life-threatening event • Consult hematology • Obtain flow cytometry study of T and B lymphocytes. • Discuss with Sponsor/Medical Monitor	• As clinically indicated

7.2.2.9. Uveitis/Iritis

All attempts should be made to rule out other causes such as metastatic disease, infection or other ocular disease (e.g., glaucoma or cataracts). However, the AE should be reported regardless of etiology. Dose modification guidelines for uveitis/iritis are provided in Table 16.

Table 16 Guidelines for Dose Modification and Management of Uveitis/Iritis[a]

Severity	Management	Follow-up
Grade 1	Symptomatic treatment as appropriate	*Symptoms resolve to baseline within 7 days:* • Provide close follow-up to evaluate for increased severity. *Symptoms ongoing > 7 days*: • Consider following algorithm for Grade 2 events
Grade 2	• Interrupt study treatment • Consultation with ophthalmologist is strongly recommended • Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics • Discuss with Sponsor/Medical Monitor	*Symptoms resolve to baseline within 7 days*: • resume study treatment *Symptoms ongoing > 7 days*: • Discontinue study treatments • If symptoms continue or worsen to Grade 3-4, follow algorithm for Grade 3-4 events
Grade 3	• Interrupt study treatment • Administer 1-2 mg/kg/day IV methylprednisolone (local administration of corticosteroids may be considered after consultation with an ophthalmologist) • Consultation with ophthalmologist is strongly recommended • Discuss with Sponsor/Medical Monitor	*Symptoms improve to Grade ≤2:* • continue steroids until improvement to Grade ≤1 or baseline; taper steroids over at least 1 month *Symptoms ongoing ≥12 weeks* • permanently discontinue study treatments
Grade 4	• Permanently discontinue study treatment • Immediately inform Sponsor/Medical Monitor	• Management as per Grade 3

a. If multiple study treatments are administered per protocol, guidance may apply to 1 or more study agents; discuss management on a case-by-case basis with the Sponsor/Medical Monitor.

7.2.2.10. Management of Left Ventricular Dysfunction

Echocardiography (ECHO) or MUGA must be performed at Screening, and if clinically indicated as outlined in the SoA (Section 2).

Participants with Grade 3 or Grade 4 (symptomatic) left ventricular (LV) systolic dysfunction that includes left ventricular ejection fraction (LVEF) decrease of >10% from baseline should interrupt study treatment and have repeat echocardiogram performed. LVEF should be monitored every 4 weeks for a total of 16 weeks or until resolution. If recovery occurs (LVEF >institutional lower limit of normal [LLN] and symptom resolution) within 4 weeks, study treatment may be restarted at a reduce dose in consultation with the Sponsor.

Participants with symptoms of 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 study treatment at the same or reduced dose with the Sponsor.

Copies of all ECHO and cardiology consultations performed on participants who experience a >10% decrease in LVEF from baseline and whose cardiac ejection fraction is <institution's LLN will be required by the Sponsor for review. Instructions for submitting qualifying ECHOs are provided in the SRM.

7.2.2.11. Management of Valvular Toxicity

Participants with a Grade 3 or Grade 4 (symptomatic, severe regurgitation/stenosis by imaging with symptoms controlled by medical intervention) valvular toxicity must interrupt study treatment. 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 participant may restart study treatment at a reduced dose in consultation with and after approval of the Sponsor.

Copies of all ECHO and cardiology consultations performed on participants who experience valvular toxicity will be required by the Sponsor for review. Instructions for submitting qualifying ECHOs are provided in the SRM.

7.3. Method of Treatment Assignment

All screened participants will be identified by a unique participant number that will remain consistent for the duration of the study. Upon completion of all the required screening assessments, eligible participants will be registered into the study by the investigator or authorized site staff. See SRM for additional information on screening and enrollment procedures.

7.4. Blinding

This is an open label study; there is no blinding.

7.5. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only participants 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 labeled storage conditions with access limited to the investigator and authorized site staff.

- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.6. Treatment Compliance

GSK1795091 in combination with either GSK3174998, GSK3359609, or pembrolizumab will be intravenously administered to participants at the site. When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. Administration will be documented in the source documents and reported in the CRF.

7.7. Concomitant Therapy

Participants will be instructed to inform the investigator before starting any new medications from the time of first dose of study treatment until the end of the study (Final Study Visit). Any concomitant medication(s), including antibiotic and probiotic use within 60 days prior to first dose, non-prescription medication(s) and herbal product(s), taken during the study will be recorded in the eCRF. The minimum requirement is that drug name, dose, and the dates of administration are to be recorded. Additionally, a complete list of all prior anticancer 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 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.

7.8. Treatment after the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition.

7.9. Dose Delay

GSK1795091 in combination with either GSK3174998, GSK3359609, or pembrolizumab may be interrupted for treatment-related AEs or other reasons such as medical / surgical events or logistical reasons not related to study therapy.

During the first 12 weeks (Part 1) of study participation (GSK1795091 Q1W dosing), if there is a dose delay between 1 and 3 days, the procedures at the original scheduled visit (including dosing) should be performed as soon as possible. If the delay is >3 days, the visit and dose(s) will be considered missed and the procedures at the next scheduled visit should be performed. After Week 12 (Part 1) of study participation (Q3W dosing), if there is a dose delay between 1 and 7 days, the procedures at the original scheduled visit (including dosing) should be performed as soon as possible. If the delay is >7 days, the visit and dose(s) will be considered missed and the procedures at the next scheduled visit should be performed.

If a biopsy sample collection is missed, it may be collected at the next possible visit. Participants with infusion delays equivalent to 2 consecutive missed doses should discontinue study treatment(s) unless the treating investigator and Sponsor agree there is strong evidence supporting continued treatment. Administration of GSK1795091 the day following the treatment mAb infusion is not considered a dose delay.

8. DISCONTINUATION CRITERIA

Participants will receive study treatment for the scheduled time period, unless 1 of the following occurs earlier: disease progression (as determined by immune-related RECIST [irRECIST]), death, unacceptable toxicity or stopping criteria are met, including meeting criteria for liver chemistry defined in Section 8.1.1.

8.1. Discontinuation of Study Treatment

In addition to the above, study treatment might be permanently discontinued for any of the following reasons:

- Deviation(s) from the protocol
- Withdrawal of consent by participant or proxy
- Discretion of the investigator
- Participant loss to follow-up by the investigative site
- Closure or termination of the study
- Criteria described in Section 7.9 (Dose Delay)
- Female participant who becomes pregnant while on study treatment
- Criteria for discontinuation of study treatment(s) as described in Section 7.2 (Dose Modification Guidelines) have been met
- Criteria described in Section 8.1.2 (QTcF) Stopping Criteria) have been met

- Criteria described in Section 8.1.3 (Stopping Rules for Clinical Deterioration) have been met

Note: Participants who require permanent discontinuation of one of the study treatments due to toxicity in a given treatment combination must permanently discontinue both treatments in that combination and the reason for discontinuation must be recorded.. The TDV must be conducted within 30 days of the last dose of study treatment(s).

The primary reason for discontinuation must be documented in the participant's medical records and eCRF. If the participant voluntarily discontinues from treatment due to toxicity, 'AE' will be recorded as the primary reason for permanent discontinuation on the eCRF.

Once a participant has permanently discontinued from study treatment(s), the participant will not be allowed to be retreated.

The assessments required at the TDV must be completed within 30 days of the last dose of study treatment(s).

Participants who permanently discontinue from study treatment(s) will no longer be followed for for PFS FU. One Survival FU visit will be performed 12wks after the last dose of study treatment or prior to the start of the next anti-cancer therapy, whichever occurs first. If a new anti-cancer therapy is started before the TDV, the OS visit is not required. The study will conclude when the last subject has completed/discontinued study treatment, completed the Treatment Discontinuation Visit (TDV) assessments, and the OS FU visit is completed (as applicable).

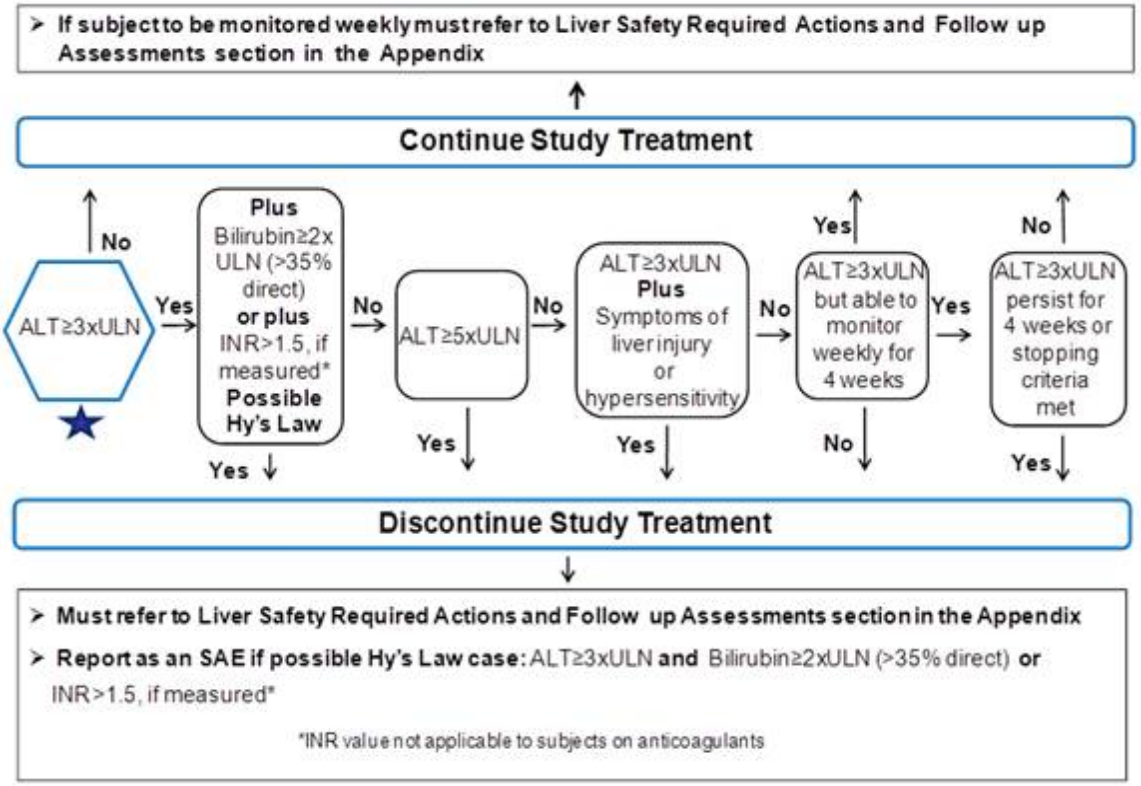
All participants who discontinue from study treatment will undergo safety assessments at the time of discontinuation and during post-study treatment follow-up as specified in the SoA (Section 2).

8.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Discontinuation of study treatment for abnormal liver tests is required when a participant meets the conditions outlined in Figure 9.

Figure 9 Liver Chemistry Stopping Criteria



Refer to Appendix 7 for required Liver Safety Actions and Follow up Assessments.

8.1.1.1. Study Treatment Restart or Rechallenge

In Canada, if liver chemistry stopping criteria are met, participants will not be allowed to restart study drugs or be rechallenged.

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

- GSK Medical Governance approval is granted
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the participant

Refer to Appendix 7 for full guidance.

8.1.2. QTcF Stopping Criteria

- The QTcF correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
- The QTcF should be based on single or averaged QTcF values of triplicate ECGs obtained over a brief (e.g., 5-10 minutes) recording period (i.e., single QTcF is

used when a single ECG is performed, and averaged QTcF is used when triplicate ECGs are performed).

- Withdrawal of subjects is to be based on an average QTcF value of triplicate ECGs. If a single ECG demonstrates a prolonged QTcF interval, then obtain 2 more ECGs over a brief period of time (e.g., 5-10 minutes) and then use the averaged QTcF values of the 3 ECGs to determine whether the subject should be discontinued from the study.

If a participant meets either of the following criteria, they must be discontinued from study treatment.

- QTcF >500 msec

OR

- Change from baseline of QTcF >60 msec

For participants with underlying **bundle branch block**, proceed with the following discontinuation criteria:

Baseline QTcF with Bundle Branch Block	Discontinuation QTcF with Bundle Branch Block
<450 msec	≥500 msec
450 – 480 msec	≥530 msec

QTcF = QT duration corrected for heart rate by Fridericia's formula

See the SoA (Section 2) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

8.1.3. Stopping Rules for Clinical Deterioration

As indicated in Section 9.1, in order to adequately assess the antitumor effect of immunotherapeutic agents, participants experiencing apparent progression as defined by RECIST version 1.1 guidelines may continue to receive treatment until progression is confirmed at the next imaging assessment at least 4 weeks later as indicated by irRECIST guidelines. These considerations should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive benefit from continued study treatment.

In cases where deterioration was assessed in the investigator's opinion to have occurred after a clinical event and is attributable to disease progression, is unlikely to reverse with continued study treatment or managed by supportive care (e.g., bisphosphonates and/or bone directed radiotherapy, thoracentesis, or paracentesis for accumulating effusions), study treatment should be discontinued. The decision to stop treatment should be discussed with the Sponsor's Medical Monitor. Examples of events that may, in the investigator's opinion, indicate a lack of clinical benefit include, but are not limited to, the following:

- ECOG PS decrease of at least 2 points from baseline
- Skeletal related events defined by the following:

  - pathologic bone fracture in the region of cancer involvement
  - cancer related surgery to bone, and/or
  - spinal cord or nerve root compression
- Development of new CNS metastases
- Any setting where the initiation of new antineoplastic therapy has been deemed beneficial to the participant even in the absence of any such documented clinical event.

8.2. Withdrawal from the Study

- A participant 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, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the SoA (Section 2) for data to be collected at the time of study discontinuation and follow-up for any further evaluations that need to be completed.

8.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 2).
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA (Section 2), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA (Section 2).

If assessments are scheduled for the same nominal time, it is recommended that the assessments should occur in the following order: 12-lead ECG, vital signs, and blood draws. 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 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 for the following assessments: safety, PK, pharmacodynamics/biomarker, or other assessments (not applicable for participants in Canada).

- The change in timing or addition of time points for any planned study assessments must be approved by the relevant GSK study team member and then archived in the study Sponsor and site study files, but this will not constitute a protocol amendment.

The IRB/ IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the informed consent form.

No more than 550 mL of blood for the purposes of this study, will be collected over the first 12 weeks of the study. The total volume will depend on how long the participant remains on treatment. There may be additional blood collection performed for non-study reasons.

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 SoA (Section 2), 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 SoA (Section 2).

9.1. Efficacy Assessments

- 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 Appendix 9 of this protocol.
- Disease assessment modalities may include imaging (e.g., computed tomography [CT] scan, magnetic resonance imaging [MRI], bone scan, plain radiography) and physical examination (as indicated for palpable/superficial lesions). Scans will be collected centrally during the study and may be reviewed or analyzed by an independent central reviewer. Details will be provided in the SRM.
- The baseline disease assessment will be completed up to 28 days prior to the first dose of study treatment. See the Schedule of Activities Tables (Section 2) for the schedule of assessments of anti-cancer activity subsequent to the baseline disease assessment.
- Assessments must be performed on a calendar schedule 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 6 weeks or more prior to the participant's withdrawal from study treatment and PD has not been documented, a disease assessment should be obtained at the time of withdrawal from study treatment.
- To ensure comparability between the baseline and subsequent assessments, the same method of assessment and the same technique will be used when assessing response.

9.1.1. Evaluation of Anti-Cancer Activity

- RECIST version 1.1 guidelines will be used to determine the overall tumor burden at baseline, select target and non-target lesions, and in the disease assessments throughout the duration of the study [Eisenhauer, 2009] as further outlined in Appendix 9 of this protocol. irRECIST assessments will be evaluated as well. Treatment decisions according to irRECIST are encouraged, including confirmatory disease assessments at least 4 weeks after the date disease progression was declared. Similarly, new lesions should be measured, as feasible, and may be incorporated into assessments of tumor burden according to irRECIST guidelines.
- Lymph nodes that have a short axis of <10 mm are considered non-pathological and should not be recorded or followed.
- Pathological lymph nodes with <15 mm and but ≥10 mm short axis are considered non-measurable.
- Pathological lymph nodes with ≥15 mm 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, fluorodeoxyglucose (FDG)-positron-emission tomography (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 grouped by organ. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.
- The following are required at baseline (up to 28 days before first dose, see Section 2): CT scan with contrast of the chest, abdomen, and pelvis is required. For participants with SCCHN, a scan of the head and neck area is required. Other areas should be evaluated as indicated by the participant's underlying disease prior to screening, including clinical disease assessment for palpable/visible lesions. Although CT scan is preferred, MRI may be used as an alternative method of baseline disease assessment, especially for those participants 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. At each post baseline assessment, evaluations of the sites of disease identified by these scans are required. Refer to RECIST version 1.1 guidelines for use of FDG-PET/CT [Eisenhauer, 2009].

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue GSK1795091 and combination partners (see Section 8).

9.2.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the start of study treatment until the follow-up visit at the time points specified in the SoA (Section 2). (However, any SAEs assessed as related to study participation [e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy] or related to a GSK product will be recorded from the time a participant consents to participate in the study).
- All AEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.
- Any AESI and 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 participant consents to participate in the study up to 90 days after the last dose of study treatment(s) or until the start of another anti-cancer therapy, whichever is first. SAEs must be reported within 24 hours to the Sponsor either by electronic media or paper.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant 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?”

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, [and non-serious AESIs (as defined in Section 9.2.8)], will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Cardiovascular and Death Events

For any CV events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the CRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV death.

The CV CRFs 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 CV section of the CRF within 1 week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within 1 week of when the death is reported.

9.2.5.1. Cardiovascular and Death Events

A CV event is defined as:
• 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

9.2.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression or hospitalization due to disease progression) does not need to be reported as a SAE.

Death due to disease under study is to be recorded on the death eCRF form.

However, if the underlying disease (i.e., progression) is greater than that which would normally be expected for the participant, or if the investigator considers that there was a causal relationship between treatment with study treatment(s) or protocol design/procedures and the disease progression, then this must be reported as a SAE.

NOTE: If either of the following conditions apply, then the event must be recorded and reported as a SAE (instead of a disease-related event):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant, or
- The investigator considers that there is a reasonable possibility that the event was related to treatment with study treatment(s).

9.2.7. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment and until 120 days after the last dose of study medication.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

9.2.8. Guidelines for Events of Special Interest

The severity of AEs will be graded utilizing the NCI-CTCAE, version 4.0. Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment(s) are provided in Section 7.

9.3. Treatment of Overdose

For this study, any dose of GSK1795091 or combination partners greater than 50% of the intended dose within a 24-hour time period will be considered an overdose.

There is no specific antidote for overdose with GSK1795091, GSK3174998, GSK3359609, or pembrolizumab. In the event of a suspected overdose, it is recommended that the appropriate supportive clinical care should be instituted, as dictated by the participant's clinical status.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities for at least 130 days.
3. Obtain a plasma sample for PK analysis within 28 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

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 participant.

9.4. Safety Assessments

Planned time points for all safety assessments are listed in the SoA (Section 2).

9.4.1. Physical Examinations

- A complete physical examination will be done at screening and TDV and will include assessments of the CV, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will be done at all other timepoints and will include assessments of the skin, lungs, CV system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- For melanoma participants, a full body dermatological examination will be performed by a dermatologist (or suitably qualified physician) to identify

abnormal skin lesions within the 28-day screening period. All findings will be photographed and identified during screening. Brief skin examinations will be performed as indicated in the SoA (Section 2) or more frequently as necessitated. Wherever possible, the same physician should perform these examinations. Follow-up skin examinations by a referral dermatologist should be conducted if clinically indicated by the ECOG PS.

- The PS will be assessed using the ECOG scale (Appendix 12) as specified in the SoA (Section 2).

9.4.2. Vital Signs

- Vital sign measurements to be measured in semi-supine position after 5 minutes rest will include temperature, systolic and diastolic blood pressure, and pulse rate.
- Vital signs will be measured more frequently if warranted by clinical condition of the participant. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.
- If a participant develops a fever, refer to Section 7.2.1.1 for fever management guidelines.

9.4.3. Electrocardiograms

Twelve-lead ECGs will be obtained at each planned ECG assessment during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 8.1.2 for QTcF stopping criteria and additional QTcF readings that may be necessary.

Before each ECG test, the participant should be at rest for approximately 10 minutes. The participant should be in the semi-recumbent or supine position; the same position must be used for all subsequent ECG tests.

For Part 1 of the study, ECG measurements will be performed in triplicate at specified times (see SoA [Section 2] including footnotes). All other measurements may be performed as single ECG measurements.

At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

ECGs will be collected centrally during the study and may be reviewed or analyzed. Details will be provided in the SRM.

9.4.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of local clinical laboratory tests to be performed and to the SoA for all protocol-required laboratory assessments, including timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment must be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology must be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 2).

Laboratory requisition forms must be completed and samples must be clearly labeled with the participant number, protocol number, site/center 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.

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

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

All study-required laboratory assessments will be performed by a central laboratory, apart from:

- Hematology
- Clinical Chemistry
- Hepatitis B and C
- Pregnancy Test
- Urinalysis, calculated creatinine clearance (CrCl)
- Thyroid Function Tests
- Lipid Panel
- The results of applicable tests must be entered into the eCRF as required.

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Appendix 2.

9.5. Pharmacokinetics

With the implementation of Amendments 05 and 06, PK will no longer be collected. However, event-driven collections (e.g. in response to hypersensitivity including infusion reactions) will be performed per Table 2 (footnote h and i) and Section 10.3.2.3.

9.5.1. Blood Sample Collection

Blood samples for PK analysis of GSK1795091, GSK3174998, GSK3359609, and pembrolizumab will be collected at the time points described in the SoA (Section 2). The actual date and time of each blood sample collection will be recorded in the eCRF. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring. Any change to the number and timing of PK samples is not applicable for participants enrolled in Canada. Details on PK blood sample collection, processing, storage, and shipping procedures are provided in the SRM.

Processing, storage and shipping procedures are provided in the SRM.

9.5.2. Blood Sample Analysis

Concentrations of GSK1795091, GSK3174998, GSK3359609, and pembrolizumab will be determined in blood samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site. Once the sample has been analyzed for study drugs any remaining sample may be analyzed for other compound-related metabolites and the results reported under a separate PTS-DMPK/Scinovo or GSK protocol.

9.6. Pharmacodynamics

See Section 9.8 below.

9.7. Genetics

Information regarding genetic research is included in Appendix 6

An important exploratory objective of the clinical study is genetic research. Participation in genetic research is optional, but all participants who are eligible for the clinical study will be given the opportunity to participate. Participants may decline participation without effect on their medical care or care during the clinical study. A separate consent signature is required for genetic research

A 6 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

Details on processes for collection and shipment and destruction of these samples can be found in the SRM.

9.8. Biomarkers/Pharmacodynamic Markers

With the implementation of Amendments 05 and 06, samples for biomarkers will no longer be collected.

9.8.1. Blood Biomarkers

Blood samples will be collected and analyzed by flow cytometry to evaluate the pharmacodynamic effects of all treatments on various immune cell populations. In addition, the binding of GSK3174998 to the OX40 receptor and GSK3359609 to the ICOS receptor may be measured in blood by flow cytometry analysis as described in Table 2.

Blood samples will also be collected for the isolation of PBMCs, plasma and serum. Plasma and serum samples may be used for an analysis of circulating soluble factors and soluble OX40, soluble ICOS, soluble OX40-drug complex, and soluble ICOS-drug complex depending on the availability of the assays. Plasma samples may also be analyzed for cell-free DNA (cfDNA), or exosomes or for novel biomarkers of immune activation or response to treatment. Additional factors to be analyzed from plasma and serum may include but are not limited to several cytokines, as well as antibodies against tumor, self, or viral antigens.

Based on the availability of sample, PBMCs will be isolated from whole blood. Isolated PBMCs will be preserved and stored for other relevant experiments, which may include but are not limited to flow cytometry of additional immune cell types, subsequent functional analysis or assessment of the diversity of the T-cell repertoire by DNA sequencing, its relationship to clinical responses, and changes in response to treatment with GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or pembrolizumab. The functional state of PBMCs may be analyzed for expression of cytokines. PBMCs may also be evaluated for genomic (DNA), gene signature analysis and gene expression (RNA) alterations to determine treatment-related changes in immune-related signatures.

Other biomarkers may be evaluated as determined by additional research and data. If predictive biomarkers are identified in samples, they may be used for the development of a diagnostic test. Details for sample collection, processing, storage, and shipment will be provided in the SRM.

9.8.2. Tumor Tissue

Based on the availability of sample, tumor biopsies and/or archival tissue will be evaluated by IHC or related technologies for expression of phenotypic and functional immune cell markers on tumor infiltrating lymphocytes and other immune cells as well as immune signaling markers (on both the surface and internal) of tumor cells, to understand antitumor immune responses. In addition, when possible, similar analyses will be performed on tumor tissue samples obtained upon progression. Additionally, tumor tissue DNA may be sequenced to assess mutational burden and/or TCR diversity, and RNA expression analysis may be performed by RNAseq or related technologies. Further

research may also evaluate changes in any DNA/RNA/protein correlating in response to treatment with GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or pembrolizumab.

Other biomarkers may be evaluated as determined by additional research and data. If predictive biomarkers are identified in samples, they may be used for the development of a diagnostic test. Details for sample collection, processing, storage, and shipment will be provided in the SRM.

9.8.3. Stool Collection for Microbiome Analysis

Stool specimens offer accessible means of evaluating the gut microbial community. Association of the stool microbiome composition with physiological and medical conditions and response to treatments has been reported in patients with various diseases, including cancer. Stool samples may be evaluated for changes in the gut microbial community as a response to treatment, and may also assess the relationship between antibiotic/probiotic use prior to treatment and antitumor response.

Details for sample collection, processing, storage, and shipment will be provided in the SRM.

9.9. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9.10. Qualitative Telephone Interview

To further evaluate disease and treatment related symptoms and associated impacts on function and health-related quality of life, participants will have the option to participate in a qualitative interview via telephone. The interview will be conducted by a trained interviewer in the participant's native language and will be audio recorded for transcription and analysis.

The telephone interview is to be completed within 21 days following completion of Day 64 and following the TDV. Participants who have the TDV within 30 days of the Day 64 interview are not required to repeat the interview.

Additional details on the optional qualitative telephone interview can be found in the SRM.

10. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

Part 1: Dose Escalation

With respect to the primary objectives and endpoints, no specific statistical hypotheses are being tested. The dose escalation part of the study will be focused on the determination of the recommended dose for dose expansion and further exploration, the safety profile, and antitumor activity of the combination of GSK1795091 with GSK3174998, GSK3359609, or pembrolizumab.

Part 2: Cohort Expansion

With the implementation of amendment 06, the study is closed to enrolment and Part 2 will not be opened.

10.1. Sample Size Determination

The planned sample size for the study was chosen to allow adequate characterization of safety, clinical activity, PK, and PD profile based on the study objectives. For dose escalation, the total sample size depends on the number needed to adequately characterize the DLT profile and determine the recomendend Part 2 dose.

With the implementation of amendment 06, the study is closed to enrolment and Part 2 will not be opened.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All Enrolled	All participants who sign the ICF to participate in the clinical trial.
All Treated	All participants who receive at least 1 dose of GSK1795091, GSK3174998, GSK3359609, or pembrolizumab.
Pharmacokinetic	All participants from the All Treated population for whom a PK sample is obtained, analysed, measureable, and valid.
Pharmacodynamic	All participants from the All Treated population for whom a pharmacodynamic/biomarker sample is obtained, analysed, and measureable.

10.3. Statistical Analyses

Data will be listed and summarized according to the GSK reporting standards, where applicable. Complete details will be documented in the Reporting and Analysis Plan (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.

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 participant will depend on efficacy and tolerability, the duration of follow-up will vary between participants. Consequently, there will be no imputation for missing data.

Demographic and baseline characteristics will be summarized.

10.3.1. Primary Analyses

10.3.1.1. Safety Analyses

The All Treated Population will be used for the analysis of safety data. All serially collected safety endpoints (e.g., laboratory tests, vital signs, 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.

10.3.1.2. Extent of Exposure

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

10.3.1.3. Adverse Events

Adverse events will be coded using the standard MedDRA and grouped by system organ class. Adverse events will be graded by the investigator according to the NCI-CTCAE (version 4.0).

Events will be summarized by frequency and proportion of total participants, 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. Adverse events, if listed in the NCI-CTCAE (version 4.0) will be summarized by the maximum grade. Otherwise, the AEs will be summarized by maximum intensity.

Characteristics (e.g., number of occurrences, action taken, grade, etc) of AESI (see Section 7.2.2.1 and Appendix 12 will be summarized separately.

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

10.3.1.4. Clinical Laboratory Evaluations

Change of hematology and clinical chemistry will be descriptively summarized by cohort. These summaries will include sample size, mean, median, standard deviation, minimum, and maximum.

The toxicity grades and the worst-case toxicity grade of hematology and clinical chemistry data will be summarized using frequencies and proportions according to NCI-CTCAE (version 4.0). Laboratory test results outside the reference ranges that do not have an associated NCI-CTCAE criteria will be summarized using proportions. Further details will be provided in the RAP.

10.3.1.5. Other Safety Measures

Vital signs (body temperature and pulse rate) and ECGs (QT and QTcF) measurements change from baseline will be descriptively summarized by cohort. These summaries will include sample size, mean, median, standard deviation, minimum, and maximum.

Vital signs and ECGs will also be tabulated according to the categories specified below. The summaries will include frequencies and corresponding percentages. Further details will be provided in the RAP.

Vital Signs:

- Increased body temperature to: ≤38.0, 38.1-38.5, 38.6-39.0, ≥39.1 ºC
- Change in body temperature from baseline by: ≤1.0, 1.1-1.5, 1.6-2.0, ≥2.1 ºC
- Increased pulse rate to: ≤100, 101-115, 116-130, ≥131 bpm
- Change in pulse rate from baseline by: ≤20, 21-35, 36-50, ≥51 bpm
- Decreased pulse rate to: <45 bpm
- Increased systolic blood pressure to: ≤140, 141-160, 161-180, ≥181 mmHg
- Decreased systolic blood pressure to: <80 mmHg
- Increased diastolic blood pressure to: ≤90, 91-100, 101-110, ≥111 mmHg
- Decreased diastolic blood pressure to: <50 mmHg

ECGs:

- PR interval: >200 msec
- QRS interval: >120 msec
- QT interval: ≤450, 451-480, 481-500, ≥501 msec
- QTcF interval: ≤450, 451-480, 481-500, ≥501 msec
- Change in QT from baseline by: ≤30, 31-60, ≥61 msec
- Change in QTcF from baseline by: ≤30, 31-60, ≥61 msec

10.3.2. Secondary Analyses

10.3.2.1. Anticancer Activity Analyses

The All Treated Population will be used for anticancer activity analyses. Anticancer activity will be evaluated based on clinical evidence and response criteria as assessed by RECIST v1.1 and specified in Appendix 9. Immune related response criteria (irRECIST) will be evaluated as an exploratory endpoint. If data warrant, the response data will be summarized by cohort.

If the data warrant, PFS, time to response, duration of response and overall survival will be calculated and listed for each participant, and be summarized by cohort. PFS is defined as time from the date of first dose to the date of disease progression according to clinical or radiological assessment or death due to any causes, whichever occurs earliest. Time to response is defined as the time from the date of first dose to the date of the first documented evidence of response (PR or CR). Duration of response is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause among participants who achieve an overall response (i.e., unconfirmed or confirmed CR or PR). If the participant does not have a documented date of event, PFS will be censored at the date of the last adequate assessment. Further details on rules of censoring will be provided in the RAP. PFS will be summarized using the Kaplan-Meier method if the data warrant. Overall survival is defined as time from the date of first dose to the date of death due to any cause. For participants who do not die, time of death will be censored at the date of last contact.

Objective response rate (ORR) and disease control rate (DCR) will be summarized by cohort. ORR is defined as percentage of participants with complete response or partial response. DCR is defined as percentage of participants with complete response or partial response or at least 12 weeks of stable disease. If data warrant, the corresponding 95% CI for ORR and DCR will also be provided. Participants with unknown or missing responses will be treated as non-responders, i.e., these participants will be included in the denominator when calculating percentages of response.

10.3.2.2. Pharmacokinetic Analyses

10.3.2.2.1. Pharmacokinetic Parameters

Pharmacokinetic analysis of study treatments will be the responsibility of the Clinical Pharmacology Modeling and Simulation (CPMS) Department.

Pharmacokinetic analysis of GSK1795091 drug concentration-time data will be conducted by non-compartmental methods under the direction of CPMS, Quantitative Sciences, GSK. PK parameters including but not limited the following will be determined if data permit:

- Maximum observed concentrations (C_{max})
- Trough plasma concentrations(C_{trough})
- $AUC_{(0-\tau)}$ (repeat dosing)

10.3.2.2.2. Statistical Analysis of Pharmacokinetic Data

Statistical analyses of the PK parameters data will be the responsibility of Clinical Statistics and Programming.

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

If data warrants, the data from this study may be combined with the data from other studies for a population PK analysis, which will be reported separately. A nonlinear mixed effects model will be used to determine population pharmacokinetic parameters and identify relevant covariates (e.g., age, weight, or disease related covariates).

10.3.2.3. Immunogenicity Analyses

Serum samples to assess the presence of anti-drug antibodies (ADA) will be collected as described in the SoA (Section 2). All samples will be assessed for anti-GSK3174998 and anti-GSK3359609 antibodies using validated immunoassays. 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.

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 (any change to the number and timing of immunogenicity samples is not applicable for participants enrolled in Canada). 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 should be taken from the participant for immunogenicity testing at the time of the event and again 30 days, 12 weeks, and 24 weeks after. For participants who withdraw from the study, immunogenicity testing will occur at withdrawal and at follow-up 30 days, 12 weeks, and 24 weeks after the last dose.

Serum will be tested for the presence of ADA using a tiered testing schema: screening, confirmation and titration steps. The presence of treatment emergent ADA will be determined using a drug-specific bridging style ADA assay with a bio-analytically determined cut-point determined during assay validation. Samples taken after dosing

with treatment mAb combination partners that have a value at or above the cut-point will be considered treatment-emergent ADA-positive. These ADA positive samples will be further evaluated in a confirmatory assay, and confirmed positive samples will be further characterized by assessment of titer. A neutralizing ADA assay may be developed for characterization of selected, stored samples. Results of ADA testing will be reported at the end of the study and will include incidence and titer.

10.3.3. Other Analyses

10.3.3.1. Translational Research Analyses

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

Further details on the translational research analyses will be addressed in the RAP.

10.3.3.1.1. *PK/Pharmacodynamic/ Analyses*

Observed or predicted concentrations or summary exposure measure (e.g., C_{max}, C_{trough}, and AUC) may be combined with safety, efficacy, or pharmacodynamic measures of interest to examine potential exposure-response relationships. Descriptive and graphical evaluation will first be performed.

Where evidence of relationship is seen, statistical models may be fitted to further explore PK/Pharmacodynamic relationship. Further model details will be provided in the RAP.

10.3.3.1.2. *Biomarker(s) Analyses*

The results of biomarker investigations, which may include but is not limited to immune cell phenotypes in blood and tumor, abundance of soluble factors such as cytokines and stress-related proteins, DNA sequence alterations, gene expression (RNA) in immune cells and tumor, tumor mutational burden, and microbiome analysis may be reported separately from the main CSR. All analyses will be descriptively and/or graphically summarized as appropriate to the data.

Performance of these investigations may be conditional on the results of the clinical trial principally, but not exclusively, on the primary measures of the clinical trial outcome and samples may be selected for analysis on the basis of the clinical outcome.

OR

These investigations may be performed irrespective of whether a response to GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or pembrolizumab is observed.

Additionally, comparative examination of post-dosing profiles in conjunction with pre-dosing profiles may yield known and novel candidate biomarkers/profiles and new insights which relate to the action of GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or pembrolizumab.

All samples may be retained for the length of time described in participant informed consent forms after the last participant completes the trial.

Where evidence of association between anticancer activity or immunologic effects and biomarkers is seen, additional exploratory analyses may be performed to further characterize the biomarker(s). Full details will be addressed in the RAP.

10.3.3.2. Pharmacogenetic Analyses

Further details on PGx analyses will be addressed in Appendix 6 and the PGx RAP.

10.3.3.3. Qualitative Telephone Interviews

The results of these qualitative telephone interviews will be descriptively summarized and may be reported separately from the main CSR.

10.3.4. Interim Analyses

No formal interim analysis is planned for this study.

10.4. N-CRM Analysis for Dose Escalation

10.4.1. Implementation of N-CRM

The N-CRM model implementation will be performed using the FACTS (Version 4.0 or higher).

10.4.2. Bayesian Prior for the Logistic Model

The N-CRM methodology requires that a Bayesian prior distribution for the dose-toxicity curve be pre-specified. The Bayesian prior used for this design was determined using the quantile method. For each dose, the most likely (median) presumed probability of DLT was specified, along with a 95% credible interval – an interval within which the team is 95% a priori certain the probability of a DLT lies. The 95% credible intervals are intentionally wide due to limited information about the toxicity profile of GSK1795091 in humans and to allow the accumulating data to have more influence on dose recommendations than the prior.

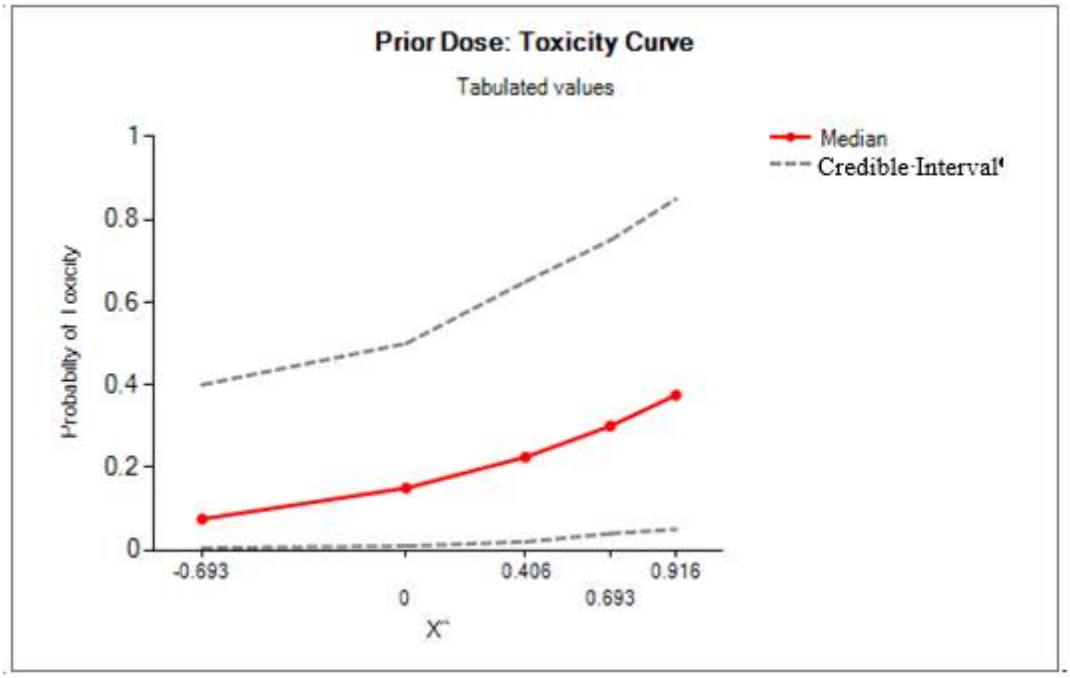
The Bayesian prior (α, ln(β)) is assumed to follow bivariate normal distribution. The Bayesian prior means (standard deviations) for dosing scheme shown in Table 17 are determined to be: E[α]=−1.889 (1.0079), E[ln(β)]=0.1807 (0.6682), with correlation between α and ln(β) as ρ=−0.3644, and use 100 ng as the reference dose.

Table 17 and Figure 10 shows the median prior probability of experiencing a DLT at the given dose along with a 95% credible interval around the median:

Table 17 Table of Specified Prior Probability of DLT (with 95% Credible Interval)

Anticipated Dose for GSK1795091 (ng)	Median Probability of Toxicity	2.5% Quantile for Probability of Toxicity	97.5% Quantile for Probability of Toxicity
50	0.075	0.005	0.4
100	0.15	0.01	0.5
150	0.225	0.02	0.65
200	0.30	0.04	0.75
250	0.375	0.05	0.85

Figure 10 Graphical Display of the Prior Distribution for the Probability of DLT Given Dose (Median with 95% Credible Interval)



Note: x-axis is natural log (dose/reference dose).

11. REFERENCES

Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8:709-714.

Astiz ME, Rackow EC, Still JG, Howell ST, Cato A, Von Eschen KB, et al. Pretreatment of normal humans with monophosphoryl lipid A induces tolerance to endotoxin: a prospective, double-blind, randomized, controlled trial. Crit Care Med. 1995 Jan;23(1):9-17.

Bahador M, Cross AS. From therapy to experimental model: a hundred years of endotoxin administration to human subjects. J Endotoxin Res. 2007;13(5):251-79. Review.

Brennan FR, Morton LD, Spindeldreher S, Kiessling A, Allenspach R, Hey A, et al. Safety and immunotoxicity assessment of immunomodulatory monoclonal antibodies. mAbs. 2010;2:233-255.

Chen DS, Mellman I. Elements of cancer immunity and the cancer-immune set point. Nature. 2017;541(7637):321-330.

Chen DS, Mellman I. Oncology meets immunology: The cancer-immunity cycle. Immunity. 2013;39:1-10.

Chow L, Morishima C, Eaton K, Baik C, Goulart BH, Anderson L, et al. Phase Ib Trial of the Toll-like Receptor 8 Agonist, Motolimod (VTX-2337), Combined with Cetuximab in Patients with Recurrent or Metastatic SCCHN. Clin Cancer Res. 2017 May 15;23(10):2442-2450.

Clark, D.A., J. Manuel, L. Lee, G. Chaouat, R.M. Gorczynski, and G.A. Levy. 2004. Ecology of danger-dependent cytokine-boosted spontaneous abortion in the CBA x DBA/2 mouse model. I. Synergistic effect of LPS and (TNF-alpha + IFN-gamma) on pregnancy loss. American journal of reproductive immunology (New York, N.Y. : 1989) 52:370-378.

Cohen E, Milhem M, Ribas A, et al. Phase 1b/2, Open-Label, Multicenter Study of Intratumoral SD-101 in Combination with Pembrolizumab in Anti-PD-1 Treatment-Naïve Patients with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma. Presented at: 2018 American Association for Cancer Research (AACR) Annual Meeting; April 14-18, 2018; Chicago, IL. Abstract CT098

de Bono JS, Dalgleish AG, Carmichael J, Diffley J, Lofts FJ, Fyffe D, et al. Phase I study of ONO-4007, a synthetic analogue of the lipid A moiety of bacterial lipopolysaccharide. Clin Cancer Res. 2000 Feb;6(2):397-405.

Dietsch G, Whiting S, Northfelt D, Ramanathan R, Cohen P, Manjarrez K, et al. Comparison of immune modulation by TLR8 agonist vtx-2337 (motolimod) in cancer patients and healthy volunteers. Journal for ImmunoTherapy of Cancer. 2014;2(Suppl 3):P165.

Dillingh M, van Poelgeest E, Malone K, Kemper E, Stroes E, Moerland M, et al. Characterization of inflammation and immune cell modulation induced by low-dose LPS administration to healthy volunteers. Journal of Inflammation. 2014;11(1).

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: Revised RECIST guidelines (version 1.1). Eur J Cancer. 2009;45:228-247.

Engelhardt R, Mackensen A, Galanos C. Phase I trial of intravenously administered endotoxin (Salmonella abortus equi) in cancer patients. Cancer Res. 1991 May 15;51(10):2524-30.

Flowers CR, Panizo C, Isufi I, Herrera AF, Okada C, Cull EH, et.al. Intratumoral G100 Induces Systemic Immunity and Abscopal Tumor Regression in Patients with Follicular Lymphoma: Results of a Phase 1/2 Study Examining G100 Alone and in Combination with Pembrolizumab [Abstract # 2771] ASH December 10, 2017; Atlanta, Georgia.

GSK Document Number 2014N212091_05. Investigator's Brochure for GSK3174998. Version 04. 2018

GSK Document Number 2014N225045_02 Study 201212. A Phase I, Open-Label Study of GSK3174998 Administered Alone and in Combination with Anticancer Agents including Pembrolizumab in Subjects with Selected Advanced Solid Tumors. 2016.

GSK Document Number 2015N236402_03 Study 204685. A 2-part randomized, double-blind (sponsor-unblinded), placebo-controlled, ascending dose and parallel group study of TLR4 agonist (GSK1795091) administered to healthy subjects. 2017.

GSK Document Number 2015N238345_03. Study 204691. A Phase I Open Label study of GSK3359609 administered alone and in combination with anticancer agents in subjects with selected advanced solid tumors. 2017.

GSK Document Number 2015N239078_04, Investigator's Brochure for GSK1795091. Version 03. 2018

GSK Document Number 2017N319717_02, Investigator's Brochure for GSK3359609. Version 04. 2019.

Guha M. Anticancer TLR agonists on the ropes. Nat Rev Drug Discov. 2012 Jun 29;11(7):503-5. doi: 10.1038/nrd3775.

Heikkinen, J., M. Mottonen, A. Alanen, and O. Lassila. 2004. Phenotypic characterization of regulatory T cells in the human decidua. Clinical and experimental immunology 136:373-378.

Hoos A. Development of immuno-oncology drugs—from CTLA4 to PD1 to the next generations. Nat Rev Drug Discov. 2016;15(4):235–47. pmid:26965203

Hunt CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatol. 2010;52:2216-2222.

Isambert N, Fumoleau P, Paul C, Ferrand C, Zanetta S, Bauer J, et al. Phase I study of OM-174, a lipid A analogue, with assessment of immunological response, in patients with refractory solid tumors. BMC Cancer. 2013 Apr 2;13:172.

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, et al. Pharmacokinetics of acetaminophen-adduct in adults with acetaminophen overdose and acute liver failure. Drug Metab Dispos. 2009;37:1779-1784.

Kanzler H, Barrat FJ, Hessel EM, Coffman RL. Therapeutic targeting of innate immunity with Toll-like receptor agonists and antagonists. Nat Med. 2007 May;13(5):552-9. Review.

KEYTRUDA (pembrolizumab) Drug Approval Package
Company: Merck Application No.: 125514 Approval Date: 9/4/2014
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125514Orig1s000PharmR.pdf

KEYTRUDA (pembrolizumab) Prescribing Information. Merck Sharp & Dohme Corporation, June, 2019.

KEYTRUDA Summary of Product Characteristics, Merck Sharp & Dohme Corporation May, 2019

Krabbe KS, Bruunsgaard H, Qvist J, Hansen CM, Møller K, Fonsmark L, et al. Hypotension during endotoxemia in aged humans. Eur J Anaesthesiol. 2001 Sep;18(9):572-5.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, et al. Quantification of hepatitis delta virus RNA in serum by consensus real-time pcr indicates different patterns of virological response to interferon therapy in chronically infected patients. J Clin Microbiol. 2005;43:2363-2369.

Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124:188-195.

Lee JJ, Liu DD. A predictive probability design for Phase II cancer clinical trials. Clin Trials. 2008;5:93-106.

Leung ACF, Kummar S, Agarwala SS, Nemunaitis JJ, Gonzales R, Dabrick JJ, et al. Phase 1b/2, open label, multicenter, study of intratumoral SD-101 in combination with pembrolizumab in anti-PD-1 naive and experienced metastatic melanoma patients. J Clin Oncol. 2017;35 (abstr 9550).

Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF, Feldman HI, et al. A New Equation to Estimate Glomerular Filtration Rate. Ann Intern Med. 2009;150:604-612.

Maude SL, Barrett D, Teachey DT, Grupp SA. Managing cytokine release syndrome associated with novel T cell-engaging therapies. Cancer J. 2014;20:119-222.

Milhem M, Gonzales R, Medina T, Kirkwood JM, Buchbinder E, Mehmi I, et al. Intratumoral toll-like receptor 9 (TLR9) agonist, CMP-001, in combination with pembrolizumab can reverse resistance to PD-1 inhibition in a phase Ib trial in subjects with advanced melanoma. [Abstract #CT144] AACR Annual Meeting, April 17, 2018; Chicago, Illinois.

Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Statistics Med. 2008;27:2420-2439.

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

Northfelt D, Ramanathan R, Cohen P, Von Hoff D, Weiss G, Dietsch G, et al. A Phase I Dose-Finding Study of the Novel Toll-like Receptor 8 Agonist VTX-2337 in Adult Subjects with Advanced Solid Tumors or Lymphoma. Clinical Cancer Research. 2014;20(14):3683-3691.

NYHA: The Criteria Committee of the New York Heart Association (NYHA). Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th Ed. Boston, Mass: Little, Brown & Co. 1994:253-256.

O'Quigley J, Pepe M, Fisher L. Continual Reassessment Method: A Practical Design for Phase I Clinical Trials in Cancer. Biometrics. 1990;46:33-48.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, et al. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009;54:84-90.

Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nature Rev Cancer. 2012; 12:252-264.

Pashenkov M, Goëss G, Wagner C, Hörmann M, Jandl T, Moser A, et al. Phase II Trial of a Toll-Like Receptor 9–Activating Oligonucleotide in Patients With Metastatic Melanoma. Journal of Clinical Oncology. 2006;24(36):5716-5724.

Paulos CM, Carpenito C, Plesa G, Suhoski MM, Varela-Rohena A, Golovina TN, et al. The Inducible Costimulator (ICOS) Is Critical for the Development of Human TH17 Cells. Sci Transl Med. 2010;2:55-78.

Riella, L.V., S. Dada, L. Chabtini, B. Smith, L. Huang, P. Dakle, B. Mfarrej, F. D'Addio, L.-T. Adams, N. Kochupurakkal, A. Vergani, P. Fiorina, A.L. Mellor, A.H. Sharpe, H.

Yagita, and I. Guleria. 2013. B7h (ICOS-L) Maintains Tolerance at the Fetomaternal Interface. The American Journal of Pathology 182:2204-2213.

Schmidt M, Kapp K, Oswald D, Matthias S, Wittig B, Zurlo A. Pharmacokinetic and pharmacodynamic data of the immunotherapeutic TLR-9 agonist MGN1703 from healthy volunteers and cancer patients. Journal of Clinical Oncology. 2015;33(15_suppl):abstract e14015.

Schmoll H-J, Wittig B, Arnold D, Riera-Knorrenschild J, Nitsche D, Kroening H, et al. Maintenance treatment with the immunomodulator MGN1703, a Toll-like receptor 9 (TLR9) agonist, in patients with metastatic colorectal carcinoma and disease control after chemotherapy: a randomised, double-blind, placebo-controlled trial. Journal of Cancer Research and Clinical Oncology. 2014;140(9):1615-1624

Schwartz LB. Diagnostic value of tryptase in anaphylaxis and mastocytosis. Immunol Allergy Clin. 2006; 26:451-463

Taveira da Silva AM, Kaulbach HC, Chuidian FS, Lambert DR, Suffredini AF, Danner RL. Brief report: shock and multiple-organ dysfunction after self-administration of Salmonella endotoxin. N Engl J Med. 1993;328(20):1457-60.

van Eijk LT, Pickkers P, Smits P, Bouw MP, van der Hoeven JG. Severe vagal response after endotoxin administration in humans. Intensive Care Med. 2004 Dec;30(12):2279-81. Epub 2004 Oct 26.

Vosika G, Barr C, Gilbertson D. Phase-I study of intravenous modified lipid A. Cancer Immunology Immunotherapy. 1984;18(2).

Wacholtz MC, Patel SS, Lipsky PE. Patterns of costimulation of T cell clones by cross-linking CD3, CD4/CD8, and class I MHC molecules. J Immunol. 1989 Jun 15;142(12):4201-12.

Wakamatsu E, Mathis D, Benoist C. Convergent and divergent effects of costimulatory molecules in conventional and regulatory CD4+ T cells. Proc Natl Acad Sci U S A. 2013 Jan 15;110(3):1023-8. doi: 10.1073/pnas.1220688110. Epub 2012 Dec 31

Weber JS, Kahler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol. 2012;30:2691-2697.

Weihrauch M, Richly H, von Bergwelt-Baildon M, Becker H, Schmidt M, Hacker U, et al. Phase I clinical study of the toll-like receptor 9 agonist MGN1703 in patients with metastatic solid tumours. European Journal of Cancer. 2015;51(2):146-156.

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

12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ADA	Antidrug antibody
AE	Adverse event(s)
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
BAL	Bronchoalveolar lavage
cfDNA	Cell-free DNA
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CrCl	Calculated creatinine clearance
C_{max}	Maximum observed concentration
CNS	Central nervous system
CPMS	Clinical Pharmacology Modeling and Simulation
CR	Complete response
CRP	C-reactive protein
CSR	Clinical Study Report
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
CV	Cardiovascular
DILI	Drug-induced liver injury
dL	Deciliter
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram(s)
ECOG	Eastern Cooperative Oncology Group
EOI	End of infusion
eCRF	Electronic case report form
FACTS	Fixed and Adaptive Clinical Trial Simulator
Fc	Fragment crystallizable region
FcR	Fragment crystallizable region receptor
FDG-PET	Fluorodeoxyglucose-positron-emission tomography
FSH	Follicle stimulating hormone
FTIH	First time in human
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GFR	Glomular filtration rate
GGT	Gamma-glutamyltransferase
GSK	GlaxoSmithKline

h	Hour(s)
HPV	Human papillomavirus
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFN	Interferon
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IL-10	Interleukin 10
INR	International normalized ratio
irAE	Immune-related adverse event(s)
IRB	Institutional Review Board(s)
irRECIST	Immune-related RECIST
IV	Intravenous
kg	Kilogram(s)
L	Liter
LPS	lipopolysaccharide
µg	Microgram
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
min	Minute(s)
mL	Milliliter(s)
mmHg	Millimeters of mercury
MRI	Magnetic resonance imaging
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
ng	Nanogram
NOAEL	No-observed-adverse-effect-level
nTregs	Natural Tregs
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PAMP	Pathogen-associated molecular pattern
PBMC	Peripheral blood mononuclear cell
PD-1	Programmed death receptor-1
PD	Progressive disease
pg	Picogram
PFS	Progression-free survival
PGx	Pharmacogenetics
PK	Pharmacokinetic(s)
PR	Partial response

PS	Performance status
Q1W	Every 1 week
Q3W	Every 3 weeks
QTc	Corrected QT interval duration
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
SAE	Serious adverse event(s)
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable disease
SRM	Study Reference Manual
TCR	T-cell receptor
TDV	Treatment discontinuation visit
TLR4	Toll-like receptor 4
TNBC	Triple-negative breast cancer
TNF	Tumor necrosis factor
TNFR	Tumor necrosis factor receptor
Tregs	Regulatory T-cells
Tr1	Type 1 regulatory
ULN	Upper limit of normal
WOCBP	Women of childbearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
FACTS
KEYTRUDA

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 18 will be performed by local laboratories.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 18 Clinical Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit *RBC Indices*: MCV MCH *WBC count with Differential:* Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry[a]	BUN Creatinine Glucose CrCl (Calculated) Potassium Sodium Calcium AST (SGOT) ALT (SGPT) Alkaline phosphatase C-reactive protein Total and direct bilirubin Total Protein Albumin Lipid panel
Thyroid function	Thyroid stimulating hormone, free T4, free T3
Routine Urinalysis	Specific gravity pH, glucose, protein, blood and ketones by dipstick Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	Hepatitis B (HBsAg) Hepatitis C (Hep C antibody) Serum or urine β-hCG Pregnancy test (as needed for WOCBP)

a. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8 and Section 7.2.2.3 . Laboratory assessments required for follow up after a liver event may require submission to the central lab. Details came be found in the SRM and Central Laboratory Manual.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; HBsAg = Hepatitis B surface antigen; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; RBC = red blood cells; WBC = white blood cells

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the CSR. 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 participants, 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.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final CSR/equivalent summary or as locally agreed. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Data Management

- For this study participant data will be entered into GSK defined eCRFs, transmitted electronically to GSK or designee, and combined with data provided from other sources in a validated data system.
- 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.
- AEs and concomitant medications terms will be coded using MedDRA and an internal validated medication dictionary, GSKDrug.
- The eCRFs (including queries and audit trails) will be retained by GSK, and copies will be made available to the investigator to maintain as the investigator copy. Participant initials will not be collected or transmitted to GSK according to GSK policy.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the SRM.

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • 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 study treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to underlying disease). • 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 before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug 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 it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses 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. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• 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 participant'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

participant's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which 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.

Definition of SAE

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).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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 inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant 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. Hospitalization to satisfy protocol-recommended observation of vital sign trends should not be considered a SAE if done for logistical purposes alone.

Complications that occur during hospitalization are AE. 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 persistent disability/incapacity

- 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 with 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 SAE 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 participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include 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 International harmonized ratio (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 participants receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form. • Refer to Section 7.2.2.3 for the required liver chemistry follow-up instructions

Definition of Cardiovascular Events

CV Events 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

Recording AE and SAE

AE 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) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant'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 case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will grade it according to the NCI-CTCAE v4.0

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/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 underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in 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 in which 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 before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- 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 participant dies during participation in the study or during a recognized follow-up period, the investigator may be asked to provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

Reporting of SAE 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
- If the electronic system is unavailable, the site will use the paper SAE data collection tool as outlined in the SRM. Site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.
- 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 participant 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 to the Medical Monitor by

telephone.

- Contacts for SAE reporting can be found in the SRM.

12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Female participant: is eligible to participate if she is not pregnant (as confirmed by a negative serum beta-human chorionic gonadotrophin), not lactating, and at least one of the following conditions applies:

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with **1** of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 19.

Table 19 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

b. Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case 2 highly effective methods of contraception should be utilized during the treatment period and for at least 120 days after the last dose of study treatment

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 participants understand how to properly use these methods of contraception. This list does not apply to WOCBP with same sex partners, when this is their preferred and usual lifestyle or for participants who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test
- Additional pregnancy testing should be performed at monthly intervals during the treatment period and at 120 days after the last dose of study treatment and as required locally
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected

Collection of Pregnancy Information

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, 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 participant's pregnancy.
- Participant 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 for medical reasons 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. 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 participant who becomes pregnant while participating

- Will discontinue study medication or be withdrawn from the study.

12.6. Appendix 6: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.
- DNA samples will be used for research related to GSK1795091, GSK3359609, GSK3174998, and pembrolizumab in combination with GSK1795091 or advanced solid tumors and related diseases. They may also be used to develop tests/assays including diagnostic tests related to GSK1795091, GSK3359609, GSK3174998, and pembrolizumab combination treatment or study treatments of this drug class, and advanced solid tumors. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome as appropriate.
- DNA samples will be analyzed if it is hypothesized that this may help further understand the clinical data.
- DNA samples will be analyzed by using appropriate descriptive and/or statistical analysis methods. A detailed description of any planned analyses will be documented in a RAP prior to initiation of the analysis.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to GSK1795091, GSK3359609, pembrolizumab and GSK3174998 or study treatments of this class. The results of genetic analyses may be reported in the CSR or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK1795091, GSK3359609, GSK3174998, and pembrolizumab combination treatment or study treatments of this class or advanced solid tumors and related diseases continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

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 participants who are most likely to benefit from a particular therapeutic product;
- Identify participants 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

- Identify participants in the population for whom the therapeutic product has been adequately studied, and found safe and effective, i.e., there is insufficient information about the safety and effectiveness of the therapeutic product in any other population

Global regulatory requirements for IVD companion diagnostic tests are evolving. If a DNA-based IVD companion diagnostic device might be needed to identify participants who are appropriate for the GSK medicinal product(s) under investigation in this protocol, then GSK should collect and retain DNA samples from participants who carry the genetic variant of interest as well as DNA samples from participants who do not carry the genetic variants of interest to validate the performance of the companion diagnostic. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis. Any IVD companion diagnostic research objectives should be described in participant informed consent forms.

12.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Phase I/II liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Phase I/II liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
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

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline[6] (see **MONITORING** below) • **Do not restart/rechallenge** participant with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to Section 12.7.1) • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and may continue participant in the study for any protocol specified follow up assessments	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • 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 PK analysis, obtained within 28 days after last dose[6]. • Serum creatine phosphokinase and lactate dehydrogenase. • 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

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 participants twice weekly until liver chemistries resolve, stabilize or return to within baseline[6] • 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 participants weekly until liver chemistries resolve, stabilize or return to within baseline[6]	concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications • Record alcohol use on the liver event alcohol intake 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 assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, MRI, or CT) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant 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 participants 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. For the purpose of these guidelines "baseline" refers to laboratory assessments performed closest and prior to first dose of study treatment

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

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
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	• Notify the medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline [1] • If at any time participant meets the liver chemistry stopping • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline[1].

1. for the purpose of these guidelines "baseline" refers to laboratory assessments performed closest and prior to first dose of study treatment

12.7.1. Liver Safety Drug Restart or Rechallenge Guidelines

In Canada, if liver chemistry stopping criteria are met, participants will not be allowed to restart study drugs or be rechallenged.

If participant meets liver chemistry stopping criteria do not restart/rechallenge participant 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 participant

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

1. 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 1 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)
- participant currently exhibits severe liver injury defined by: ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total), or INR≥1.5
- serious AE 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 DILI. Because of the risks associated with rechallenge after DILI this should only be considered for a participant 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 participant who is receiving compelling benefit (partial response or complete response) with study treatment that exceeds risk, and no effective alternative therapy is available.
- The ALT at the time of rechallenge is <3xULN.
- The participant did not have additional risk factors for a fatal outcome following the initial injury including hypersensitivity, jaundice, bilirubin >2xULN (direct bilirubin >35% of total), or INR >1.5.
- IRB or IEC approval for rechallenge with study treatment must be obtained, as required.
- If the rechallenge is approved by GSK Medical Governance in writing, the participant 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 participant 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.
- Participants 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, participant meets protocol-defined liver chemistry stopping criteria, study treatment should be permanently discontinued.
- Medical Monitor, and the IRB or IEC as required, must be informed of the participant's outcome following study treatment rechallenge.
- GSK to be notified of any AEs, as per Appendix 4.

2. 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

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).
- Possible study treatment-induced liver injury has been excluded by the investigator and the study team. This includes the absence of markers of hypersensitivity (otherwise unexplained fever, rash, eosinophilia). Where a study treatment has an identified genetic marker associated with liver injury (e.g., lapatinib, abacavir, amoxicillin/clavulanate), the presence of the marker should be excluded. If study treatment-related liver injury cannot be excluded, the guidance on rechallenge in Section 8.1.1.1 will apply.
- There is no evidence of alcoholic hepatitis.
- IRB or IEC approval of study treatment restart must be obtained, as required.
- If restart of study treatment is approved by GSK Medical Governance in writing, the participant 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 participant 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.
- Participants 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, participant meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.

- Medical Monitor, and the IRB or IEC as required, must be informed of the participant's outcome following study treatment restart.
- GSK to be notified of any AEs, as per Appendix 4.

12.8. Appendix 8: Country-specific requirements: Canada

The following country specific requirements apply to Canada only:

Section # and Name	Country Requirement
Section 5.1, Overall Design	Participants with confirmed PR or CR will be followed for response duration and may be eligible **(outside of Canada)** for continued study treatment at the time of relapse/progression. The decision whether a participant will receive additional treatment will be discussed and agreed upon by the treating investigator and the Sponsor/Medical Monitor on a case-by-case basis.
Section 2, Schedule of Activities and Section 9, Study Assessments and procedures, Section 9.5.1, Blood Sample Collection and Section 10.3.2.3, Immunogenicity	Section 2: • **Two bullets below do not apply to those sites in Canada**. • The timing and number of planned study assessments, including safety, laboratory, imaging, tumor biopsy, pharmacokinetic (PK), and pharmacodynamic/biomarker assessments included in the tables below 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. • Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The Institutional Review Board (IRB)/ Independent Ethics Committees (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). Section 9: The timing and number of planned study 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 for the following assessments: safety, PK, pharmacodynamics/biomarker, or other assessments (not applicable for participants in Canada). Section 9.5.1: The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring. **Any change to the number and timing of PK samples is not applicable for participants enrolled in Canada**.

Section # and Name	**Country Requirement**
	Section 10.3.2.3: 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 **(any change to the number and timing of immunogenicity samples is not applicable for participants enrolled in Canada).**
Section 7.2.2.3, Management of Hepatotoxicity, Section 8.1.1.1, Study Treatment Restart and Rechallenge and Section 12.7.1, Liver Safety Drug Restart or Rechallenge Guidelines	**In Canada, if liver chemistry stopping criteria are met, participants will not be allowed to restart study drugs or be rechallenged.**

12.9. Appendix 9: Guidelines for Assessment of Disease, Disease Progression and Response Criteria – adapted from RECIST version 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). In the case of skin lesions, documentation by color photography, including a ruler/calipers to measure the size of the lesion, is required [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 optimized 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].

Guidelines for Evaluation of Disease

Measurable and Non-Measurable Definitions

Measurable lesion:

A non-nodal lesion that can be accurately measured in at least 1 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 1 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. Note: non-measurable only disease is not allowed per protocol.

Immune-Related RECIST Response Criteria

Table 20 Evaluation of Target Lesions

New, measurable[a] lesions	Incorporated into tumor burden
New, non-measurable lesions	Do not define progression (but preclude CR)
irCR	Disappearance of all lesions in 2 consecutive observations not less than 4 weeks apart. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
irPR	≥30% decrease in tumor burden compared with baseline in 2 observations at least 4 weeks apart
irSD	30% decrease in tumor burden compared with baseline cannot be established nor 20% increase compared with nadir
irPD[b]	At least 20% increase in tumor burden compared with nadir (at any single time point) in 2 consecutive observations at least 4 weeks apart. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

a. Measurable according to RECIST version 1.1.
b. Treatment decisions may be based upon the immune-related RECIST guidelines.

Antitumor response based on total measurable tumor burden

For Modified RECIST based on RECIST version 1.1 and irRECIST [Wolchok, 2009; Nishino, 2013], the initial target ('index") and measurable new lesions are taken into account. At the baseline tumor assessment, the sum of the diameters in the plane of measurement of all target lesions (maximum of 5 lesions in total and a maximum of 2 lesions per organ representative of all involved organs) is calculated.

Note: If pathological lymph nodes are included in the sum of diameters, the short axis of the lymph node(s) is added into the sum. The short axis is the longest perpendicular diameter to the longest diameter of a lymph node or nodal mass. At each subsequent tumor assessment, the sum of diameters of the baseline target lesions and of new, measurable nodal and non-nodal lesions (≥10 mm), up to 2 new lesions per organ are added together to provide the total tumor burden:

$$\text{Tumor Burden} = \text{Sum of diameters}_{\text{target lesions}} + \text{sum of diameters}_{\text{new, measurable lesions}}$$

Time-point response assessment using the Immune-Related RECIST criteria

Percentage changes in tumor burden per assessment time point describe the size and growth kinetics of both conventional and new, measurable lesions as they appear. At each tumor assessment, the response in index and new, measurable lesions is defined based on the change in tumor burden (after ruling out irPD). Decreases in tumor burden must be assessed relative to baseline measurements (i.e., the sum of diameters of all target lesions at screening).

Response Criteria

Evaluation of target lesions

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

- CR: Disappearance of all target lesions. Any pathological lymph nodes must be <10mm in the short axis.
- 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).
- SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
- 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 1 of the 5 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 <u>not</u> assessed, sum of the diameters <u>cannot</u> 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.

Evaluation of non-target lesions

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

- Complete Response: 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: Unequivocal progression of existing non-target lesions.
- Not Applicable (NA): No non-target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by 1 of the 4 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.
- 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").

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.

Evaluation of overall response

Table 21 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 participants with measurable disease at baseline.

Table 21 Evaluation of Overall Response for Participants 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

Note:

- Participants 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.

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 the first dose at a minimum interval of the first scheduled tumor evaluation.
- 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, participants lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

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.

12.10. Appendix 10: CKD-EPI Formula

Chronic Kidney Disease (CKD) stage: Kidney Disease Outcomes Quality Initiative CKD stages 3/4/5 defined by estimated glomular filtration rate (GFR) using the CKD Epidemiology Collaboration formula [Levey, 2009].

$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black]

where:
S_{cr} is serum creatinine in mg/dL,
κ is 0.7 for females and 0.9 for males,
α is -0.329 for females and -0.411 for males,
min indicates the minimum of S_{cr}/κ or 1, and
max indicates the maximum of S_{cr}/κ or 1.

12.11. Appendix 11: Adverse Events of Special Interest

The list of terms and reporting requirements for AESI are provided below. These are selected non-serious AEs and SAEs that **must be reported to the GSK medical monitor within 24 hours** regardless of relationship to study treatment. Any event that meets the criteria described below must be reported regardless of investigator-determined relationship to study treatment or if considered immune-related (unless otherwise specified). Investigators/study coordinators/designated site personnel are required to record these experiences in the eCRF (as described in the eCRF completion guidance document) and to provide supplemental information (such as medical history, concomitant medications, investigations, etc.) about the event.

Cytokine-related AEs

Cardiopulmonary or hemodynamic toxicity starting within 24 hours of study treatment that requires >40% FiO2, vasopressor administration, antiarrhythmic agent or other significant medical intervention. Asystole, as measured by ECG, or bradycardia that is symptomatic and requires medical intervention.

Immune-related AEs

Pneumonitis (reported as AESI if ≥ Grade 2)		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis (reported as AESI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine (reported as AESI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis	Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA)	
Endocrine (reported as AESI)		
Type 1 diabetes mellitus (if new onset)		
Hematologic (reported as AESI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic Thrombocytopenic Purpura (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Hemolytic Uremic Syndrome (HUS)
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic (reported as AESI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Hepatitis	Autoimmune hepatitis	Transaminase elevations (ALT and/or AST)
Infusion Reactions (reported as AESI for any grade)		
Allergic reaction	Anaphylaxis	

Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic (reported as AESI for any grade)		
Autoimmune neuropathy	Guillain-Barré syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular (report as AESI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Uveitis	Iritis	
Renal (reported as AESI if ≥ Grade 2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as AESI if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin (reported as AESI for any grade)		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		
Skin (reported as AESI if ≥ Grade 3)		
Pruritus	Rash	Rash generalized
Rash maculo-papular		
Any rash considered clinically significant in the physician's judgment		
Other (reported as AESI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

12.12. Appendix 12: ECOG Performance Status[a]

Grade	Descriptions
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.	

a. Oken, 1982.

12.13. Appendix 13: mAb Monotherapy Dosing Period

The following information is a guidance for participants who are treated with mAb monotherapy.

Schedule of Activities in Section 2 should be followed with the following clarifications:

Table 1: Part 1 Dose Escalation and PK/Pharmacodynamic Cohorts: Safety, Laboratory, Efficacy, Study Treatment Procedures

1. Vital Signs: Predose mAb and mAb EOI+2h. After 2h, as clinically indicated.
2. ECG: As single measurement, Predose mAb and mAb EOI+2h. After 2h as clinically indicated.
3. Optional Consent Procedures
    a. Tumor Biopsies: Participants can opt out of the optional procedure including those in the PK/PD cohort.
    b. Telephone Interview: Participants can opt out of the optional procedure
4. PK/PD subjects: Participants can opt out of the mandatory fresh biopsy required at Week 9. Optional Week 12 fresh biopsy is not mandatory per protocol.

Table 2: Part 1 Dose Escalation and PK/Pharmacodynamics Cohorts: Pharmacokinetic, Pharmacodynamic, Anti-drug Antibody, and Genetic Assessments

Scheduled assessments will not be collected. However, event-driven collections (e.g. in response to hypersensitivity including infusion reactions) will be performed per Table 2 (footnote h and i) and Section 10.3.2.3.

12.14. Appendix 14: COVID-19

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.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 should be noted in participant notes and recorded as a COVID-19 protocol deviation.

12.15. Appendix 15 : Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1 08-December-2017

Overall Rationale for the Amendment: Amendment 1 incorporates changes to the protocol as requested by the United States Food and Drug Administration (FDA).

Section # and Name	Description of Change	Brief Rationale
Whole Document	• Administrative corrections of minor typographical, and/or inconsistent language throughout the protocol	Provide clarity and correction
Synopsis	• Updated study design to remove 240 mg dose level of GSK3174998 • Reduced overall number of study participants in line with the removal of the GSK3174998 240 mg dose level	Updated in line with main document
Section 2 SoA	Table 1 and Table 3: • Added additional vital sign and ECG monitoring at specified study visits • Removal of Circulating Tumor Cells (CTC) collection Table 2 and Table 4: • Added additional GSK1795091 PK assessments at 2 hours and 4-hour post GSK1795091 injection at Day 1 to align with ECG assessments	Table 1 and Table 3: • Additional monitoring and alignment of ECG assessments with PK GSK1795091 assessments as requested by FDA • Clarified timing of predose GSK1795091 and GSK3174998 vital sign and ECG assessments • Expected limited expression of CTCs in this patient pollution. Table 2 and Table 4: • Request of FDA to capture the PK profile after intravenous injection coinciding with ECG assessments
Section 5,	Section 5.1, Section 5.4, Section	Updated as requested and agreed with

Section # and Name	Description of Change	Brief Rationale
Study Design	5.5: • Updates made through out section to remove GSK3174998 240 mg dose level in Part 1 Dose Escalation and Part 2 Expansion Cohort and confirm one dose of GSK3174998 (24 mg) to be used in combination with GSK1795091 • Included GSK3174998 -1 dose level (8 mg) in case dose reduction is needed below GSK3174998 24 mg + GSK1795091 50 ng • Updated DLT criterial in Table 6 Section 5.2, Number of Participants: • Reduced overall number of study participants in line with the removal of the GSK3174998 240 mg dose level	FDA
Section 6, Study Population	Updated inclusion criteria for participants in Part 2	Provided additional inclusion criteria for prior lines of treatment
Section 7, Treatments Administered	• Added additional safety monitoring following first dose of GSK1795091 and first two doses of combination GSK3174998 and GSK1795091 • Clarified meaning of phrase, “that requires oxygen > 40%” by replacing text with “oxygen >40% FiO2”. Also updated in Section 5/DLT criteria • Updated Table 8	• Extended duration of monitoring for AEs including changes to vital signs and ECGs following first doses of GSK1795091 monotherapy and in combination with GSK3174998 • Clarification supported by publication Lee et al • Table updated to remove 240 mg dose

Section # and Name	Description of Change	Brief Rationale
		of GSK3174998
Section 7.3	Removed direction to register participants into GSK registration and medication ordering system	System will not be used for participant registration. Study Reference Manual will include details for participant registration and enrollment
Section 10, Statistical Considerations and Data Analysis (10.1, 10.3.4, 10.4.2) Immunogenicity Analysis (10.3.2.3)	• Removed reference to two cohorts in Part 2 Expansion Cohort • Added option for development of a neutralizing ADA assay	• 240 mg dose level of GSK3174998 removed • Included per recommendation from FDA to allow for further characterization of stored samples
Section 12.7.1, Liver Safety Drug Restart or Rechallenge Guidelines	Added additional criteria for consideration of rechallenge with study treatment after a liver event	Criteria added to increase safeguards when considering possible study treatment rechallenge

Amendment 01, Country Specific (Canada) 06-MAR-2018

Overall Rationale for the Amendment: Prot-Ament1-CAN-1 incorporates changes to the protocol specific to sites in Canada only as requested by and agreed with Health Canada.

Section # and Name	Description of Change	Brief Rationale
Section 5.1, Overall Design	Removed text to allow participants who progress after confirmed CR or PR to continue on study treatment if in agreement with sponsor and study investigator	Requested by Health Canada to follow stopping rules outlined in the protocol and remove Investigator discretion to request a participant continue to receive study drugs
Section 5.1.1, Part 1: Dose Escalation of GSK1795091 and GSK3174998	Removed text to allow participants who experienced a DLT, unacceptability or an increase in ALT, and not attributable to another cause, to continue on study treatment if in agreement with investigator and sponsor	Requested by Health Canada to follow stopping rules outlined in the protocol that a participant experiencing DLT or unacceptable toxicity stop study treatment

Section # and Name	Description of Change	Brief Rationale
Section 5.1.3, Alternative Dosing Schedule	Removed text that an alternative dosing schedule for GSK1795091 may be evaluated if emerging data suggest that the protocol-specified schedule will result in excessive toxicity or limited efficacy	Requested by Health Canada that any change to protocol dosing schedule will require a protocol amendment
5.1.4, Dose-Limiting Toxicity	Removed text to allow participants who experienced a DLT to continue on study treatment if in agreement with sponsor and study investigator	Requested by Health Canada to follow stopping rules outlined in the protocol and remove Investigator discretion to request a participant continue to receive study drugs
Section 2, Schedule of Activities and Section 9, Study Assessments and procedures, Section 9.5.1, Blood Sample Collection and Section 10.3.2.3, Immunogenicity	Removed text to allow adjustment for the timing and number of planned study assessments during the course of the study based on newly available data.	Requested by Health Canada that any change to timing or number of study assessments will require a protocol amendment
Section 7.2.2.3, Management of Hepatotoxicity, Section 8.1.1.1, Study Treatment Restart and Rechallenge and Section 12.7.1, Liver Safety Drug Restart or Rechallenge Guidelines	Added text that the option to restart or rechallenge study treatment following meeting the liver chemistry stopping criteria will not apply for participants in Canada	Requested by Health Canada to follow stopping rules outlined in the protocol and remove option to restart or rechallenge after liver stopping event
Section 10.1, Sample Size	Added text describing the application of enrolment stopping rules to document how the criteria	Clarify the proposed sample size and enrollment stopping rules for Part 2

Section # and Name	Description of Change	Brief Rationale
Determination	in Table 17 and assessment of futility will be applied for Part 2 Expansion Cohort.	Expansion Cohort

Amendment 2 25-JUL-2018

Overall Rationale for the Amendment: Amendment 2 incorporates changes to the protocol to consolidate Canada country-specific amendment 01 CAN-1 and include two additional immunotherapy combination partners.

Section # and Name	Description of Change	Brief Rationale
Whole Document	• Administrative corrections of minor typographical, and/or inconsistent language throughout the protocol • Language updated throughout to add two treatment arms: GSK1795091 with GSK3359609, and GSK1795091 with pembrolizumab • Combined with country-specific (Canada) protocol amendment	• Provides clarity and correction • To expand the assessment of GSK1795091 administered in combination with other immunotherapies • Incorporates changes requested by Health Canada in the country-specific amendment into global document
Synopsis	• Aligned with changes to study design and participant number in main text	• Updated in line with main document
Section 2 SoA	Table 1, Table 3: • Added evaluations for new treatment arms • Added microbiome specimen collection Table 2, Table 4: • Added assessments for new treatment arms	Table 1, Table 3: • Provides instruction for new treatment arms Table 2, Table 4: • Provides instruction for new treatment arms
Section 3 Introduction	• Added background information and rationale for targeting ICOS and PD-1 in combination	• Supports decision to include new treatment arms

Section # and Name	Description of Change	Brief Rationale
	with GSK1795091 • Added risk considerations for GSK3359609 and pembrolizumab in Risk Assessment table	
Section 4 Objectives and Endpoints	• Added exploratory endpoint for Microbiome Analysis • Added exploratory endpoint for PK of combination partners	• Provides additional information for new treatment arms
Section 5, Study Design	Section 5.1, Overall Design • Study schematic updated • Exclusions to Canadian participants identified • Table 5 removed from Section 5.2, Number of Participants • Part 2 numbers increased to reflect new treatment combinations	• Provides specific instructions for conducting modified study
Section 6, Study Population	• Updated inclusion and exclusion criteria for participants in Part 2c	• Provides additional criteria for prior lines of treatment
Section 7, Treatments Administered	• Updated Table 8 and Table 9 • Added Table 10 and Table 11	• Includes descriptions for GSK3359609 and pembrolizumab • Dose Modification and Treatment Guidelines presented in table format
Section 8, Discontinuation Criteria	• Added withdrawal of subjects is to be based on an average QTcF value of triplicate ECGs	• Clarification of QTcF Stopping Criteria
Section 9, Study Assessments	• Added description for Stool Specimen collection	• Provides direction for sample collection
Section 10,	• Clarifications to sample size	• Provides updated numbers of study

Section # and Name	Description of Change	Brief Rationale
Statistical Considerations and Data Analysis	determination to account for new treatment arms	participants
Section 11, References	• References added for ICOS and pembrolizumab information	• Supports new treatment arms

Amendment 3 14-SEP-2018

Overall Rationale for the Amendment: Amendment 3 incorporates changes to the protocol to include the most recent information for pembrolizumab combination studies and changes to biomarker sample collections to evaluate TLR4 responses.

Section # and Name	Description of Change	Brief Rationale
Section 2 Schedule of Activities Tables	Biomarker sample collection aligned with TLR4 dosing	Ensures cytokine response data and flow cytometry data collected at consistent times post TLR4 administration to evaluate TLR4 responses as opposed to the combination partners
Section 3.2.4.1 Clinical Experience in Combination with other TLR Agonists	Conclusions from other pembrolizumab studies and the frequency of cytokine-associated AEs and were included	Alignment with the updated CRA report
Section 3.2.5 Combination Background	Pembrolizumab survival curve duration updated	Alignment with published report
Section 3.3.1 Risk Assessment Table	Information added to CRS Mitigation Strategies	Provides additional information on risk mitigation
Section 5.5.1.5 Combination Considerations	Dose justifications for combination treatments were added	Alignment with the updated CRA report
Section 7.2.1 General Guidelines for Cytokine-Related Adverse Events and Infusion Reactions	Clarification of verbatim terms used to report “cytokine-related AEs” or “infusion reactions”	Provides instruction on AE terminology
Section 12.11 Adverse Events of Special Interest	Cytokine Release Syndrome removed from Infusion Reactions (reported as AESI for any grade)	Provides instruction on AE terminology
Whole Document	Minor typographical errors corrected, clarifications and formatting changes	

Amendment 4: 12-AUG-2019

Overall Rationale for the Amendment: Amendment 4 incorporates changes to the protocol to include the most recent safety information, changes to futility stopping criteria and biomarker sample collections.

Section # and Name	Description of Change	Brief Rationale
Section 2 Schedule of Activities Tables	Number of biomarker and clinical chemistry samples collected increased	Ensures sufficient cytokine response data and flow cytometry data collected to evaluate TLR4 responses
Section 2 Schedule of Activities Tables	Table 1:Footnote for tumor biopsy clarified to state biopsy can be collected next visit if missed for treatment delay	Ensures appropriate biopsy sample may be collected
Section 2 Schedule of Activities Tables	Table 4:Footnotes for immunogenicity and hypersensitivity reactions clarified that participants will be with drawn from treatment, not study	Clarification
Section 3.2.1.2.1	Descripton of another participant with elevated ALT added from new safety data	Accuracy and completeness of safety data
Section 5.1	Minimum number of participants in the Part 2 expansion cohorts changed from 6 to 8	Improves chances of seeing efficacious response
Section 5.1.3	Text added to describe replacement of participants with DLT	Clarification
Section 5.2	Text added to describe the replacement of participants in Part 2	Clarification
Section 6	Modified requirements for previous therapy	More reflective of real-world study population
Section 7 Table 8	Removed unit dose strength and dosing instructions	Available in the investigator's brochure
Section 7.2	Stated AEs wil be graded by NCI-CTCAE unless otherwise specified	Include Lee 2014 reference
Section 10	Alternative hypothesis adjusted based on change to minimum numbers, Table 19 and Table 20 updated	Reflects change to minimum number of participants
Whole document	References updated	New references available

Amendment 5: 02-Mar-2020

Overall Rationale for the Amendment: Amendment 5 addresses mAb monotherapy (GSK3174998, GSK3359609, or pembrolizumab) and the activities that are modified for this occurrence.

Section # and Name	Description of Change	Brief Rationale
Section 2 Schedule of Activities Tables: Table 1 and Table 2	Footnote added to direct reader to Appendix 13 for SOA modifications.	Ensures that only those activities that are required are collected from the participant. Reduces burden on participant.
Section 7.2 Dose Modification	Included language allowing continued treatment if only mAb monotherapy is administered.	Provides instruction for continuing in the trial on mAb monotherapy
Appendix 13: mAb Monotherapy Dosing Period	Added guidance on modifications that should be taken if only mAb monotherapy is administered.	Provided details on the changes to the activities required. Reduces burden on participant.