TITLE PAGE

Protocol Title: A Phase I/II, Open-label, Two Part Study of GSK3359609 in Combination with Tremelimumab in Participants with Selected, Advanced Solid Tumors

Protocol Number: 207871/Amendment 01

Compound Number: GSK3359609

Study Phase: Phase I/Phase II

Short Title: GSK3359609 plus Tremelimumab for the Treatment of Advanced Solid Tumors

Sponsor Name and Legal Registered Address:

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Regulatory Agency Identifying Number(s):

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SPONSOR SIGNATORY:

PPD

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 1	*20-Sep-2018*	*2018N362439_01*
Original Protocol	*03-Aug-2018*	*2018N362439_00*

Amendment 1 [20-SEP-2018]

Overall Rationale for the Amendment: Protocol was amended at the request of a regulatory authority to provide additional clarification and guidance on specific aspects of the protocol as described in the table below.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 1.3 Schedule of Activities	SoA line for EQ-5D needs to change in notes/footnote from Week 21 to Week 22	Correct typo.
Section 7.1.1 Discontinuation of Study Treatment	Clarification of the RECIST guideline to be followed in allowing continuation of study treatment beyond progression: original text was by iRECIST; the revised text is by RECISTv1.1	Request of the regulatory authority,
Section 7.1.3: Stopping Rules for Clinical Deterioration	Clarification that the decrease in the ECOG represents a worsening of performance status from baseline.	Request by the regulatory authority.
Section 8.1.3.1	Jensen references (2) have incorrect years (2014 changed to 2015 and the 2016 changed to 2017)	Corrected typos
Section 10.6.2.1: Rechallenge Following Liver Stopping Events that are Possibly Related to Study Treatment	Modified the first bullet (addition underlined) to read, "Investigator requests consideration of <u>rechallenge</u> with study treatment for a participant who is receiving compelling benefit <u>(partial response or complete response)</u> with study treatment that exceeds risks, and no effective alternative therapy is available. Add the following requirements: • The ALT at the time of	Request by the regulatory authority.

Section # and Name	Description of Change	Brief Rationale
	rechallenge is <3x ULN • The participant did not have additional risk factors for a fatal outcome following the initial injury including hypersensitivity, jaundice, bilirubin >2x ULN, (direct bilirubin >35% of total bilirubin), or INR >1.5.	
Section 11. References	Jensen references (2) have incorrect years (2014 changed to 2015 and the 2016 changed to 2017)	Correct typos

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase I/II, Open-label, Two Part Study of GSK3359609 in Combination with Tremelimumab in Participants with Selected, Advanced Solid Tumors

Short Title: GSK3359609 plus Tremelimumab for the Treatment of Advanced Solid Tumors

Rationale: GSK3359609 is an inducible T cell co-stimulator (ICOS) agonist antibody and tremelimumab is a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antagonist antibody. In nonclinical and clinical studies in a variety of tumors, it has been shown that ICOS expression on T cells is upregulated after CTLA-4 treatment. Additionally, ICOS+CD4 T cells have been shown to have a positive association with response in tremelimumab treated chemotherapy-resistant malignant mesothelioma patients. It is hypothesized that the combination of these two agents will provide greater antitumoral response than either agent alone. The purpose of this study is to evaluate if the combination of GSK3359609 and tremelimumab is safe and tolerable (Part 1) and provides significant survival benefit to participants with relapsed/refractory (R/R) Head and Neck Squamous Cell Carcinomas (HNSCC) to warrant further clinical investigation.

Objectives and Endpoints:

PART 1

Objectives	Endpoints
Primary	
• Determine safety, tolerability and the R2PD of GSK3359609 in combination with tremelimumab	• Frequency and severity of DLTs, AEs, AESI, SAEs and AE/SAE/DLTs leading to dose modifications/delays/withdrawals; changes in laboratory, vital signs, and ECG safety assessment parameters
Secondary	
• Evaluate clinical activity of GSK3359609 in combination with tremelimumab	• ORR, DCR
• Characterize the PK properties of GSK3359609 and tremelimumab when administered in combination	• Cmax, Cmin, AUC (0-t) of GSK3359609 and tremelimumab as data permit
• Determine immunogenicity of GSK3359609 and tremelimumab when administered in combination	• Detection and characterization of ADA against GSK3359609 and/or tremelimumab

AEs = adverse events; SAEs = serious adverse events; DLTs = dose limiting toxicities; AESI = adverse events of special interest; RP2D = recommended phase 2 dose; ECG = electrocardiogram; ORR = overall response rate; DCR = disease control rate; Cmax = maximum observed concentration; Cmin = minimum observed concentration; AUC (0-t) = area under the concentration-time curve over the dosing interval; ADA = anti-drug antibodies

PART 2

Objectives	Endpoints
Primary	
• Evaluate clinical activity of GSK3359609 in combination with tremelimumab compared to SOC	• OS
Secondary	
• Further evaluate the clinical activity of GSK3359609 in combination with tremelimumab compared to SOC	• ORR, DCR, PFS, TTR, DoR
• Further evaluate the PK properties of GSK3359609 and tremelimumab when administered in combination	• Cmax, Cmin, AUC (0-t) of GSK3359609 and tremelimumab as data permit
• Further evaluate immunogenicity of GSK3359609 and tremelimumab when administered in combination	• ADA incidence
• Further evaluate the safety and tolerability of GSK3359609 and tremelimumab when administered in combination	• Frequency and severity of AEs, AESI, SAEs and AE/SAEs leading to dose modifications/delays/withdrawals; changes in laboratory, vital signs, and ECG safety assessment parameters

OS = overall survival; SOC = standard of care; ORR = overall response rate; DCR = disease control rate; PFS = progression-free survival; TTR = time to response; DoR = duration of response; TCR = T cell receptor; ADA = anti-drug antibodies; AEs = adverse events; SAEs = serious adverse events; Cmax = maximum observed concentration; Cmin = minimum observed concentration; AUC (0-t) = area under the concentration-time curve over the dosing interval.

Overall Design:

This is a Phase I/II, open-label, 2-part study of GSK3359609 in combination with tremelimumab. As shown in Figure 1, Part 1 is dose escalation and will enroll participants with advanced, selected solid tumors and Part 2 is randomized expansion and will enroll participants with R/R HNSCC who have disease progression after receiving at least 1 platinum-based chemotherapy and at least 1 anti-PD-1/PD-L1 therapy, whether in combination or separately. In Part 2, participants will be stratified by line of anti-PD-(L)1 therapy (i.e., received in the first line or second line).

Part 1 dose escalation will initiate with 8 mg GSK3359609 and 75 mg tremelimumab (termed dose level [DL] 1), the planned lowest dose for each agent. The highest planned doses are 80 mg GSK3359609 and 225 mg tremelimumab. GSK3359609 will be administered every 3 weeks and tremelimumab will be administered every 3 weeks for 6 doses, followed by every 12 weeks. Tremelimumab is to be administered first as an IV infusion over 60 minutes. GSK3359609 will be administered as a 30-minute IV infusion beginning at least 1 hour and no more than 2 hours following the end of the tremelimumab infusion. Dose escalation will occur using a zone-based approach; each

zone must clear for safety prior to the next zone being opened to enrollment. Dose escalation will be guided by the bivariate Continuous Reassessment Method (CRM) model until the maximum tolerated dose (MTD) or maximum administered dose (MAD) dose combination(s) are determined. Unplanned dose combinations within the range of the planned doses of each agent may be investigated to support the identification of optimal doses to administer in combination. Additionally, doses lower than planned of either agent may be investigated. PK/pharmacodynamic cohort(s) may be initiated at any DL(s), once safety is cleared, with mandatory paired tumor sample collections to inform on dose selection for Part 2 of the study.

The severity of all toxicities will be graded using National Cancer Institute - Common Toxicity Criteria for Adverse Events (NCI-CTCAE) (version 5.0). The DLT observation period is 28 days in length and begins on the day GSK3359609 and tremelimumab are first administered to the participant.

A single dose combination will be selected as the recommended Phase 2 dose (RP2D) and carried forward from Part 1 into Part 2. The totality of data will be used to determine whether to proceed to Part 2 and which dose combination will be chosen as the RP2D.

Part 2 expansion is randomized and open-label to evaluate the efficacy of the selected RP2D dose combination compared to the Investigator's choice of selected current standard of care (SOC) in the treatment of R/R HNSCC who have progressed after receiving at least 1 platinum-based chemotherapy and at least 1 anti-PD-1/PD-L1 therapy, whether in combination or separately. Randomization is 2:1 to the investigational and SOC arms, respectively. Part 2 will also characterize PK and pharmacodynamic effects. Additional tumor type cohorts may be added either as a single arm expansion or with an appropriate comparator if a signal is identified in Part 1, based on the totality of the evidence and would be the subject of a future amendment.

Disclosure Statement: Part 1 is a single group treatment part with 1 arm. Part 2 is a parallel group random treatment assignment part with 2 arms.

Number of Participants: Approximately 114 participants will be enrolled in this study; up to 24 in Part 1 and 90 in Part 2.

Intervention Groups and Duration: The study is comprised of 3 periods (further details in the Schedule of Activities (SoA).

Screening: Participants may sign the informed consent form up to 45 days prior to first dose and screening procedures should be completed within 30 days prior to first dose or as described in the SoA.

Treatment: Study intervention is defined as GSK3359609 in combination with tremelimumab and in Part 2, participants will be randomized to study intervention or SOC (Part 2 only; Investigator's choice of paclitaxel, docetaxel or cetuximab). Participants will receive study intervention or SOC until disease progression, unacceptable toxicity or death.

Follow-up: Participants will be followed for survival and subsequent anticancer therapy once study intervention/SOC has been discontinued. Note: Participants who discontinue

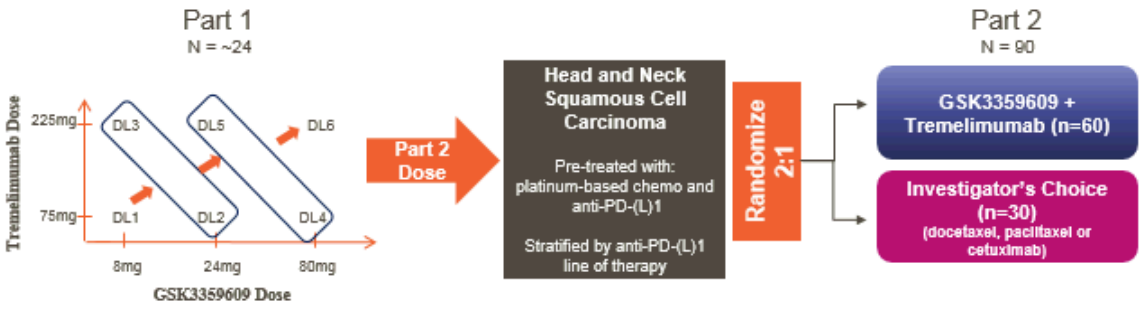
study intervention/SOC prior to progression or prior to confirmed progression by iRECIST will also be followed for progression or confirmation of progression by iRECIST.

The total duration of study participation begins with the signing of the informed consent form (ICF) through the final protocol-defined follow-up assessment for survival and is estimated to be up to 4 years (~2 years on treatment and ~2 years in survival follow-up); however, participants deriving benefit may be on study intervention beyond 2 years.

Data Monitoring Committee: There will not be a formal data monitoring committee for this study. The Dose Escalation and Selection Plan will describe the process for making dose escalation/selection decisions and responsible personnel.

1.2. Schema

Figure 1 Study Design Schema



1.3. Schedule of Activities (SoA)

Protocol waivers or exemptions are not allowed except for immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Schedule of Activities, are essential and required for study conduct.

The following points must be noted:

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

1. 12-lead ECG
2. Vital signs
3. Blood draws (e.g., PK blood draws)

Note: Other assessments not listed may occur at any time; however, the timing of ALL the assessments must allow the blood draw to occur at the exact nominal time.

Procedure	Screen ng (up to 30 days before Day 1 un ess otherw se noted)	Treatment Period Weeks (±3 days)								Upon conf rmed PR/CR or progress on (±7 days)	TDV*	Fo ow-up (±10 days)	**Notes:** *The assessments required at TDV must be completed within 40 days from the date study intervention or SOC was discontinued and must occur prior to the start of subsequent anticancer therapy. Do not repeat tests that have already been performed within 3 days or scans within 4 weeks of the TDV.
		1; (Day 1)	2	4	7	10	13	16	>16				
Assessments and Safety													
Informed consent	X												ICF can be signed up to 45 days before Day 1.
Inclusion and exclusion criteria	X	X											Recheck criteria prior to first dose. See Section 8.2.6 for further details regarding clinical laboratory test eligibility.
Demography, disease history, medical history (past and current medical conditions), prior anticancer treatments	X												
Enrollment/ Randomization		X											Randomization in Part 2 may occur any time after all eligibility criteria have been confirmed and prior to first dose, taking into consideration on-site availability of study intervention/SOC.
AE/AESI/SAE Review	X										X	X	See Section 8.3.1 for specific details of timeframes to collect each.
Concomitant medication review	X										X	X*	Concomitant medications to be assessed at each visit during the study treatment period. *Concomitant medications used to treat AEs/AESI/SAEs during the follow-up period are to be reported.

Procedure	Screen ng (up to 30 days before Day 1 un ess otherw se noted)	**Treatment Period Weeks (±3 days)**							Upon conf rmed PR/CR or progress on (±7 days)	TDV*	Fo ow-up (±10 days)	**Notes:** *The assessments required at TDV must be completed within 40 days from the date study intervention or SOC was discontinued and must occur prior to the start of subsequent anticancer therapy. Do not repeat tests that have already been performed within 3 days or scans within 4 weeks of the TDV.
		1; (Day 1)	2	4	7	10	13	16	>16			
Physical examination, including height* and weight	X	X		X	X	X	X	X	Q3W		X		Full physical exam required at Screening; brief physical exam thereafter. Exams to be performed and assessed pre-dose. *Height required at Screening only.
Vital signs	X	X		X	X	X	X	X	Q3W		X		Performed and assessed pre-dose.
ECOG PS	X	X		X	X	X	X	X	Q3W		X		Assess pre-dose.
Laboratory assessments*^	X	X+		X	X	X	X	X	Q3W		X		*Includes hematology, clinical chemistry, and urinalysis (see Table 16). Must be drawn pre-dose on dosing days. ^For SOC only: Additionally, any lab results required to administer the SOC agent, per Institutional guidelines, should be collected in the eCRF for each dose administered (e.g., ANC). +Day 1 testing only required if tests performed at Screening were >72 hours from time of scheduled first dose.
Pancreatic Function laboratory testing	X	X		X	X	X	X	X	Q3W		X		Labs taken pre-dose on dosing days.
Thyroid Function laboratory testing	X				X		X		Q6W*		X		Labs taken pre-dose on dosing days. *Week 19 and then Q6W.

Procedure	Screen ng (up to 30 days before Day 1 un ess otherw se noted)	**Treatment Period Weeks (±3 days)**								Upon conf rmed PR/CR or progress on (±7 days)	TDV*	Fo ow-up (±10 days)	**Notes:** *The assessments required at TDV must be completed within 40 days from the date study intervention or SOC was discontinued and must occur prior to the start of subsequent anticancer therapy. Do not repeat tests that have already been performed within 3 days or scans within 4 weeks of the TDV.
		1; (Day 1)	2	4	7	10	13	16	>16				
Serum pregnancy test	X												Required in WOCBP; test must be within 72 hours of time of scheduled first dose of study intervention or SOC.
Hepatitis B, C, HIV laboratory testing	X												If test otherwise performed within 3 months prior to first dose of study intervention or SOC, testing at screening is not required.
Cardiac Function laboratory testing	X												
Coagulation laboratory testing	X												
12-lead ECG	X	X*											*ECGs should be performed pre-dose on Day 1 and then as clinically indicated.
Echocardiogram/MUGA	X												Required at Screening and then as clinically indicated. Same modality to be used throughout study.
Disease Assessments	X					X		X	X*		X^	X^	*Week 22, then Q6W through Week 52, then Q12W. ^Perform as indicated in Section 7.1. Disease assessments after Screening have a window of ±7 days.

Procedure	Screen ng (up to 30 days before Day 1 un ess otherw se noted)	Treatment Period Weeks (±3 days)								Upon conf rmed PR/CR or progress on (±7 days)	TDV*	Fo ow-up (±10 days)	**Notes:** *The assessments required at TDV must be completed within 40 days from the date study intervention or SOC was discontinued and must occur prior to the start of subsequent anticancer therapy. Do not repeat tests that have already been performed within 3 days or scans within 4 weeks of the TDV.
		1; (Day 1)	2	4	7	10	13	16	>16				
Pre-Baseline scans for Tumor Growth Kinetics	X*												*Optional. Up to 3 pre-Screening scans (within 6 months before the Screening scan) will be collected to assess tumor growth rate to support exploratory investigation of tumor growth kinetics.
Survival Follow-up and Anticancer Therapy												Q12W	Follow-up for survival and subsequent anticancer therapy begins once study intervention/SOC has been discontinued.
Study Intervention													
GSK3359609		X		X	X	X	X	X	Q3W				
Tremelimumab		X		X	X	X	X	X	Q12W				
Part 2: SOC		X											Paclitaxel or cetuximab given Q1W; docetaxel given Q3W, as per Table 6.

Procedure	Screen ng (up to 30 days before Day 1 un ess otherw se noted)	Treatment Period Weeks (±3 days)							Upon conf rmed PR/CR or progress on (±7 days)	TDV*	Fo ow-up (±10 days)	Notes: *The assessments required at TDV must be completed within 40 days from the date study intervention or SOC was discontinued and must occur prior to the start of subsequent anticancer therapy. Do not repeat tests that have already been performed within 3 days or scans within 4 weeks of the TDV.
		1; (Day 1)	2	4	7	10	13	16	>16			
PK and Immunogenicity												
Plasma PK GSK3359609		X*	X	X	X	X	X	X	X^+			Participants receiving GSK3359609: Samples drawn pre-dose on treatment visits. Additionally, PK samples are to be collected with every pharmacodynamic sample which is collected on a non-treatment day. See Table 12 for further details. *Additional samples drawn at Week 1 at EOI and EOI+4h. ^Week 19 and 25 and then Q12W. +Additional sample at Week 19 and 25 drawn at EOI.
Serum PK tremelimumab		X*	X	X	X	X	X	X	Q12W			Participants receiving tremelimumab: Pre-dose on treatment visits. Additionally, PK samples are to be collected with every pharmacodynamic sample which is collected on a non-treatment day. See Table 12 for further details. *Additional samples at Week 1 drawn at EOI and EOI+4h.

Procedure	Screen ng (up to 30 days before Day 1 un ess otherw se noted)	Treatment Period Weeks (±3 days)							Upon conf rmed PR/CR or progress on (±7 days)	TDV*	Fo ow-up (±10 days)	**Notes:** *The assessments required at TDV must be completed within 40 days from the date study intervention or SOC was discontinued and must occur prior to the start of subsequent anticancer therapy. Do not repeat tests that have already been performed within 3 days or scans within 4 weeks of the TDV.
		1; (Day 1)	2	4	7	10	13	16	>16			
Serum ADA GSK3359609		X		X	X	X	X	X	X*		X		Participants receiving GSK3359609: Pre-dose on treatment visits. Samples taken on non-treatment days may be drawn at any time. For participants with a positive ADA result at last visit an additional sample will be drawn at 6 months post last dose. See Table 12 for further details. *Week 19, 22 and 25 and then Q12W.
Serum ADA tremelimumab		X		X	X	X	X	X	Q12W		X		Participants receiving tremelimumab: Pre-dose on ALL treatment visits. Samples taken on non-treatment days may be drawn at any time. For participants with a positive ADA result at last visit an additional sample will be drawn at 6 months post last dose. See Table 12 for further details.
Biomarkers and Genetics												
Whole blood for immune cell profiling		X	X	X	X		X		X*		X		*Week 25 only
Serum		X	X	X	X	X	X		X*	X	X		*Week 25 only
Whole blood for PBMC		X	X	X	X	X	X		X*	X	X		*Week 25 only
Plasma		X			X					X	X		

Procedure	Screen ng (up to 30 days before Day 1 un ess otherw se noted)	Treatment Period Weeks (±3 days)							Upon conf rmed PR/CR or progress on (±7 days)	TDV*	Fo ow-up (±10 days)	Notes: *The assessments required at TDV must be completed within 40 days from the date study intervention or SOC was discontinued and must occur prior to the start of subsequent anticancer therapy. Do not repeat tests that have already been performed within 3 days or scans within 4 weeks of the TDV.
		1; (Day 1)	2	4	7	10	13	16	>16			
Whole blood (RNA)		X		X	X					X	X		
Fresh Tumor biopsy		X*+			X^					X^			Fresh tumor biopsy samples may be optional. See Section 8.8.2 for further details. +Only collect after eligibility confirmed. *Pre-dose, window of -7 days. ^Window is ±7 days.
Archival Tissue	X+												
Blood sample for genetics research		X											Collected only if Genetics research optional consent signed: Prefer collection on Day 1, pre-dose but may be collected any time after eligibility confirmed.
Part 2 Only: Patient Reported Outcomes												
EORTC QLQ-C30, EORTC QLQ-HN35, PROMIS – PF, FACT GP5, PRO-CTCAE		X	X	X	X	X	X	X	X*		X		*Week 22, then Q6W through Week 52, then Q12W.
EQ-5D		X			X		X	X	X*		X		*Week 22, then Q12W.

Abbreviations: ADA = Anti-drug antibodies; AE = Adverse event; AESI = Adverse events of special interest; ANC = Absolute neutrophil count; CR = complete response; ECG = Electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOI = End of infusion; EORTC QLQ-C30 and HN35 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 and head and neck 35 module; EQ-5D = EuroQOL Group EQ-5D; FACT GP5 = Functional Assessment of Cancer Therapy - General Physical Well Being Item 5; HIV = Human immunodeficiency virus; ICF = Informed consent form; iRECIST = Modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; MUGA = Multigated acquisition scan; PBMC = peripheral mononuclear cells; PD = Progressive Disease; PK = Pharmacokinetics; PR = Partial response; PRO-CTCAE Patient Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; PROMIS PF = Patient-Reported Outcome Measurement Information System – Physical Function; Q = Every; RNA = Ribonucleic acid; SAE = Serious adverse event; SOC = Standard of care; TDV = Treatment Discontinuation Visit; W = Week; WOCBP = Women of childbearing potential

2. INTRODUCTION

2.1. Study Rationale

GSK3359609 is an inducible T cell co-stimulator (ICOS) agonist antibody and tremelimumab is a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antagonist antibody. In nonclinical and clinical studies in a variety of tumors, it has been shown that ICOS expression on T cells is upregulated after CTLA-4 treatment [Fan, 2014; Fu, 2011; Tang, 2013]. Additionally, ICOS+CD4 T cells have been shown to have a positive association with response in tremelimumab treated chemotherapy-resistant malignant mesothelioma patients [Calabrò, 2013]. It is hypothesized that the combination of these two agents will provide a significant antitumoral response. The purpose of this study is to evaluate if the combination of GSK3359609 and tremelimumab is safe and tolerable (Part 1) and provides significant survival benefit to participants with relapsed/refractory (R/R) Head and Neck Squamous Cell Carcinomas (HNSCC) to warrant further clinical investigation (Part 2).

Part 1

In Part 1 of study 207871, study intervention will be tested at escalating dose combinations in participants with advanced, selected solid tumors that are relapsed/refractory to standard therapies to determine the best dose combination of tremelimumab and GSK3359609. The selection of these solid tumors was based on evidence of their reported response to immune checkpoint therapies [Swaika, 2015; Zamarin, 2015] and/or of exhibiting features indicating a greater likelihood of susceptibility to immune directed therapies, such as tumor mutation load or number/phenotype of tumor infiltrating lymphocytes [Powles, 2014].

Part 2

Head and neck cancers are the ninth most common malignancies in the world with over 90% of these being squamous cell carcinomas [Gupta, 2016]. Although these patients are treated with potentially curative treatments, many develop recurrent or metastatic disease. This patient population continues to have a high unmet medical need, as median overall survival is less than 1 year [Argiris, 2017]. For recurrent, unresectable or metastatic disease without an option for radiation, platinum-based chemotherapy alone or in combination with other chemotherapeutic agents is also among the preferred first line treatment options [NCCN, 2018]. While immunotherapy has been shown to prolong progression-free survival and increase the 1-year overall survival rate over standard of care (SOC) single agent therapies [Ferris, 2016] and is now recommended as second line therapy [NCCN, 2018], the prognosis for these patients remains poor.

R/R HNSCC was chosen as a tumor type of interest in Part 2 of this study due to the high unmet medical need in patients who have failed platinum-based chemotherapy and anti-PD-(L)1 therapy. Several studies have indicated that infiltration with immune cells correlated with favourable clinical outcomes in HNSCC [Mandal, 2016; Ferris, 2015]. ICOS and CTLA-4 expression has been seen on T cells in the in-silico analysis of the TCGA database in a proportion of HNSCC surgically resected tumor samples and

multiplex IHC based studies have shown ICOS and CTLA-4 expression on TILS to a varying extent between HNSCC patients from surgically resected samples including both CD8 and CD4 T cells and both conventional and regulatory CD4 T cells [Kim, 2016]. The combination of an ICOS agonist antibody with a CTLA4 blocking antibody could enhance activation of the CD8 and CD4 T-conventional cells while controlling the T-reg suppressive effects and is therefore hypothesized to have a significant antitumor effect in HNSCC.

The choice of chemotherapy for R/R HNSCC following failure of first line therapy and failure of second line anti-PD-(L)1 therapy is not well defined and is based on several factors, including previous chemotherapy exposure, performance status, and comorbid conditions. Several single agent chemotherapy options existed as second line therapy for patients who are not appropriate for a platinum-containing regimen. These agents now fall into the third line post-approval of the anti-PD-(L)1 agents. In the United States and the EU, ASCO, NCCN and ESMO recommendations include best supportive care, clinical trials, and single agents including paclitaxel, docetaxel, 5-fluorouracil, methotrexate, cetuximab, ifosfamide, bleomycin, gemcitabine, capecitabine, and vinorelbine [NCCN, 2018; Mesia, 2013]. Methotrexate and bleomycin have FDA approved indications for head and neck cancer; however, both agents are considered toxic in the setting of newer chemotherapy agents and methotrexate had poor performance in the recent Phase III study [Ferris, 2016]. Furthermore, the bleomycin label contains the following language, “the response to bleomycin is poorer in patients with previously irradiated head and neck cancer”. This population is expected to be the majority of participants in this study and thus bleomycin will not be included in the SOC options in this study. The Investigator’s choice of SOC will consist of the following agents: cetuximab (where it is approved for use as a single agent for recurrent HNSCC), paclitaxel (which is incorporated into regimens in early lines of disease and is commonly used in late line as a single agent), and docetaxel (which appears to be the most active agent in the platinum refractory setting, has approved indications as a single agent and has demonstrated activity in this setting) [Ferris, 2016].

2.2. Background

A model of cancer immunity is described as a cyclic multistep process that functions to elicit an effective antitumor response [Chen, 2013]. Each step can be negatively regulated, thus providing the tumor with redundant mechanisms by which to block an antitumor immune response. In some cases, tumors will be highly dependent on a single mechanism, and in these cases, there is the potential to achieve significant clinical activity with a single agent immunomodulatory therapy. However, it is expected that tumors often utilize redundant mechanisms to evade antitumor immune responses and in these cases, combination therapies are likely required.

Robust antitumor responses including complete cure in some cancers have been achieved by modulating a patient’s immune system. Antibodies targeting the checkpoint receptors or their cognate ligands engaged in negative regulation of T cell responses, such as CTLA-4 and PD-1 (Programmed death receptor-1)/PD-L1 (PD Ligand), have demonstrated efficacy and are proven effective as anticancer immunotherapies in a broad

range of tumors including some solid tumors otherwise considered poorly immunogenic [Chen, 2015; Brahmer, 2012; Topalian, 2012; Meng, 2017].

However, the majority of tumors are non-responsive to this class of agents when given as monotherapy as these tumors may possess features that enable them to evade immune surveillance, suppress immune reactivity, proliferate and survive within an inflammatory microenvironment. In addition, multiple mechanisms of immune suppression could exist which may prohibit effective antitumor immune responses. In these instances, combination therapies will likely be required. The clinical data generated by the combination of ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) in patients with metastatic melanoma is an example of the practice changing clinical benefit of such combinations [Wolchok, 2013; Larkin , 2015]

In some patients, inhibition of negative immune checkpoint pathways alone may not elicit an effective antitumor response. To reinstate immunosurveillance, treatment approaches may require combinations with agents that provide co-stimulatory signals or target different processes within the immune cascade; these regimens may include chemotherapies which possess advantageous immunological effects [Galluzzi, 2015].

Immunomodulatory agents that target other components of the cancer immunity cycle are needed to expand the population of patients and range of tumor types that may respond to immunotherapy as well as enhance the magnitude and duration of antitumor responses in patients whose tumors are already sensitive to current immunotherapy approaches. Ultimately, the aim is to improve patient survival outcome in all disease settings including the advanced setting which is considered non-curative by nature.

GSK3359609 is a humanized IgG4 anti-ICOS agonist monoclonal antibody [Mayes, 2018] selected for its nanomolar (nM) binding to and agonist activity in ICOS-expressing CD4+ and CD8+ effector T cells. GSK3359609 is specifically engineered as an Immunoglobulin (Ig)G4 hinge-stabilized isotype, IgG4PE, to markedly decrease binding affinity of the Fc (Fragment crystallizable) region of the mAb to activating Fcγ receptors and C1q, and thereby diminish the cytotoxic potential of GSK3359609 that would result in depletion of ICOS-positive T cells through antibody-dependent or complement-dependent cell mediated mechanisms, respectively. Moreover, the IgG4PE isotype retains functional binding to the Fcγ inhibitor receptor, FcγRIIb, a feature described as critical for modulating antibody agonist activity [Li, 2011], which also may be essential for optimal ICOS agonist activity and its associated antitumor effects in humans.

ICOS is a co-stimulatory receptor belonging to the CD28/CTLA immunoglobulin super family with expression restricted to T cells [Hutloff, 1999]. ICOS is weakly expressed on resting TH17, follicular helper T and regulatory T (Treg) cells, yet is highly induced on CD4+ and CD8+ T cells upon T cell receptor (TCR) engagement and activation [Paulos, 2010; Wakamatsu, 2013]. Upregulation of ICOS leads to both Th1 and Th2 cytokine secretion and sustained effector T cell proliferation and function [Sharpe, 2002]. A growing body of evidence supports the concept that activating ICOS on CD4+ and CD8+ effector T cells has antitumor potential.

The rationale for targeting ICOS in cancer has been established by multiple lines of nonclinical and clinical evidence. Engagement of the ICOS pathway with an ICOS-L-Fc fusion protein is shown to have potent antitumor activity in multiple syngeneic mouse tumor models [Ara, 2003]. GSK3359609 has been tested in combination with anti-CTLA-4 monoclonal antibodies (mAb) (ipilimumab) in either ex-vivo human PBMC assays or in a modified MLR assay. The GSK3359609 and anti-CTLA-4 combination resulted in a significant enhancement in IFN γ production compared to either agent alone in both the PBMC assay as well as the MLR assay. Refer to the GSK3359609 Investigator's Brochure (IB) [GSK Document Number 2017N319717_01] for further details.

Tremelimumab is a human immunoglobulin (Ig)G2 mAb that is directed against CTLA-4; cluster of differentiation [CD]152, a cell surface receptor that is expressed primarily on activated T cells and acts to inhibit their activation. Tremelimumab completely blocks the interaction of human CTLA-4 with CD80 and CD86, resulting in increased release of cytokines (interleukin [IL]-2 and interferon [IFN]-γ) from human T cells, peripheral blood mononuclear cells and whole blood [Tarhini, 2008]. Tremelimumab is being developed by AstraZeneca for use in the treatment of cancer.

To date, tremelimumab has been given to more than 1500 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Refer to the current tremelimumab IB [AstraZeneca, 2017] for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

Emerging data from patients treated with anti-CTLA-4 antibodies suggest a positive role of ICOS+ effector T cells in mediating an antitumor immune response. Patients with metastatic melanoma [Di Giacomo, 2013], urothelial [Carthon, 2010], breast [Vonderheide, 2010] or prostate cancer [Chen, 2009] who have increased absolute counts of circulating and tumor infiltrating CD4+ICOS+ and CD8+ICOS+ T cells after ipilimumab treatment have significantly better treatment related outcomes than patients where little or no increases are observed. Importantly, it was shown that ipilimumab changes the ICOS+ T effector to Treg ratio, reversing an abundance of Tregs pre-treatment to a significant abundance of T effectors vs. Tregs following treatment [Liakou, 2008; Vonderheide, 2010]. As evidenced by the clinical data, ICOS+ T effector cells may be a positive predictive biomarker of ipilimumab response, and activation of this population of cells with an ICOS agonist antibody may show enhanced clinical activity than either agent alone. As suggested in the literature [Melero, 2013], the complimentary mechanisms of actions of CTLA-4 blocking antibodies which inhibit the suppressive action on T cells thus 'taking off the brakes' and activating them while combining with an ICOS agonist antibody which further co-stimulates the activated T cells for enhanced effector function and proliferation has the potential to mount a more robust immune antitumor response.

As evident from the clinical efficacy of antibodies directed against checkpoint inhibitors indicated for the treatment of cancers, targeting immune checkpoint modulators is an established concept that has resulted in patients deriving transformational clinical benefit. The unique mechanistic profile of an anti-ICOS agonist antibody provides an opportunity to investigate the antitumor potential of targeting a T cell co-stimulator in combination

with other immune-targeted agents that regulate key immune pathways or immune cell populations as well as tumor targeted agents, either in development or already in clinical use. The aim of this approach is to achieve synergistic antitumor responses that translate into improvement in patient survival.

2.3. Benefit/Risk Assessment

GSK3359609 is being currently investigated in a Phase 1 study 204691 with doses ranging from 0.001 mg/kg to 3 mg/kg as monotherapy and from 0.01 mg/kg to 3 mg/kg in combination with a PD-1 inhibitor. GSK3359609 has been generally well tolerated in the 204691 study and the majority of AEs reported in participants receiving monotherapy were Grade 1 or Grade 2. More detailed information about the known and expected benefits and risks and reasonably expected AEs is provided in the GSK3359609 IB [GSK Document Number 2017N319717_01]. Risks with tremelimumab monotherapy include, but are not limited to: GI effects (colitis, diarrhea, enterocolitis and intestinal perforation); endocrine disorders (hypo and hyperthyroidism, hypophysitis and adrenal insufficiency); skin effects (rash, and pruritus); elevations in lipase and amylase and clinical manifestations of pancreatitis; other gastrointestinal events e.g., ulcerative colitis, dehydration, nausea and vomiting; hepatic events including hepatitis, and liver enzyme elevations; pneumonitis and ILD; nervous system events including encephalitis, peripheral motor and sensory neuropathies, Guillain-Barre and proximal muscle weakness; cytopenias including thrombocytopenia, anemia and neutropenia; infusion-related reactions, anaphylaxis, and allergic reactions; renal events including renal failure, acute kidney injury, nephritis, nephrotic syndrome, autoimmune nephritis and electrolyte abnormalities such as hypokalemia; autoimmune diseases including autoimmune arthritis, Sjogren's syndrome and giant cell temporal arteritis; hyperglycemia and diabetes mellitus; and pyrexia. However, while tremelimumab has been used extensively with a clearly defined toxicity profile, the data at the doses and schedule studied in the study is limited. Therefore, the combination of GSK3359609 and tremelimumab could have an unknown toxicity profile. More detailed information about the known and expected benefits and risks and reasonably expected AEs are provided in the tremelimumab IB [AstraZeneca, 2017].

2.3.1. Risk Assessment

The risk assessment and mitigation strategy for GSK3359609 in combination with tremelimumab in this protocol is outlined in Table 1.

Table 1 Risk Assessment and Mitigation Strategy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Immune-related AEs	• Inflammatory AEs such as diarrhea/colitis, pneumonitis, nephritis, and hepatotoxicity are well established as treatment emergent AEs with immune-modulating agents, and are consistent with the immune-	• Participants with the following medical history are ineligible for this study ○ Toxicity (≥Grade 3) related to prior immunotherapy leading to study intervention discontinuation

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	stimulatory mechanism of action of these agents.	○ Active autoimmune disease (refer to Section 5.2) ○ Severe hypersensitivity to another mAb • Established management algorithms for irAEs • Refer to Section 6.6.1 for further details on the identification, evaluation, and management of toxicities with a potential immune etiology.
Hypersensitivity reaction	• Risk for infusion reactions and hypersensitivity is inherent to many mAbs [Brennan, 2010]	• Participants with history of severe hypersensitivity to another mAb or to the chemotherapies under investigation including any ingredient used in the formulation are ineligible for this study • Refer to Section 6.6.2 for further details on management of infusion reactions.
Severe cytokine release syndrome (sCRS)	• ICOS is a costimulatory receptor that can stimulate proliferation and activation of T cells • GSK3359609 is an ICOS agonist that can co-stimulate T cell activation in the context of TCR signal.	• Refer to Section 6.6.2 for further details on management of CRS.
Immune complex disease	• Immune complex formation and deposition findings in nonclinical safety studies (refer to the individual IBs)	• Clinical laboratory safety assessments and immunogenicity testing

Abbreviations: AE= adverse event; CRS=cytokine release syndrome; ICOS=inducible T cell co-stimulator; IB=Investigator's brochure; mAb=monoclonal antibody; TCR=T cell receptor

2.3.2. Benefit Assessment

This is a Phase I/II open-label study of GSK3359609 in combination with tremelimumab conducted in participants with select advanced solid tumors that are relapsed/refractory to standard therapies. Both GSK3359609 and tremelimumab monotherapies and the combination of the two targets have demonstrated preclinical activity; however, whether the combination of GSK3359609 and tremelimumab together clinically will have a

greater antitumoral response is unknown. Therefore, any potential beneficial effect for an individual participant attributable to combination therapy with GSK3359609 and tremelimumab is unknown.

2.3.3. Overall Benefit: Risk Conclusion

Data from nonclinical models suggest the combination of anti-ICOS agonist and anti-CTLA-4 antibodies has the potential for enhanced antitumor activity through complementary mechanisms (refer to Section 2.2). Measures are taken to minimize the risks to participants participating in this study (e.g., frequent safety and disease assessments). Therefore, the potential risks identified in association with GSK3359609 as a combination therapy with tremelimumab are justified by the anticipated benefits that may be afforded to participants with relapsed/refractory solid tumors. The participants in this study have exhausted other standard therapy options resulting in a great unmet medical need for alternate therapies. Thus, the risk to these participants is justified when weighed against the potential benefits of combination therapy.

3. OBJECTIVES AND ENDPOINTS

3.1. Part 1: Dose Escalation of GSK3359609 in Combination with Tremelimumab

Objectives	Endpoints
Primary	
• Determine safety, tolerability and the RP2D of GSK3359609 in combination with tremelimumab	• Frequency and severity of DLTs, AEs, AESI, SAEs and DLT/AE/SAEs leading to dose modifications/delays/withdrawals; changes in laboratory, vital signs, and ECG safety assessment parameters
Secondary	
• Evaluate clinical activity of GSK3359609 in combination with tremelimumab	• ORR, DCR
• Characterize the PK properties of GSK3359609 and tremelimumab when administered in combination	• Cmax, Cmin, AUC (0-t) of GSK3359609 and tremelimumab as data permit
• Determine immunogenicity of GSK3359609 and tremelimumab when administered in combination	• Detection and characterization of ADA against GSK3359609 and/or tremelimumab
Exploratory	
• Evaluate clinical activity of GSK3359609 in combination with tremelimumab	• PFS, OS, TTR, DoR
• Evaluate pharmacodynamic changes in markers of target engagement, immune cell profiles, immune activation and function or tumor biology post treatment	• Immunophenotyping and functional analysis • Other biomarkers such as gene

Objectives	Endpoints
compared to that at screening	expression changes, relevant transcripts, TCR diversity, and/or soluble analytes

AEs = adverse events; SAEs = serious adverse events; DLTs = dose limiting toxicities; AESI = adverse events of special interest; RP2D = recommended phase 2 dose; ORR = overall response rate; DCR = disease control rate; Cmax = maximum observed concentration; Cmin = minimum observed concentration; AUC (o-t) = area under the concentration-time curve over the dosing interval; ADA = anti-drug antibodies; PFS = progression-free survival; OS = overall survival; TTR = time to response; DoR = duration of response; TCR = T cell receptor.

3.2. Part 2: Cohort Expansion of the RP2D Dose Combination vs. SOC in R/R HNSCC

Objectives	Endpoints
Primary	
• Evaluate clinical activity of GSK3359609 in combination with tremelimumab compared to SOC	• OS
Secondary	
• Further evaluate the clinical activity of GSK3359609 in combination with tremelimumab compared to SOC	• ORR, DCR, PFS, TTR, DoR
• Further evaluate the PK properties of GSK3359609 and tremelimumab when administered in combination	• Cmax, Cmin, AUC (0-t) of GSK3359609 and tremelimumab as data permit
• Further evaluate immunogenicity of GSK3359609 and tremelimumab when administered in combination	• ADA incidence
• Further evaluate the safety and tolerability of GSK3359609 and tremelimumab when administered in combination	• Frequency and severity of AEs, AESI, SAEs and AE/SAEs leading to dose modifications/delays/withdrawals; changes in laboratory, vital signs, and ECG safety assessment parameters
Exploratory	
• Examine potential relationships between anticancer activity and changes in markers of target engagement immune cell profiles, immune activation and function or tumor biology post treatment compared to that at screening	• Immunophenotyping and functional analysis, anticancer activity parameters • Other biomarkers such as gene expression changes, relevant transcripts, TCR diversity, and/or soluble analytes
• Evaluate other measures of antitumor activity	• Evaluation of tumor growth kinetic parameters which may be measured by the following methods: including, but not limited to, RECIST 1.1, uni-dimensional,

Objectives	Endpoints
	bi-dimensional, and volumetric tumor measurements
• Explore relationship between antitumor activity, PK parameters, pharmacodynamic activity and other participant characteristics	• Antitumor activity (CR, PR, SD, PD), tumor kinetic parameters, PK parameters, pharmacodynamic activity, and other participant characteristics as data permit
• Examine potential relationships between anticancer activity and various biomarkers • Evaluate potential markers of sensitivity and/or resistance to the treatment	• Target expression, immune phenotypes, HPV positivity for HNSCC tumors, TCR (T cell receptor) sequencing, genetic polymorphisms in the target or other related gene expression and/or tumor mutational burden
• Evaluate disease and treatment related symptoms and impact on function and health-related quality of life	• Health-related quality of life as measured by the EORTC-QLQ-C30 and HN35, PROMIS-PF, and EQ-5D
• Evaluate participant-reported tolerability	• PRO-CTCAE and FACT GP5

OS = overall survival; SOC = standard of care; ORR = overall response rate; DCR = disease control rate; ; PFS = progression-free survival; TTR = time to response; Cmax = maximum observed concentration; Cmin = minimum observed concentration; AUC (0-t) = area under the concentration-time curve over the dosing interval ; DoR = duration of response; TCR = T cell receptor; ADA = anti-drug antibodies; AEs = adverse events; SAEs = serious adverse events; RECIST = response evaluation criteria in solid tumors; PK = pharmacokinetic; EORTC QLQ-C30 and HN35 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 and head and neck cancer 35 module; EQ-5D = = EuroQOL Group EQ-5D; FACT GP5 = Functional Assessment of Cancer Therapy – General Physical Well Being Item 5; PROMIS PF = Patient-Reported Outcome Measurement Information System – Physical Function; Impression of Change; PRO-CTCAE = Patient Reported Outcomes – Common Terminology Criteria for AEs

4. STUDY DESIGN

4.1. Overall Design

This is a Phase I/II, open-label, 2-part study of GSK3359609 in combination with tremelimumab. As illustrated in Figure 1 in Section 1.2, Part 1 is dose escalation and will enroll participants with advanced, selected solid tumors and Part 2 is randomized expansion and will enroll participants with R/R HNSCC who have progressed after receiving at least 1 platinum-based chemotherapy and at least 1 anti-PD-1/PD-L1 therapy, whether in combination or separately.

Study intervention will be defined as treatment with GSK3359609 and tremelimumab, given in combination. In Part 2 participants will be randomized at a ratio of 2:1 to either the study intervention or SOC, respectively.

The study is comprised of 3 periods: screening (assessments up to 30 prior to first dose), treatment (until disease progression, unacceptable toxicity or death), and follow-up. The total duration of study participation begins with the signing of the informed consent form

(ICF) through the final protocol-defined follow-up assessment for survival and is estimated to be up to 4 years (~2 years on treatment and ~2 years in survival follow-up); however, participants deriving benefit may be on study intervention beyond 2 years.

4.1.1. Part 1: Dose Escalation of Tremelimumab and GSK3359609

In Part 1 dose escalation, eligible participants will receive GSK3359609 in combination with tremelimumab at a defined dosing schedule (see Section 6.1). Part 1 will initiate with 8 mg GSK3359609 and 75 mg tremelimumab (termed dose level [DL] 1), the planned lowest doses for each agent. The highest planned doses are 80 mg GSK3359609 and 225 mg tremelimumab (termed DL6). GSK3359609 will be administered every 3 weeks and tremelimumab will be administered every 3 weeks for 6 doses, followed by every 12 weeks. Tremelimumab is to be administered first as an IV infusion over 60 minutes. GSK3359609 will be administered as a 30-minute IV infusion beginning at least 1 hour and no more than 2 hours following the end of the tremelimumab infusion. As shown in Figure 1, dosing will begin at DL1 and continue using zone-based dose escalation rules whereby each zone must be cleared for safety prior to opening the next zone of DLs.

DL1 and DL2 will enroll one participant each to obtain preliminary safety data that will inform the toxicity probability model; these DLs will be expanded to enroll at least two additional participants if a Grade 2 or above toxicity attributable to either agent or a Dose Limiting Toxicity (DLT) is observed. DL3, DL4, DL5, and DL6 will enroll as full safety cohorts, i.e., 3 to 9 participants will be enrolled for each DL guided by the bivariate CRM model [Neuenschwander, 2008; Neuenschwander, 2014] until the MTD or MAD dose combinations are determined. Unplanned DLs within the range of the planned doses of each agent may be investigated to support the identification of optimal doses to administer in combination. Additionally, doses lower than planned of either agent may be investigated. If a participant withdraws from the study before the completion of the 28-day DLT evaluation period for reasons other than DLT, then the participant may be replaced.

In the absence of DLTs, the dose escalation rules are deterministic. Participant allocation in this stage is determined entirely by the preferred dose order. If DLTs are observed, a bivariate CRM model will be used to guide dose recommendations. This model will provide posterior probability of observing a DLT at all dose combination levels based on emerging DLT data and prior information. In addition to the zone-based escalation rule, dose escalation will follow two rules. First, if the next preferred DL has excessive risk of toxicity, then that DL cannot be assigned. Instead, a new participant will be assigned to the highest preferred DL without such risk of toxicity. It is noted that the recommended DL should not be in a zone if “lower” zones have not been “cleared”. Second, if one DL emerges as having a much higher chance of having a DLT rate in the target toxicity interval (DLT rate between 16% and 33%), that DL will be opened for enrollment. This latter situation occurs rarely with the sample size anticipated in this study. Thus, the most common use of the model is to eliminate allocation to potentially unsafe doses in combination. Details of the bivariate CRM method are provided in Appendix 10.

Dose recommendations based on the bivariate CRM analysis will be used as guidance for the data review team. To ensure safety of participants, additional participants may be

enrolled at a current DL at the discretion of the data review team, even though a higher dose is recommended by CRM analysis.

PK/pharmacodynamic cohort(s) may be initiated at any DL(s), once safety is cleared, with mandatory paired tumor sample collections to inform on dose selection for Part 2 of the study. In DLs enrolling more than 1 participant, treatment will be administered at least three days apart between the first two participants enrolled; the third and any subsequent participants will be administered treatment at a minimum of 24 hours apart. This staggered approach allows for an initial assessment of safety in a participant accrued to a dose level before initiating the next participant's treatment.

A single dose combination will be selected as the recommended Phase 2 dose (RP2D) and carried forward from Part 1 into Part 2. The totality of data, including safety/tolerability, PK, pharmacodynamic, and efficacy will be used to determine whether to proceed to Part 2 and which dose combination will be chosen as the RP2D.

At the time of each dose escalation decision for which the bivariate CRM model would be implemented, the Fixed and Adaptive Clinical Trial Simulator (FACTS™ version 6.1 or above) will be used. The recommended dose 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 in the excessive toxicity or unacceptable toxicity range is less than 25% (see details in Section 10.10.1).

4.1.1.1. Dose Limiting Toxicity

The severity of all toxicities will be graded using the NCI-CTCAE (version 5.0) [NCI, 2017]. The DLT observation period is 28 days in length and begins on the day GSK3359609 and tremelimumab are first administrated to the participant.

A DLT is defined as an AE that meets at least one of the criteria listed in Table 2 and is considered by the Investigator to be clinically relevant and attributed (probably, or possibly) to the study intervention during the 28-day DLT observation period. An AE considered related to the underlying disease under study is not defined as a DLT.

Table 2 Dose-Limiting Toxicity Criteria

Toxicity	DLT Definition
Hematologic	• Febrile neutropenia • Grade 4 neutropenia of >7 days in duration or requiring G-CSF • Grade 4 anemia • Grade 3 thrombocytopenia with bleeding or Grade 4 thrombocytopenia
Non-hematologic	• Grade 4 toxicity • Grade 3 pneumonitis • Any ≥ Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care • Grade 3 toxicity that does not resolve to ≤Grade 1 or baseline within 3 days despite optimal supportive care[a] • Any Grade 2 ocular toxicity requiring systemic steroids, or any ≥ Grade 3 ocular toxicity
Other	• Any other toxicity considered to be dose-limiting which in the judgment of the Investigator and Medical Monitor that occurs within or beyond four weeks will be considered in the selection of the dose to recommend for expansion cohorts

a. Suggested toxicity management guidelines are described in Section 6.6.1 and may include systemic corticosteroids for immune-related toxicities; if systemic corticosteroids use delays administration of the second dose(s) of study intervention and the event does not otherwise meet the DLT criteria for non-hematologic toxicity, the dose delay will not be considered a DLT.

If a participant experiences a DLT during the DLT observation period, the participant may resume dosing at the same or lower dose level provided the toxicity did not meet study treatment discontinuation criteria and following approval by the Sponsor.

4.1.1.2. Non-Limiting Toxicities

The following toxicities have been deemed to be non-limiting for the purposes of this study. These toxicities will not be taken into account for dose escalation decisions unless, in the opinion of the investigator and the Medical Monitor, they represent a DLT.

- Grade 3 and Grade 4 clinically asymptomatic laboratory abnormalities (e.g., amylase or lipase)
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the participant is asymptomatic
- Grade 3 nausea, vomiting, or fatigue that resolves to ≤Grade 1 within 7 days with optimal supportive care
- Grade 3 and Grade 4 infusion-related reactions (IRRs) in participants not receiving prophylaxis for IRRs
- Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc)

4.1.1.3. Dose Escalation Decisions and Selection of Part 2 Dose

A data review team, consisting (at a minimum) of the participating Investigator(s), Medical Monitor, pharmacokineticist, and statistician, will be responsible for determining whether dose escalation during Part 1 should continue as planned and for determining the Part 2 dose. Prior to the dose escalation/selection decision, the data review team will review available relevant data on all AEs including non-DLTs, laboratory assessments and other safety evaluations, as well as available PK and pharmacodynamic data. The dose escalation/selection decisions and rationale will be documented in writing with copies maintained at each study site and in the master study files at GlaxoSmithKline (GSK). Further details may be found in the Dose Escalation and Selection Plan.

4.1.2. Part 2: Cohort Expansion of the RP2D Dose Combination vs. SOC

In Part 2, eligible participants will be randomized 2:1 to open-label GSK3359609 plus tremelimumab at the RP2D (n 60) or a SOC single-agent therapy of the Investigator's choice to include paclitaxel, docetaxel or cetuximab (n 30). See Section 6.1 for details.

Part 2 will employ a Bayesian analysis to estimate the predictive probability of observing a significant improvement of OS in a hypothetical future Phase 3 trial enrolling 345 participants (230 participants for investigational RP2D dose combination and 115 participants for SOC), based on the treatment effect difference in OS between the two arms in Part 2.

4.2. Scientific Rationale for Study Design

The combination of GSK3359609 and tremelimumab was selected based on complementary mechanisms of action and anticipated robust antitumor activity.

Eligibility criteria require that participants have disease that has 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. These participants have an unmet medical need.

In Part 1, dose escalation will be performed using bivariate CRM model to optimize the allocation of participants to dose combinations with a 16-33% DLT frequency. The DLT criteria are based on typical oncology rules with additional modifications for toxicities expected for the individual agents in the combination.

In Part 2, the cohort expansion design provides efficiencies in the evaluation of anticancer activity of the investigational dose combination when compared with the SOC. The GSK3359609/tremelimumab combination regimen will subsequently graduate to separate Phase 3 confirmatory studies if the prespecified probability threshold is met at the final analyses.

4.3. Justification for Dose

4.3.1. GSK3359609 Dose Rationale

Preliminary PK data from study 204691 was utilized to develop a population PK model and estimate median steady-state peak and trough exposures at different fixed doses. The 8, 24, 80, and 240 mg dose corresponds to an approximate 0.1, 0.3, 1, and 3 mg/kg dose assuming median body weight of 80 kg as described in Section 4.3.1.2.

The functional effect of GSK3359609 has been characterized in several *in vitro* experiments yielding different activity coefficients depending on cell type, co-stimulation status, and cytokines analysed. The ICOS receptor occupancy (RO) based on CD4+ or CD8+ T cells at any given systemic exposure of GSK3359609 can be predicted by employing the *in vitro* potency values generated from different binding/activation assays in the range of 0.09 to 4.14 µg/mL as listed in Table 3.

Sufficiently high CD4+ RO is expected at peak exposures (89% to >99% RO) as well as at trough exposures (69% to >99% RO) at steady-state with a GSK3359609 dose of 80 mg.

Collectively, based on the safety and exposure data from the Phase 1 study and the predicted target engagement, 8, 24, and 80 mg doses are proposed to be evaluated in combination with tremelimumab in this study. No drug-drug interaction related changes are expected in GSK3359609 PK with tremelimumab co-administration. Additionally, doses lower than the planned lowest 8 mg dose may be investigated based on emerging data.

Table 3 Projected CD^{4+} Receptor Occupancy from Population PK Predicted Median Steady-state Peak and Trough Exposures of GSK3359609 based on in vitro potency estimates.

Dose (mg)	Cmax (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 Cmax	At Cτ	At Cmax	At Cτ	At Cmax	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

Refer to GSK3359609 IB [GSK Document Number 2017N319717_01] for further details.

4.3.1.1. GSK3359609 Dosing Frequency

The systemic half-life of GSK3359609 is approximately 25 days based on the preliminary population PK analysis of exposure data from ongoing study 204691. The existing GSK3359609 Q3W regimen in the ongoing clinical study is also consistent with

the Q3W dosing regimen typical with IgG4 based monoclonal antibody therapies. Thus, GSK3359609 will be dosed Q3W in combination with tremelimumab.

4.3.1.2. GSK3359609 Rationale for Fixed Dose

Therapeutic monoclonal antibodies are often dosed based on body-size due to the concept that this reduces inter-participant variability in drug exposure. However, body-weight dependency of PK parameters does not always explain the observed variability in the exposure of monoclonal antibodies [Zhao, 2017]. The advantage of body-weight based versus fixed dosing in this study was evaluated through population PK modelling and simulation efforts. A preliminary population PK model was developed from monotherapy dose escalation (data up to doses of 1 mg/kg; n 19 participants).

Simulations were performed by considering body weight distribution similar to that observed in the preliminary dataset. At the 5th percentile of body weight (40 47 kg), there was a 70-100% increase in median steady-state AUC(0-τ); GSK3359609 exposures higher than these increases have been evaluated in the Phase 1 study 204691 with the 3 mg/kg dose regimen. At the 95th percentile of body weight (107 118 kg), there was a 23-32% decrease in median steady-state AUC(0-τ) as compared to the median 80 kg exposure providing adequate RO with the minimal lowering of exposure. A similar outcome is expected for steady-state C_{max} and trough concentrations between body weight-based and fixed dosing.

Overall, these preliminary population PK simulations indicate that using fixed dosing would result in a similar range of exposures as that of body weight-based dosing. Also, fixed dosing offers the advantage of reduced dosing errors, reduced drug wastage, shortened preparation time, and improved ease of administration. Thus, switching to a fixed dose based on a reference body weight of 80 kg is reasonable and appropriate.

4.3.2. Tremelimumab Dose Rationale

Tremelimumab is an IgG2 mAb against human CTLA-4. In clinical studies, Tremelimumab exhibited dose-proportional PK following IV infusion following single IV doses of 0.1 to 15 mg/kg. Refer to tremelimumab IB [AstraZeneca, 2017] for further details.

The current study will administer tremelimumab as a flat dose regimen of 75 mg and 225 mg approximating the 1 mg/kg and 3 mg/kg regimens already evaluated in multiple tremelimumab mono- and combination therapy studies. Tremelimumab has also been evaluated at a 10 mg/kg dose in combination with durvalumab, an anti-PD-L1 antibody, where tremelimumab was administered as 10 mg/kg Q4W for 6 cycles followed by 10 mg/kg Q12W [Antonia, 2016]. The dosing regimen for the proposed doses in this study is Q3W for the first six doses and Q12W thereafter. This Q3W dosing frequency for tremelimumab matches the GSK3359609 Q3W dosing frequency providing greater patient convenience. The overall tremelimumab systemic exposures with the highest proposed 225 mg regimen (225 mg Q3W for 6 cycles followed by 225 mg Q12W) in the current study are expected to be well below the exposures observed with 10 mg/kg regimen (10 mg/kg Q4W for 6 cycles followed by 10 mg/kg Q12W) studied as

monotherapy and combination therapy. No drug-drug interaction related changes are expected in GSK3359609 PK with tremelimumab co-administration.

4.4. End of Study Definition

The end of the study is defined as the date of the completion of the last participant's required follow-up visit or contact after study intervention/SOC discontinuation, death, or final visit or contact following discontinuation for any reason.

4.4.1. Participant Completion

For Part 1, dose escalation, participants will be considered as having completed the study if they:

- complete screening assessments, and receive at least two doses of study intervention or receive one dose but experience a DLT, and are observed during the 28-day DLT observation period, and the follow-up visit for safety (if required), or

- complete screening assessments and have died while receiving study intervention or during the follow-up period for safety

For Part 2, the dose expansion part of the study, participants will be considered as having completed the study if they:

- complete the screening assessments, and receive at least one dose of study intervention or SOC, and discontinue study intervention or SOC for reasons other than lost to follow-up or non-compliance, and complete the follow-up visit for safety (if required), and are followed until death, or

- complete screening assessments and have died while receiving study intervention or SOC or during the post-study follow-up period for safety

Document the cause of death in the 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.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

1. Capable of giving signed informed consent/assent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

2. Male or female, aged 18 years or older.

3. Body weight ≥ 30 kg.

4. Histological or cytological documentation of an invasive malignancy that was diagnosed as locally advanced/metastatic or relapsed/refractory and is of one of the following tumor types:
    a. Part 1:
        i. Cutaneous Melanoma
        ii. Head and Neck Squamous Cell Carcinoma (HNSCC) (oral cavity, larynx, oropharynx, hypopharynx, nasal cavity/paranasal sinuses)
        iii. Non-Small Cell Lung Cancer (Squamous and Non-squamous)
        iv. Urothelial carcinoma of the upper and lower urinary tract
        v. Clear Cell Renal Carcinoma
        vi. Castrate Resistant Prostate Adenocarcinoma
    b. Part 2:
        Head and Neck Squamous Cell Carcinoma (oral cavity, larynx, pharynx, paranasal sinuses)

5. Part 1 only: Disease that has progressed after standard therapy for the specific tumor type, or for which standard therapy has proven to be ineffective, intolerable, or is considered inappropriate, or if no further standard therapy exists, or where standard therapy is refused. May be anti-PD-1/anti-PD-L1 experienced or naïve.

6. Part 2 only: Disease that has progressed after receiving platinum-based chemotherapy (unless medically contraindicated or discontinued due to toxicity) and anti-PD-1/anti-PD-L1 therapy (in combination or as separate lines of therapy in either sequence).

7. Measurable disease per response evaluation criteria in solid tumors (RECIST) version 1.1 guidelines. Palpable lesions that are not measurable by radiographic or photographic evaluations may not be utilized as the only measurable lesion. Any measurable lesion biopsied at Screening cannot be followed as a target/index lesion unless agreed upon by GSK.

8. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score of 0 or 1.

9. Adequate organ function as defined in Table 4.

Table 4 Definitions of Adequate Organ Function

System	Laboratory Values
Hematologic[a]	
Absolute neutrophil count	≥1.5x10^9/L
Absolute lymphocyte count	≥800/mm^3
Hemoglobin	≥9 g/dL
Platelets	≥100x10^9/L
Hepatic	
Albumin	≥2.5 g/dL
ALT	≤2.5xUpper Limit of Normal (ULN) or ≤5xULN for participants with documented liver metastases
Total bilirubin	Bilirubin ≤1.5xULN (isolated bilirubin ≤1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
Renal	
Calculated CrCl[b]	≥30 mL/min
Cardiac	
Ejection fraction[c]	≥50%

a. Participants may be transfused or receive growth factor treatment to meet minimum hematologic values up to 7 days prior to determining eligibility
b. Calculated CrCl is required to be calculated using one of the formulas described in Appendix 8. Either formula is acceptable and must be used consistently for each participant throughout the study.
c. Multigated acquisition scan (MUGA) is acceptable if ECHO is not available; if measured with ECHO or MUGA, the same modality must be used for all subsequent evaluations (refer to Section 8.2.5).

10. A female participant is eligible to participate if she is not pregnant (see Appendix 4), not breastfeeding, and at least one of the following conditions apply:

    a. Not a woman of childbearing potential (WOCBP) as defined in Appendix 4; or,

    b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 while receiving study intervention and for at least 180 days after the last dose of study intervention. Note: If the participant is randomized to the SOC regimen only, then the duration of contraception after the last dose of SOC should be based on the package insert and Institutional guidelines.

11. A male participant must agree to use a highly effective contraception as detailed in Appendix 4 of this protocol while receiving study intervention and for at least 180 days after the last dose of study intervention and refrain from donating sperm during this period. Note: If the participant is randomized to the SOC regimen only, then the duration of contraception after the last dose of SOC should be based on the package insert and Institutional guidelines.

12. Agree to collection of tumor tissue:

a. Part 1 and Part 2: Archival tumor tissue collected any time from the initial diagnosis of invasive malignancy; a fresh tumor biopsy will be required if archival specimen is unavailable prior to first dose.

b. Part 1 PK/pharmacodynamic cohort(s): Archival tissue as noted in point (a) above. Paired tumor biopsies: tumor tissue collected any time after completion of dosing of the last therapy and prior to first dose and an on-treatment biopsy.

c. Part 2: A minimum of 15 participants from each arm will be required to provide paired tumor biopsies (in addition to the archival tissues as noted in point (a) above): tumor tissue collected any time after completion of dosing of the last therapy and prior to first dose and an on-treatment biopsy.

5.2. Exclusion Criteria

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

1. Received prior treatment with the following therapies; calculation is based on date of last therapy to date of first dose of study intervention or SOC:

    a. CTLA-4 (including tremelimumab) or ICOS-directed therapies at any time.

    b. ≥4 lines of prior anticancer treatment:

        i. In participants that relapse or progress within 1 year from the beginning of adjuvant or concurrent therapy, the adjuvant/concurrent therapy is considered first line therapy

    c. Systemic anticancer therapy or investigational therapy within 30 days, or 5 half-lives, whichever is shorter; at least 14 days must have elapsed between the date of the last prior therapy to the date of first dose of study intervention or SOC.

2. Prior radiation therapy: permissible if at least one non-irradiated measurable lesion is available for assessment per RECIST v1.1 or if a solitary measurable lesion was irradiated, objective progression is documented. At least 14 days must have elapses between the date of the last dosage of radiation and the first dose of study intervention/SOC.

3. Invasive malignancy or history of invasive malignancy other than disease under study within the last two years, <u>except</u> as noted below:

    a. Any other invasive malignancy for which the participant was definitively treated, has been disease-free for ≤2 years and in the opinion of the Investigator and Medical Monitor will not affect the evaluation of the effects of the study intervention or SOC on the currently targeted malignancy, may be included in this clinical study.

b. Curatively treated non-melanoma skin cancer or successfully treated in-situ carcinoma

4. Toxicity from previous anticancer treatment that includes:

   a. ≥Grade 3 toxicity considered related to prior immunotherapy and that led to treatment discontinuation.

   b. Toxicity related to prior treatment that has not resolved to ≤Grade 1 (except alopecia, vitiligo, hearing loss, endocrinopathy managed with replacement therapy, and peripheral neuropathy which must be ≤Grade 2).

5. Central nervous system (CNS) metastases, with the following exception: Participants with previously treated CNS metastases who are clinically stable and had no requirement for steroids during at least 14 days prior to first dose of study intervention or SOC.

   Note: Participants with carcinomatous meningitis or leptomeningeal spread are excluded regardless of clinical stability.

6. Major surgery ≤28 days of first dose of study intervention or SOC.

   Note: Tracheostomy is not considered major surgery.

7. Autoimmune disease (current or history) or syndrome that required systemic treatment within the past 2 years. Replacement therapies which include physiological doses of corticosteroids for treatment of endocrinopathies (i.e., adrenal insufficiency) are not considered systemic treatments.

8. Recent history (within 24 weeks) of gastrointestinal obstruction that required surgery, acute diverticulitis, inflammatory bowel disease, or intra-abdominal abscess.

9. Receiving systemic steroids (≥10 mg oral prednisone or equivalent) or other immunosuppressive agents within 7 days prior to first dose of study intervention or SOC.

   Note: Steroids as premedication for hypersensitivity reactions (e.g., computed tomography [CT] scan premedication) are permitted.

10. Prior allogeneic/autologous bone marrow or solid organ transplantation.

11. Received live-virus vaccine within 30 days from start of study intervention or SOC.

    Note: Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (for example, FluMist™) are live attenuated vaccines and are not allowed.

12. Current or history of idiopathic pulmonary fibrosis, pneumonitis (for past, participant is excluded if steroids were required), interstitial lung disease or organizing pneumonia

Note: Post-radiation changes in the lung and/or asymptomatic radiation-induced pneumonitis not requiring treatment may be permitted if agreed upon by the Investigator and Medical Monitor.

13. Recent history (within 24 weeks) of uncontrolled, symptomatic ascites, pleural or pericardial effusions.

14. History or evidence of cardiac abnormalities within the 24 weeks prior to enrollment which include:

    a. Serious uncontrolled cardiac arrhythmia or clinically significant electrocardiogram abnormalities including second degree (Type II) or third degree atrioventricular block.

    b. Cardiomyopathy, myocardial infarction, acute coronary syndromes (including unstable angina pectoris), coronary angioplasty, stenting, or bypass grafting.

    c. Symptomatic pericarditis.

15. Current unstable liver or biliary disease per Investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis. NOTE: Stable chronic liver disease (including Gilbert's syndrome or asymptomatic gallstones) is acceptable.

16. Active infection requiring systemic therapy.

17. Known human immunodeficiency virus infection; positive test for hepatitis B active infection (presence of hepatitis B surface antigen) or hepatitis C active infection; refer to Table 16 for additional details.

18. History of severe hypersensitivity to monoclonal antibodies, the Standard of Care agents, including any ingredient used in the formulation, based on which treatment the participant is to receive.

19. Any serious and/or unstable pre-existing medical (aside from malignancy), psychiatric disorder, or other conditions that could interfere with participant's safety, obtaining informed consent or compliance to the study procedures, in the opinion of the Investigator.

20. For participants receiving SOC: Requires therapy with a medication that may alter the PK of the SOC agent (e.g., strong inducers or inhibitors of CYP3A4 for participants receiving docetaxel or paclitaxel) during the study treatment period. Please refer to the package insert for the agent the participant is to receive.

21. For participants receiving SOC: Any contraindication, per the package insert and/or Institutional guidelines, to the treatment the participant is to receive.

5.3. Lifestyle Considerations

Participants should refrain from donating blood while participating in this study.

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting. For participants receiving SOC, the Investigator should refer to the applicable package insert and/or Institutional guidelines for foods to avoid during the study treatment period (e.g., grapefruit, star fruit and pomegranate are known CYP3A4 inhibitors and should not be consumed while receiving docetaxel or paclitaxel).

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are never subsequently assigned a randomization number. 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 (CONSORT) 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. Rescreened participants must be assigned a new unique participant number that is different from the initial number.

6. STUDY INTERVENTION

6.1. Study Intervention(s) Administered

GSK3359609 and tremelimumab will be provided to sites by the study Sponsor. Investigator's choice of SOC in Part 2 (paclitaxel, docetaxel or cetuximab) will be provided by the site per standard of care.

The route of administration for all agents is IV, thus they should be administered to participants at each study site under medical supervision of an Investigator or designee (see Table 5).

Tremelimumab is to be administered first as an IV infusion over 60 minutes. GSK3359609 will be administered as a 30-minute IV infusion beginning at least 1 hour and no more than 2 hours following the end of the tremelimumab infusion. Infusion time of each may be adjusted based on infusion-related reactions.

Standard of care agents should be administered as per local and Institutional guidelines (Table 6). Participants may receive necessary premedication regimens according to the approved product label or standard practice (i.e., corticosteroids, antihistamines, etc).

Table 5 Description and Administration of Study Interventions

	Study Intervention	
Product Name:	GSK3359609	Tremelimumab
Product Description	Humanized anti-ICOS agonist IgG4 mAb	Humanized anti-CTLA-4 IgG2 mAb
Dosage form /strength:	10 mg/mL solution	20 mg/mL solution
Planned dosage level(s):	**Part 1**: Dose escalation GSK3359609/tremelimumab: 8 mg/75 mg; 8 mg/225 mg; 24 mg/75 mg; 24 mg/225 mg; 80 mg/75 mg; 80 mg/225 mg **Part 2**: RP2D determined from Part 1	
Route of Administration	IV infusion	IV infusion
Dosing instructions/ Frequency:	Administer diluted product/Q3W	Administer diluted product/Q3W for 6 doses then Q12W thereafter
Manufacturer	GSK	MedImmune

Table 6 Standard of Care Agents

Product Name:	**Docetaxel**	**Paclitaxel**	**Cetuximab**
Description	Microtubule stabilizer/ small molecule	Microtubule stabilizer/ small molecule	Recombinant, human/mouse chimeric anti-EGFR mAb
Dosage form/strength	Refer to package insert	Refer to package insert	Refer to package insert
Dosage/frequency	75 mg/m^2 administered once every 3 weeks	80 mg/m^2 administered once weekly	Administer a loading dose of 400 mg/m^2 followed by 250 mg/m^2 once weekly
Route of administration	IV infusion	IV infusion	IV infusion

6.2. Preparation/Handling/Storage/Accountability

Refer to the Study Reference Manual (SRM) for instructions on the preparation of investigational study interventions (both GSK3359609 and tremelimumab). Standard of Care agents should be prepared and handled per local and Institutional guidelines.

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for each study intervention received and any discrepancies are reported and resolved before use of the study intervention.

- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions 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 intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study intervention are provided in the SRM.
- Under normal conditions of handling and administration, study intervention 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 (MSDS)/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.

6.3. Measures to Minimize Bias: Randomization and Blinding

In Part 2 of the study, once determined to be eligible for the study, all participants will be centrally randomized using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and directions for the IWRS will be provided to each site.

This is an open-label study; however, participants will be randomized to study intervention or SOC in Part 2 of the study using an IVRS/IWRS to reduce potential bias.

6.4. Study Intervention Compliance

Study interventions will be intravenously administered to participants at the site. Administration will be documented in the source documents and reported in the CRF.

6.5. Concomitant Therapy

Participants will be instructed to inform the Investigator prior to starting any new medications from the screening visit until discontinuation of study intervention. Any permitted concomitant medication(s), including non-prescription medication(s) and herbal product(s), taken during the study will be recorded in the eCRF. The minimum requirement for reporting is drug name, dose, dates of administration, and the reason for medication.

Questions regarding concomitant medications must be directed to GSK for clarification.

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

For participants randomized to SOC, refer to the drug interaction information in the product package inserts for precautions and prohibited concomitant medications related to the SOC chosen by the Investigator.

6.5.1. Permitted Medications and Non-Drug Therapies

All participants should receive full supportive care during the treatment course of the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate. Seasonal flu vaccine is permitted as an injection only, i.e., intra-nasal flu vaccine is not permitted. Elective palliative surgery or radiation may be permitted on a case-by-case basis in consultation with GSK Medical Monitor.

The following medications are permitted as indicated:

a. Bisphosphonates and receptor activator of nuclear factor-kappaB ligand (RANKL) inhibitors (e.g., denosumab): Participants are required to have been on a stable dose for at least 4 weeks prior to receiving first dose of study intervention. Prophylactic use in participants without evidence or history of bone metastasis is not permitted, except for the treatment of osteoporosis.

b. Growth factors: Initiation of growth factors is not permitted during the first 4 weeks of study intervention, unless clinically indicated for toxicity management and agreed upon by the Investigator and the GSK Medical Monitor.

c. Steroids: Participants with pre-existing conditions requiring steroids are permitted to continue taking up to a maximum of 10 mg of prednisone or equivalent provided the participant has been on a stable dose for at least 28 days before first dose of study intervention; see exclusion criteria in Section 5.2 for further requirements. Steroids used for premedication of SOC and hypersensitivity reactions (e.g., CT scan premedication) are permitted.

d. Treatment with cannabinoids prescribed by a Physician are permitted.

6.5.2. Prohibited Medications and Non-Drug Therapies

The following medications are prohibited before the first dose of study intervention/SOC (see Section 5.2 for specific time requirements) and during the study treatment period:

a. Anticancer therapies other than those referred to as study intervention that include, but are not limited to chemotherapy, immunotherapy, biologic therapy, hormonal therapy (other than physiologic replacement), surgery, and radiation therapy (other than palliative intervention as described in Section 6.5.1)

b. Any investigational drug(s) other than those referred to as study intervention

c. Live vaccines such as intra-nasal flu vaccine (see exclusion criteria in Section 5.2 for further details).

d. For participants receiving SOC, any medication that may alter the PK of the SOC agent (e.g., strong inducers or inhibitors of CYP3A4 for participants receiving docetaxel or paclitaxel) as per the package insert and/or Institutional guidelines.

6.6. Dose Modification and Safety Management Guidelines

Distinct safety management guidelines, including dose modification algorithms, are provided in this section for participants treated with the combination of GSK3359609 and tremelimumab.

Please note: In instances where the Investigator is directed to permanently discontinue study intervention per Table 7, this is mandatory for tremelimumab and at the discretion of the Investigator for GSK3359609. However, GSK3356909 may only be restarted if the event resolves to ≤ Grade 1 within 14 days AND has been stable at ≤ Grade 1 for at least 7 days and requires approval from the Medical Monitor.

Refer to SOC prescribing information or standard practice guidelines for the management of AEs or potential safety-related issues.

All AEs are to be graded according to NCI-CTCAE (version 5.0) [NCI, 2017]. All dose modifications and the reason(s) for the dose modification must be documented in the eCRF.

6.6.1. General Guidelines for Immune-Related Adverse Events

AEs associated with immunotherapy treatment may be immune-mediated. These immune-related AEs (irAEs) may occur shortly after the first dose, several months after the last dose of treatment, or during the treatment course, and may affect more than one body system simultaneously. Therefore, early recognition of and initiation of treatment for these events is critical to reduce potential complications.

For suspected irAEs, ensure adequate evaluation to confirm the etiology or exclude other causes. Additional procedures or tests such as, but not limited to, bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue treatment and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with immunotherapies are provided in Table 7, though irAEs may occur in nearly all organs, some of them not noted in the guidelines. **Note**: This guidance does not apply to participants randomized to SOC in Part 2.

Before administration of study intervention, investigators are to review a participant's AEs, concomitant medications, and clinical evaluation results, e.g., vital signs, laboratory results, ECG, ECOG PS, physical examination findings, responses, etc. as outlined in the Schedule of Activities (Section 1.3) to monitor for new or worsening irAEs and ensure continues dosing is appropriate.

Adverse Events of Special Interest (AESI)

AESI are defined as events of potential immunologic etiology, including irAEs. Such events recently reported after treatment with other immune modulatory therapy include

colitis, uveitis, hepatitis, pneumonitis, diarrhea, endocrine disorders, and specific cutaneous toxicities, as well as other events that may be immune mediated.

Table 7 Dose Modification and Toxicity Management Guidelines for Immune-related AEs

General Instructions for dose modifications:	
Grade 1	No dose modifications
Grade 2	Hold study intervention until Grade 2 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or Grade 4. Study intervention can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. Participants with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study intervention on the following conditions: • The event stabilizes and is controlled. • The participant is clinically stable as per Investigator clinical judgement. • Doses of prednisone are at ≤10 mg/day or equivalent. Consider whether study intervention should be permanently discontinued in events with high likelihood for morbidity and/or mortality (e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines) when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper.
Grade 3	Depending on the individual toxicity, study intervention may be permanently discontinued. Please refer to guidelines below. Note: For Grade ≥3 asymptomatic amylase or lipase levels, hold study intervention, and if complete work up shows no evidence of pancreatitis, study intervention may be continued or resumed. Note: Study intervention should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines.
Grade 4	Permanently discontinue study intervention. Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (e.g., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).
Additionally, permanently discontinue study intervention for the following conditions: • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) within 12 weeks after last dose of study intervention. • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing.	
General Instructions for toxicity management:	
It is possible that events with an inflammatory or immune-mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. Whether specific irAEs (and/or laboratory indicators of such events) are noted in these guidelines or not, participants should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. • Symptomatic and topical therapy should be considered for low grade (Grade 1 or 2, unless otherwise specified) events. • For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. • Some events with high likelihood for morbidity and/or mortality (e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines) should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the Medical Monitor, and promptly pursue specialist consultation. • If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper). • More potent immunosuppressives such as TNF inhibitors (e.g., infliximab) (also refer to the individual	

sections of the irAEs for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality (e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines) when these events are not responding to systemic steroids.

- With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring.
- Discontinuation of study intervention is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study intervention in this situation should be based upon a benefit-risk analysis for that participant.

Specific Immune-Related AEs:

Immune-related AEs	Severity grade (CTCAEv5.0) or conditions	Dose Modification / General Guidance	Toxicity Management
Pneumonitis / Interstitial Lung Disease (ILD)	**Any Grade**		• Monitor participants for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Participants should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. • Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study intervention dose as clinically appropriate and during diagnostic work-up for other etiologies.	• Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. • Consider Pulmonary and Infectious disease consult.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental activities of daily living [ADLs])	Hold study intervention until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then the decision to reinitiate study intervention will be based upon treating physician's clinical judgment and after completion of steroid taper.	• Monitor symptoms daily and consider hospitalization. • Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). • Reimage as clinically indicated. • If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started • If still no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. • Once the participant is improving,

			gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment. • Consider pulmonary and infectious disease consult. • Consider, as necessary, discussing with Medical Monitor.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy or intubation])	Permanently discontinue study intervention.	• Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. • Obtain Pulmonary and Infectious disease consult; consider, as necessary, discussing with Medical Monitor. • Hospitalize the participant. • Supportive care (e.g., oxygen). • If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. • Once the participant is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment.
Diarrhea / Colitis	**Any Grade**		• Monitor for symptoms that may be related to diarrhea/enterocolitis (e.g., abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (e.g., sepsis, peritoneal signs, and ileus). • Participants should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. • Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, to prevent potential progression to higher grade event. • Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). • Participants should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other

			medications, or infections), including testing for clostridium difficile toxin, etc. • Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, to prevent potential progression to higher grade event. • Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only)	No dose modifications.	• Monitor closely for worsening symptoms. • Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
	Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day) (Colitis: abdominal pain; mucus or blood in stool)	Hold study intervention until resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study intervention can be resumed after completion of steroid taper.	• Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. • Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. • If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. • If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks. Caution: it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. • Consider, as necessary, discussing with Medical Monitor if no resolution to Grade ≤1 in 3 to 4 days. • Once the participant is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment.
	Grade 3 or 4 (Grade 3 diarrhea: stool frequency of ≥7 over baseline	**Grade 3** Permanently discontinue if toxicity does not improve to Grade ≤1 within 14	• Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. • Monitor stool frequency and volume and

	per day; Grade 4 diarrhea: life threatening consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs; Grade 4 colitis: life-threatening consequences, urgent intervention indicated)	days; study intervention can be resumed after completion of steroid taper. **Grade 4** Permanently discontinue study intervention.	maintain hydration. • Urgent GI consult and imaging and/or colonoscopy as appropriate. • If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g., infliximab at 5 mg/kg once every 2 weeks). Caution: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. • Once the participant is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment.
Hepatitis (elevated liver function tests [LFTs])	**Any grade**		• Monitor and evaluate LFTs: AST, AST, alkaline phosphatase, bilirubin. • Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	Grade 1 (AST or ALT >ULN and ≤3.0xULN and/or bilirubin > ULN and ≤1.5xULN)	No dose modifications. If event worsens, treat as Grade 2.	• Continue LFT monitoring per protocol.
	Grade 2 (AST or ALT >3.0xULN and ≤5.0xULN and/or bilirubin >1.5xULN and ≤3.0xULN)	**Refer to Section 7.1.1 for stopping criteria and required follow up.** ONLY if labs do not meet stopping criteria: • Study intervention should be held until Grade 2 resolution to Grade ≤1. • If toxicity improves to Grade ≤1 or baseline, resume study intervention after completion of steroid taper. If toxicity worsens, then treat as Grade 3 or 4.	• Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved. • If no resolution to Grade ≤1 in 1 to 2 days, consider, as necessary, discussing with Medical Monitor. • If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. • If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional work up and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. • If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e., mycophenolate mofetil). Discuss with Medical Monitor if mycophenolate mofetil is not available. **Infliximab should NOT be used.** • Once the participant is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment.
	Grade 3 or 4 (Grade 3: AST or ALT >5.0xULN and	**Refer to Section 7.1.1 for stopping criteria and required follow up.**	• Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent.

	≤20.0xULN and/or bilirubin >3.0xULN and ≤10.0xULN) (Grade 4: AST or ALT >20xULN and/or bilirubin >10xULN)		• If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (i.e., mycophenolate mofetil). Discuss with Medical Monitor if mycophenolate is not available. **Infliximab should NOT be used.** • Perform hepatology consult, abdominal workup, and imaging as appropriate. • Once the participant is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment.
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade**		• Consult with nephrologist. • Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). • Participants should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections). • Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.

	Grade 1 (Serum creatinine > 1 to 1.5 x baseline; > ULN to 1.5xULN)	No dose modifications.	• Monitor serum creatinine weekly and any accompanying symptoms.
			  ○ If creatinine returns to baseline, resume its regular monitoring per study protocol.
			  ○ If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4.
			• Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.

	Grade 2 (serum creatinine >1.5 to 3.0 x baseline; >1.5 to 3.0 x ULN)	Hold study intervention until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study intervention after completion of steroid taper.	• Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. • Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. • Consult nephrologist and consider renal biopsy if clinically indicated. • If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. • If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent,

			additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. • Once the participant is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment. • When event returns to baseline, resume study intervention and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: serum creatinine >3.0 x baseline; >3.0 to 6.0 x ULN; Grade 4: serum creatinine >6.0 x ULN)	Permanently discontinue study intervention.	• Carefully monitor serum creatinine on daily basis. • Consult nephrologist and consider renal biopsy if clinically indicated. • Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. • If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. • Once the participant is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment.
Rash (excluding bullous skin formations)	**Any Grade**		• Monitor for signs and symptoms of dermatitis (rash and pruritus). • IF THERE IS ANY BULLOUS FORMATION, THE MEDICAL MONITOR SHOULD BE CONTACTED AND STUDY DRUG DISCONTINUED.
	Grade 1	No dose modifications.	• Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study intervention until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume intervention after completion of steroid taper.	• Obtain dermatology consult. • Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). • Consider moderate-strength topical steroid. • If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with Medical Monitor and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. • Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
	Grade 3 or 4	**Grade 3**	• Consult dermatology.

		Hold study intervention until resolution to Grade ≤1 or baseline. If temporarily holding the study intervention does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study intervention. **Grade 4** Permanently discontinue study intervention.	• Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. • Consider hospitalization. • Monitor extent of rash [Rule of Nines]. • Consider skin biopsy (preferably more than 1) as clinically feasible. • Once the participant is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment. • Consider, as necessary, discussing with Medical Monitor.
Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	**Any Grade**		• Consider consulting an endocrinologist for endocrine events. • Consider, as necessary, discussing with Medical Monitor. • Monitor participants for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. • Participants should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). • Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). • For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. • If a participant experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
	Grade 1 (including those with asymptomatic endocrinopathy)	No dose modifications.	• Monitor participant with appropriate endocrine function tests. • For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones,

			and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). • If TSH < 0.5xLLN, or TSH >2xULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
	Grade 2 (including those with symptomatic endocrinopathy)	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study intervention dose until participant is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study intervention can be resumed once event stabilizes and after completion of steroid taper. Participants with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study intervention on the following conditions: • The event stabilizes and is controlled. • The participant is clinically stable as per investigator or treating physician's clinical judgement. • Doses of prednisone are ≤10 mg/day or equivalent.	• Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. • For all participants with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). • Isolated hypothyroidism may be treated with replacement therapy, without study intervention interruption, and without corticosteroids. • Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study intervention interruption, and without corticosteroids. • Once participants on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment. • For participants with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study intervention dose until endocrinopathy symptom(s) are controlled. Study intervention can be resumed once event stabilizes and after completion of steroid taper. Participants with	• Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. • For all participants with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone

		endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study intervention on the following conditions: • The event stabilizes and is controlled. • The participant is clinically stable as per investigator or treating physician's clinical judgement. • Doses of prednisone are ≤10 mg/day or equivalent.	replacement (e.g., hydrocortisone, sex hormones). • For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. • Isolated hypothyroidism may be treated with replacement therapy, without study intervention interruption, and without corticosteroids. • Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study intervention interruption, and without corticosteroids. • Once participants on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment.
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade**		• Participants should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). • Monitor participant for general symptoms (headache, nausea, vertigo, behavior change, or weakness). • Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). • Perform symptomatic treatment with neurological consult as appropriate.
	Grade 1	No dose modifications.	• See "Any Grade" recommendations above.
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study intervention dose until resolution to Grade ≤1. For sensory neuropathy/neuropathic pain, consider holding study intervention dose until resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or 4. Study intervention can be resumed once event improves to Grade ≤1 and after completion of steroid taper.	• Consider, as necessary, discussing with the Medical Monitor. • Obtain neurology consult. • Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). • Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. • If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (e.g., IV immunoglobulin therapy [IVIG]).
	Grade 3 or 4	**Grade 3** Hold study intervention dose until resolution to Grade ≤1.	• Consider, as necessary, discussing with Medical Monitor. • Obtain neurology consult. • Consider hospitalization.

		Permanently discontinue study intervention if Grade 3 irAE does not resolve to Grade ≤1 within 30 days. **Grade 4** Permanently discontinue study intervention.	• Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. • If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., IVIG). • Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade**		• The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain participants may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. • Participants should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in participants with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. • Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. • It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Participants requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.
	Grade 1	No dose modifications.	• Consider, as necessary, discussing with the Medical Monitor. • Care should be taken to monitor participants for sentinel symptoms of a

			potential decompensation as described above. • Obtain a neurology consult.
	Grade 2	Hold study intervention dose until resolution to Grade ≤1. Permanently discontinue study intervention if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	• Consider, as necessary, discussing with the Medical Monitor. • Care should be taken to monitor participants for sentinel symptoms of a potential decompensation as described above. • Obtain a neurology consult • Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). MYASTHENIA GRAVIS: • Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. • Participants unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. Such decisions are best made in consultation with a neurologist, considering the unique needs of each participant. • If myasthenia gravis-like neurotoxicity is present, consider starting AchE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. GUILLAIN-BARRE: • It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. • Participants requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.
	Grade 3 or 4 (severe or life-threatening events)	**Grade 3** Hold study intervention dose until resolution to Grade ≤1. Permanently discontinue study intervention if Grade 3 irAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **Grade 4** **Permanently discontinue study intervention.**	• Consider, as necessary, discussing with Medical Monitor. • Recommend hospitalization. • Monitor symptoms and obtain neurological consult. MYASTHENIA GRAVIS: • Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. • Participants unable to tolerate steroids may be candidates for treatment with

			plasmapheresis or IVIG. • If myasthenia gravis-like neurotoxicity present, consider starting AchE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. GUILLAIN-BARRE: • It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. • typically considered effective. • Participants requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.
Myocarditis	**Any Grade**	Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	• The prompt diagnosis of immune-mediated myocarditis is important, particularly in participants with baseline cardiopulmonary disease and reduced cardiac function. • Consider, as necessary, discussing with the Medical Monitor. • Monitor participants for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. • Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. • Participants should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
	Grade 1 (asymptomatic with laboratory (e.g., BNP) or cardiac imaging abnormalities)	No dose modifications required unless clinical suspicion is high, in which case hold study intervention dose during diagnostic work-up for	• Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. • Consider using steroids if clinical

		other etiologies. If study intervention is held, resume after complete resolution to Grade 0.	suspicion is high.
	Grade 2, 3 or 4 (Grade 2: Symptoms with mild to moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support))	**Grade 2** Hold study intervention dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study intervention will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. Discontinue study intervention. **Grade 3 or 4** Permanently discontinue study intervention.	• Monitor symptoms daily, hospitalize. • Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. • Supportive care (e.g., oxygen). • If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. • Once the participant is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment.
Myositis / Polymyositis ("Poly/myositis")	**Any Grade**		• Monitor participants for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also, difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. • If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. • Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. • Consider, as necessary, discussing with the Medical Monitor. • Initial work-up should include clinical evaluation, creatine kinase, aldolase,

			LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. • Participants should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
	Grade 1 (mild pain)	No dose modifications.	• Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. • Consider Neurology consult. • Consider, as necessary, discussing with the Medical Monitor.
	Grade 2 (moderate pain associated with weakness; pain limiting instrumental ADLs)	Hold study intervention dose until resolution to Grade ≤1. • Permanently discontinue study intervention if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	• Monitor symptoms daily and consider hospitalization. • Obtain Neurology consult, and initiate evaluation. • Consider, as necessary, discussing with the Medical Monitor. • If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant • If clinical course is not rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day • If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. • Once the participant is improving,

			gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment.
	Grade 3 or 4 (pain associated with severe weakness; limiting self-care ADLs; severe or life-threatening events)	**Grade 3** Hold study intervention dose until resolution to Grade ≤1. Permanently discontinue study intervention if Grade 3 irAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **Grade 4** Permanently discontinue study intervention.	• Monitor symptoms closely; recommend hospitalization. • Obtain Neurology consult, and complete full evaluation. • Consider, as necessary, discussing with the Medical Monitor. • Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. • If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. • Consider whether participant may require IVIG, plasmapheresis. • Once the participant is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment.

6.6.2. Dose Modification and Toxicity Management of Infusion-Reactions Related to Immunotherapy Treatment

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

Infusion reactions may affect any organ system in the body. Most are mild in severity, although severe and even fatal reactions occur. As a group, infusion reactions (including both cytokine-mediated and allergic) usually occur during or within a few hours of drug infusion. Occasionally, a reaction may occur one to two days after administration. The NCI-CTCAE (version 5.0) [NCI, 2017] for grading adverse reactions during chemotherapy administration has a scale for grading the severity of infusion reactions and separate grading scales for allergic reactions and anaphylaxis. While use of these separate grading scales may be useful for classifying the nature of an infusion reaction for research purposes, they are less useful for clinical care, since it may not be obvious if the participant is having an allergic infusion reaction or a non- allergic infusion reaction.

Clinically, infusion reactions may present with 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. See Table 9 and Table 10 for dose modification and treatment guidance for GSK3359609 and tremelimumab infusion reactions, respectively.

To better understand the underlying etiology of these events, serum tryptase, C-reactive protein (CRP), ferritin, and a cytokine panel should be drawn during the occurrence of an infusion reaction/CRS of any grade as outlined in Table 8. The serum tryptase, CRP and ferritin panels may be performed at the Investigator's designated local laboratory, if available. The serum cytokine panel will be performed at a GSK designated laboratory. These data will aid in the classifying (albeit retrospectively) the etiology of the AE.

Table 8 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-13, and IL-17)	* 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-g = Interferon gamma; TNF-a = Tumor necrosis factor alpha; IL = Interleukin.

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

b. Performed by GSK designated laboratory

These guidelines are suggestions. Investigators and site staff may also follow their site standard operating procedures for the treatment of these events.

Table 9 Immunotherapy Infusion Reaction Dose Modification and Treatment Guidelines for GSK3359609

NCI-CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be pre-medicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment	Participant may be pre-medicated 1.5h (± 30 minutes) prior to infusion of GSK3359609 with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the NCI-CTCAE v5.0 [NCI, 2017]		

Table 10 Immunotherapy Infusion Reaction Dose Modification and Treatment Guidelines for Tremelimumab

NCI-CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Any Grade	Management per Institutional standard at the discretion of investigator. Monitor participants for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes etc) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, tachycardia).	
Grade 1	The infusion rate of tremelimumab may be decreased by 50% or temporarily interrupted until resolution of the event. Acetaminophen and/or antihistamines may be administered per Institutional standard at the discretion of the investigator.	Consider premedication per Institutional standard prior to subsequent doses
Grade 2	The infusion rate of tremelimumab may be decreased 50% or temporarily interrupted until resolution of the event (up to 4 hours). Subsequent infusions may be given at 50% of the initial infusion rate. Acetaminophen and/or antihistamines may be administered per Institutional standard at the discretion of the investigator.	Consider premedication per Institutional standard prior to subsequent doses
Grade 3/4	Permanently discontinue. Manage severe infusion-related reactions per Institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).	

6.6.3. Dose Delay

For GSK3359609 in combination with tremelimumab, 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. Subsequent visits will follow as originally scheduled. If the delay is ≥8 days, the visit and dose(s) will be considered missed. The procedures at the next scheduled visit should be performed as originally scheduled, and subsequent visits will continue to follow Q3W. For all dose delays, disease assessments should continue as per Section 8.1.1.2. Participants with infusion delays greater than three weeks due to toxicity should discontinue study intervention unless the treating Investigator and Sponsor/Medical Monitor agree there is strong evidence supporting continued treatment. For participants requiring elective surgery or radiation therapy, every effort should be made to wait one to two weeks after the last dose of study intervention before performing surgery or starting radiation. Study intervention should not be administered again until one to two weeks after recovery from surgery or radiation (refer to Section 6.5.1 for details on permitted medications and non-drug therapies).

For participants randomized to receive SOC, Investigators should follow the applicable package insert and/or Institutional guidelines for dose delays. Protocol-defined assessments (e.g., safety assessments, disease assessments) should continue as outlined in the SoA, Section 1.3

6.7. Intervention after the End of the Study

The study participants will not receive any additional treatment from GSK after permanent discontinuation of study intervention. The Investigator is responsible for

ensuring that consideration is given to the post-study care of the participant's medical condition.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Participants will receive study intervention or SOC for the scheduled period as indicated in the SoA, unless one of the following events occurs earlier:

- disease progression (as determined by iRECIST)
- death
- unacceptable toxicity, including meeting stopping criteria for liver chemistry abnormalities, QTc prolongation or clinical deterioration

In addition, study intervention or SOC may be permanently discontinued for any of the following reasons:

- Deviation(s) from the protocol
- Request of the participant or proxy (withdrawal of consent by participant or proxy)
- Discretion of the Investigator
- Participant is lost to follow-up
- Closure or termination of the study
- Study intervention must be permanently discontinued in the case of pregnancy

A participant may withdraw consent at any time; no further assessments will be required and the Investigator must document this in the site study records.

All participants who discontinue from study intervention or SOC (early or permanent) for any reason will have safety assessments at the time of discontinuation and during follow-up as specified in the SoA.

All participants who permanently discontinue study intervention or SOC without disease progression will be followed for progression according to the protocol-defined on-treatment disease assessment schedule until one or more of the following occur:

- a new anticancer therapy is initiated
- disease progression
- death

Participants permanently discontinuing study intervention after progression by RECIST 1.1 but prior to confirmed progression by iRECIST should be followed to confirm progression (see Table 18).

All participants who permanently discontinue study intervention or SOC for any reason will be followed for survival and new anticancer therapy (including radiotherapy) every 12 weeks until death, termination of the overall study or an arm by the Sponsor. The every 12-week schedule should begin once the study intervention/SOC has been discontinued. If participants are unable or unwilling to attend clinic visits during follow-up, contact to assess survival may be made via another form of communication (e.g., telephone, email, etc.).

Early discontinuation of GSK3359609 and tremelimumab (early discontinuation will not per se constitute permanent discontinuation) may be considered for participants who have attained a confirmed complete response per RECIST 1.1 and who received study intervention for at least 24 weeks and had at least two treatments of GSK3359609 beyond the date when the initial CR was declared; these participants will undergo disease assessments at a frequency of 12 weeks. These participants may be permitted to resume study intervention upon disease progression following consultation with the Investigator and GSK Medical Monitor and upon written consent by the participant. If study intervention is restarted, participants will be required to resume assessments outlined in the SoA in Section 1.3. See Section 7.1.1 for specific conditions under which a participant may continue study intervention beyond disease progression.

If the study is terminated by the Sponsor for reasons unrelated to safety, and a participant is currently active in the study, receiving study intervention, and is deriving benefit from that intervention without evidence of disease progression in the opinion of the Investigator, the participant may continue to receive study intervention upon agreement between the Sponsor and Investigator.

7.1.1. Continuation of Treatment Upon Confirmed Disease Progression

Participants who have confirmed disease progression (unequivocal disease progression) by RECIST 1.1 may continue study intervention at the discretion of the Investigator with approval from the Medical Monitor, and upon separate written consent of the participant. Continuation on study intervention with confirmed disease progression is contingent upon the following conditions:

- participant has documented clinical benefit
- absence of clinical signs or symptoms indicating clinically significant disease progression
- no decline in ECOG performance status
- absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g., CNS metastasis, respiratory failure due to tumor compression, or spinal cord compression) requiring urgent alternative medical intervention
- no significant, unacceptable, or irreversible toxicities related to study intervention

7.1.2. 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 intervention for abnormal liver tests is required when a participant meets one of the conditions outlined in the algorithm in Figure 2 or for participants with documented liver metastases in Figure 3.

Figure 2 Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm for Participants with ALT up to 2.5 X ULN at Baseline

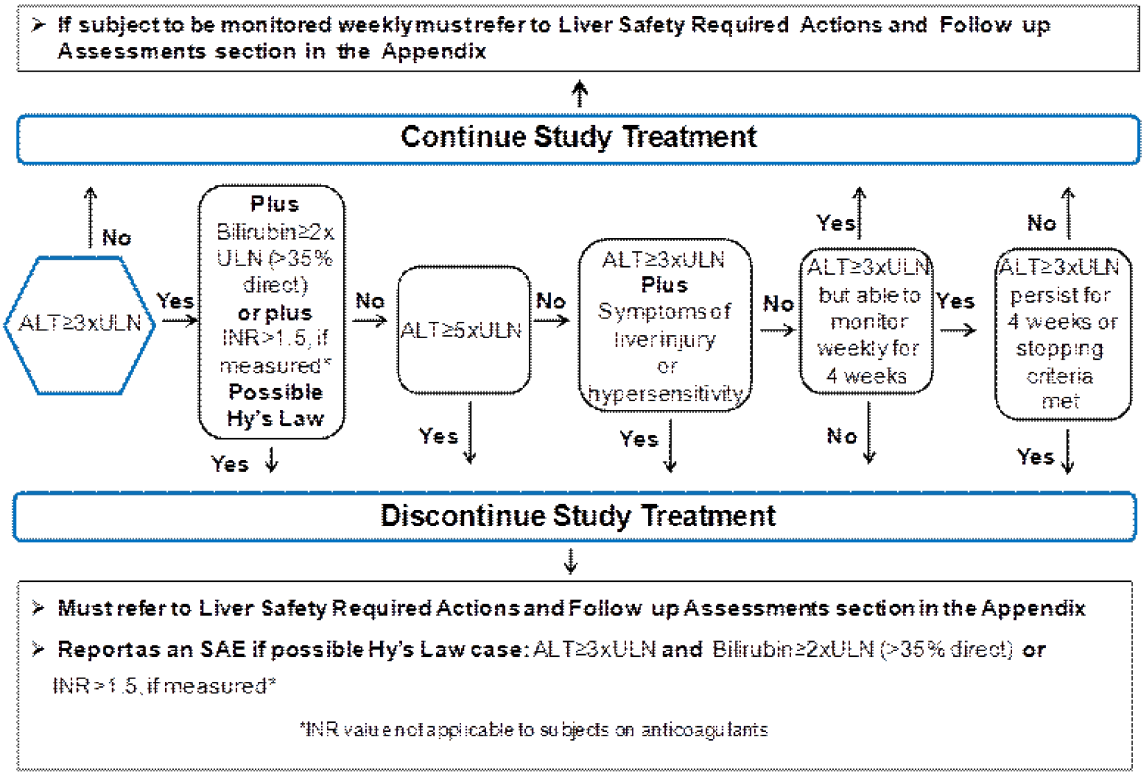
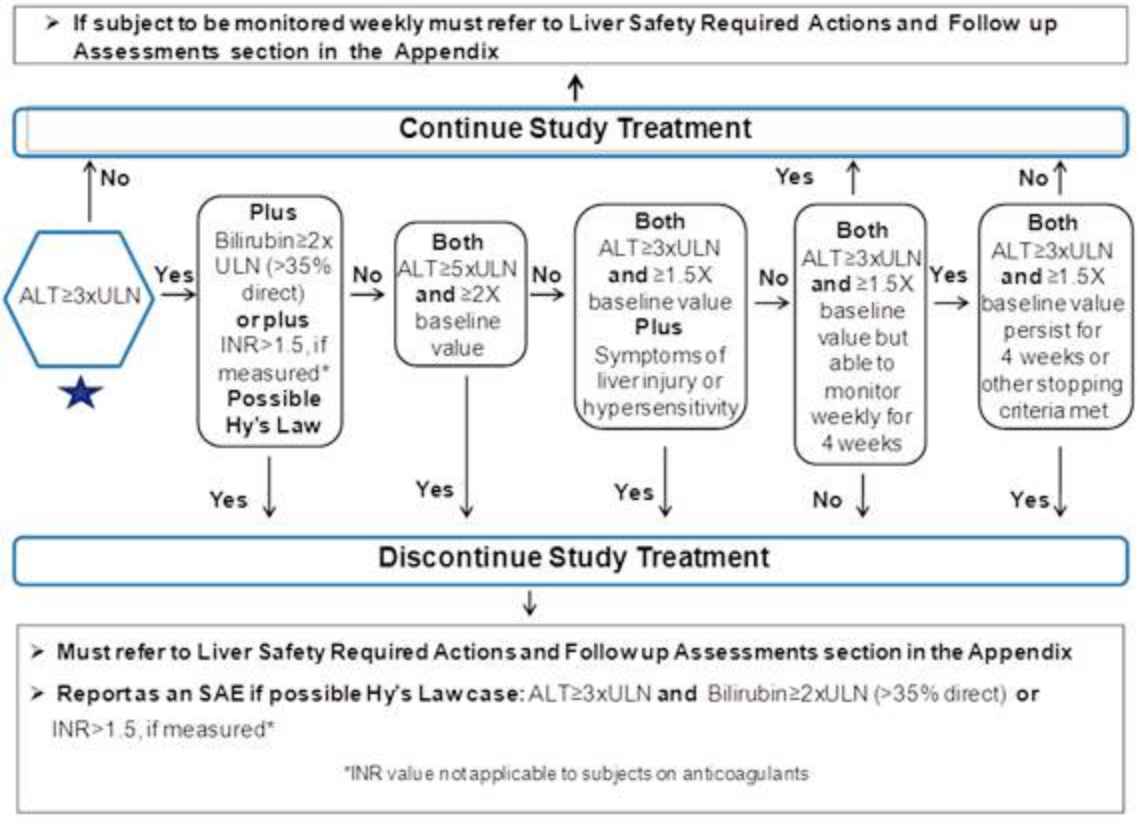


Figure 3 Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm for Participants with documented liver metastases with ALT up to 5 X ULN at Baseline



The details on follow-up procedures are outlined in Section 10.6.

7.1.2.1. Study Intervention Restart or Rechallenge after Liver Stopping Criteria Met

Study intervention restart or rechallenge is not allowed after liver chemistry stopping criteria are met by any participant in this study 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 Section 10.6 for additional information.

7.1.3. Stopping Rules for Clinical Deterioration

To adequately assess the antitumor effect of immunotherapeutic agents, it is reasonable to allow participants experiencing apparent progression as defined by RECIST 1.1 guidelines to continue to receive treatment until progression is confirmed at the next imaging assessment at least 4 weeks later as indicated by iRECIST guidelines. Nevertheless, these considerations should be balanced by clinical judgment as to whether

the participant is clinically deteriorating and unlikely to receive any benefit from continued study intervention.

In cases where deterioration was assessed to have occurred after a clinical event that, in the Investigator's opinion, is attributable to disease progression and is unlikely to reverse with continued study intervention or managed by supportive care (e.g., bisphosphonates and/or bone directed radiotherapy, thoracentesis, or paracentesis for accumulating effusions), study intervention should be discontinued. In these cases, the decision to continue treatment must 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:

- Worsening of ECOG PS from baseline by at least 2 points
- 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.

7.2. Participant Discontinuation/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. This is expected to be uncommon.

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

At the time of discontinuation from the study intervention or SOC, if possible, a treatment discontinuation visit should be conducted, as shown in the SoA. See the SoA for data to be collected at the time of study intervention/SOC discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. 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.

Discontinuation of specific sites or of the study are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- 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 intervention.
- Adherence to the study design requirements, including those specified in the SoA, 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.
- The maximum amount of blood collected from each participant from screening through Week 10, including any extra assessments that may be required, will not exceed 480 mL. If a participant completes 2 years of study intervention and all required assessments, no more than 850 mL of blood will be collected.
    - Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

8.1.1. Tumor Imaging and Disease Assessments

RECIST 1.1 will be used in the assessment of disease burden (target and non-target lesions determination) at screening and as the primary measure of tumor response endpoints. iRECIST will be used by the Investigator to assess tumor response and progression and make treatment decisions.

A description of the adaptations and iRECIST process is provided in Appendix 7, with additional details in the iRECIST publication [Seymour, 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 18 and illustrated as a flowchart in Figure 4 in Appendix 7.

Tumor images will be obtained and transmitted to a central imaging vendor for potential central review. The process for tumor imaging and transmission to the central imaging vendor are detailed in the Imaging Manual. Tumor imaging is strongly preferred to be acquired by IV/oral contrast enhanced CT. When CT with iodinated contrast is contraindicated or when mandated by local practice, MRI may be used. MRI is the preferred modality for imaging the brain and spine. The same imaging modality, ideally the same scanner, scanning technique and the use of contrast should be used for a participant throughout the study to optimize reproducibility and accuracy of assessment of existing and new tumor burden.

Notes:

1. Imaging must include the chest, abdomen, and pelvis.
2. Brain imaging should be conducted, if clinically indicated, at screening and throughout the study for evaluation of brain metastases. MRI is preferred however CT imaging with IV contrast is acceptable if MRI is medically contraindicated.
3. Bone scans are optional for participants with a history of bone metastases or for those participants with new bone pain. Any supplemental imaging done to support a positive or negative bone scan, such as plain X-rays that may be acquired for correlation, should be submitted to the central imaging vendor.

All bone scan abnormalities at screening that could indicate metastases should be evaluated by X-ray, CT, or MRI to determine if they represent malignant lesions. If a bone scan was performed within 6 weeks prior to the first dose it does not need to be repeated (in the absence of new or worsening clinical symptoms suggesting bone involvement). Typically bone scanning will be performed using bone scintigraphy; however, positron emission tomography (PET) scan ([18F]-fluorodeoxyglucose or [18F]-fluoride) is acceptable, providing coverage is sufficient to evaluate total spine, clavicle, ribs, pelvis and long bones.

8.1.1.1. Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 30 days prior to Day 1. Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if it is of diagnostic quality, is performed within 30 days prior to Day 1 and can be assessed by the central imaging vendor.

8.1.1.2. Tumor Imaging During the Study

The first on-study imaging assessment must be performed 9 weeks after the first dose of study intervention or SOC. Subsequent tumor imaging must be performed every 6 weeks until Week 52 and every 12 weeks thereafter. Imaging timing should follow calendar days and should not be adjusted for dosing delays. Imaging should continue to be

performed until confirmed disease progression is identified by the Investigator, per iRECIST (Appendix 7).

Objective response (CR or PR) must be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR must be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later and tumor imaging may resume at the subsequent scheduled imaging time point.

Per iRECIST, disease progression should be confirmed by the site at least 4 weeks and up to 8 weeks after site-assessed first radiologic evidence of PD. Participants who have unconfirmed PD may continue study intervention at the discretion of the Investigator until progression is confirmed by the site, provided they have met the conditions detailed in Appendix 7.

8.1.1.3. End of Treatment Imaging

Disease assessments at the TDV and during follow-up should be performed as outlined in Section 7.1.

8.1.2. Tumor Growth Kinetics

To evaluate the effect of study intervention on the growth rate of individual tumor lesions, pre-baseline images (within 6 months before the baseline scan) will be requested to support exploratory investigation of tumor growth kinetics. Up to 3 pre-baseline scans may be requested and submitted. Only those participants who consent to this collection will have their pre-baseline images submitted to the central vendor for these analyses.

8.1.3. Patient Reported Outcomes (PRO)

Planned time points for all assessments related to PROs are listed in the SoA and will apply to Part 2 of the study only. PRO assessments will be administered based on the availability of appropriate translated versions. Cancer can have a profound impact on patients' health related quality of life (HRQL); both the symptoms of the disease as well as the tolerability profile of treatments impact HRQL. The patient-reported outcomes (PRO) in this study (Table 11) aim to measure changes in HNSCC symptoms (EORTC-HN35), physical functioning (PROMIS-PF), and symptomatic side effects and tolerability (PRO-CTCAE and FACT-G Item 5). Cancer related HRQL will be measured with the EORTC-QLC-C30 and EQ-5D-3L.

Table 11 PRO Outcomes Assessed in Study 207871

Instrument	Role	Rationale & Overview
EORTC QLQ-C30 EORTC QLQ-HN35	Disease specific HRQoL	The current standard in disease-specific instruments for assessing cancer (specific type as well) HRQoL in clinical trials. A modular system of instruments consisting of the core 30 items (C30) and HN35 module.
PROMIS – PF	Physical Function in Cancer	Physical function can be affected by both disease symptoms and treatment-related adverse events, and needs to be evaluated separately. Physical function questions will be selected from the PROMIS PF item bank.
FACT GP5	Symptomatic AEs (Global)	Single question from the well-established FACT-G (V4), to assess overall tolerability from participant's perspective
PRO-CTCAE	Symptomatic AEs (Specific)	A standard and flexible approach to describe and evaluate symptomatic adverse events as they are experienced and reported by participants themselves.
EQ-5D-3L	Health Status	The EQ-5D is a generic instrument for describing and valuing health. It is based on a descriptive system that defines health in terms of 5 dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression.

EORTC QLQ-C30 and HN35 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 and head and neck cancer 35 module; FACT GP5 = Functional Assessment of Cancer Therapy – General Physical Well Being Item 5; PROMIS PF = Patient-Reported Outcome Measurement Information System – Physical Function; Impression of Change; PRO-CTCAE = Patient Reported Outcomes – Common Terminology Criteria for AEs; EQ-5D-3L = EuroQOL Group EQ-5D 3 Level Version.

Completion of PRO Questionnaires

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

8.1.3.1. PROMIS Physical Function

PROMIS (Patient Reported Outcome Measurement Information System) is a set of self-report measurement tools developed by the US National Institutes for Health (NIH) [Rose, 2014]. The PROMIS Physical Function item bank is a domain-based item bank developed using modern psychometric theory, containing questions assessing physical function across a range of baseline functional status.

The most recent version of the PROMIS Physical Function Item Bank (version 2.0) contains 165 items that assess a range of abilities. There also exists a 45-Item PROMIS-Cancer Item Bank (PROMIS Ca Bank version 1.1) [Jensen, 2015; Jensen, 2017] containing a subset of items that may be relevant to patients with cancer. Participants enrolled will self-complete a subset of PROMIS Physical Function items.

8.1.3.2. EORTC QLQ-C30 & HN35

The EORTC quality of life questionnaire (QLQ) is an integrated system for assessing the health-related quality of life of cancer patients participating in international clinical trials [Aaronson, 1993]. The EORTC has adopted a modular approach to QoL assessment, consisting of a core questionnaire (EORTC QLQ-C30) to be administered, if necessary, with a module specific to tumor site, treatment modality or a QoL dimension.

The QLQ-C30 is the product of more than a decade of collaborative research. It is a questionnaire for participant self-completion, composed of multi-item and single scales. These include 5 functional scales (physical, role, emotional, social and cognitive), 3 symptom scales (fatigue, nausea & vomiting and pain) and a global health status/QoL scale and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties).

The head and neck cancer module of the EORTC Quality of Life Questionnaire is a 35-item cancer specific module to be administered with the QLQ-C30 [Bjordal, 1999]. It is comprised of seven multi-item scales and 11 single items. It measures symptoms of the head and neck cancer participants including assessing pain, swallowing, senses (taste and smell), speech, social eating, social contact, sexuality, pain medication/nutritional supplements, and weight change.

8.1.3.3. FACT GP5

The FACT-G (Version 4) is a 27-item compilation of general questions divided into 4 primary QoL domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being [Cella, 1993]. It is considered appropriate for use with patients with any form of cancer, and has also been used and validated in other chronic illness condition (for example, HIV/AIDS and multiple sclerosis) and in the general population (using a slightly modified version).

The FACT GP5 item is a single item from the FACT-G, which assesses how bothersome the side of effects of treatment are for cancer patients. The recall period is the previous 7 days, and the item has a 5-category response scale ranging from "CCI [redacted]" to "CCI [redacted]". This item is being included to assess the overall tolerability of treatment from the participant's perspective.

8.1.3.4. PRO-CTCAE

The Patient Reported Outcomes Version of the Common Terminology Criteria for AEs (PRO-CTCAE) is a patient-reported outcome measure developed to evaluate symptomatic toxicity in patients on cancer clinical trials [Basch, 2014]. The PRO-CTCAE was designed to be used as a companion to the Common Terminology Criteria for AEs (CTCAE), the standard lexicon for AE reporting in cancer trials. The PRO-CTCAE includes an item library of 124 items representing 78 symptomatic toxicities drawn from the CTCAE. PRO-CTCAE provides a systematic yet flexible tool for descriptive reporting of symptomatic treatment side effects in cancer clinical trials. In the present study, a subset of items selected from the PRO-CTCAE Version 1.0 Item library will be administered.

8.1.3.5. EuroQOL Group EQ-5D 3 Level Version

EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal [EuroQol, 1990]. The EQ-5D is applicable to a wide range of health conditions and treatments and provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care. The EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problems. The respondent is asked to indicate his/her health state by selecting the most appropriate statement in each of the 5 dimensions. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. These should be performed and assessed pre-dose on dosing days. These are required at a minimum and may be performed more frequently as clinically appropriate (e.g., for weekly dosing of SOC agents). Additional time points for safety testing may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.

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

- Height will be recorded at Screening only.

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

8.2.2. Performance Status

Performance status will be assessed using the ECOG scale (Appendix 9).

8.2.3. Vital Signs

Vital signs will be measured after 5 minutes of rest and will include temperature, systolic and diastolic blood pressure, pulse rate, respiratory rate and oxygen saturation via pulse oximetry. Blood pressure should be taken in the same position throughout the study and captured in the eCRF.

- Vital signs will be measured more frequently if warranted by clinical condition of the participant.

- If a participant develops fever and infusion related reaction or cytokine release syndrome is suspected, refer to management guidelines (Section 6.6 and subsections).

8.2.4. Electrocardiograms

Single12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures the PR, QRS, QT, and QTcF intervals; manual calculation of QTcF is permitted. In addition to the times indicated in the SoA, an ECG may be repeated as clinically indicated.

8.2.5. Echocardiograms

Echocardiograms (ECHO) will be performed locally at screening to assess cardiac ejection fraction for study eligibility, as specified in the SoA (Section 1.3). Additional ECHO assessments may be performed if clinically warranted. The evaluation of the echocardiography should include an evaluation for left ventricular ejection fraction (LVEF) and both right and left-sided valvular lesions. Multigated Acquisition Scan (MUGA) can be used in lieu of ECHO (if not feasible) in the assessment of LVEF; the same modality should be used in any subsequent assessments.

8.2.6. Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of protocol-required laboratory tests to be performed and to the SoA for the timing and frequency. All protocol-required safety laboratory assessments will be performed at the institution's local laboratory. Reference ranges for all safety parameters must be provided to the site by the laboratory responsible for the assessments. The results of each test must be recorded in the eCRF. 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 (for example, SAE or AE or dose modification) the results must also be recorded in the eCRF.

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

For all other protocol-required blood and tissue sample collections, laboratory requisition forms must be completed and samples must be clearly labelled with the participant number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples that are required to be tested by a central laboratory will be provided by the laboratory and are detailed in the laboratory manual. Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

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 eCRF. 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 intervention should 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 should be identified and the Sponsor notified.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

The Investigator and any qualified 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 intervention, SOC or the study, or that caused the participant to discontinue the study intervention or SOC (see Section 7).

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

All AESIs and SAEs will be collected from the start of treatment until 90 days after the last dose of study intervention or SOC at the time points specified in the SoA (Section 1.3). However, any AESI or SAEs assessed as related to study participation (e.g., study intervention, 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. If subsequent anticancer treatment is initiated during the 90-day follow-up period, AESIs and SAEs must continue to be collected and documentation of the subsequent anticancer treatment will be recorded in the eCRF.

All AEs will be collected from the start of study intervention or SOC until 30 days after discontinuing study intervention or SOC at the time points specified in the SoA (Section 1.3.

Medical occurrences that begin before the start of study intervention/SOC but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section.

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 3. 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 after the conclusion of the study participation. 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 intervention/SOC or study participation, the Investigator must promptly notify the Sponsor.

8.3.2. Method of Detecting AEs and SAEs

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 3.

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.

8.3.3. 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 AESI (as defined in Section 6.6.1) will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention 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 intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (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 Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 180 days after the last dose of study intervention.

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 4.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF will

be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

8.4. Treatment of Overdose

An overdose of GSK3359609 is defined as administration of a dose that is at least 50% greater than the intended dose. An overdose of tremelimumab is defined as administration of a dose that is greater than the protocol-defined dose.

In the event of an overdose of either GSK3359609 or tremelimumab the Investigator must:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AEs/SAEs and laboratory abnormalities for at least 130 days.
3. Obtain a sample for PK analysis within 28 days from the date of the last dose of study intervention 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.

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

Refer to the instructions in the approved product labels in the event of an overdose of docetaxel, paclitaxel or cetuximab. Contact the Medical Monitor immediately and closely monitor the participant for AEs/SAEs.

8.5. Pharmacokinetics

Planned time points for all pharmacokinetics assessments are listed in Table 12 and in the SoA.

8.5.1. Blood Sample Collection

The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure adequate PK monitoring.

Details on PK blood sample collection, processing, storage, and shipping procedures are provided in the SRM/laboratory manual. Windows for sample collection are provided in the SRM.

Table 12 Blood sample collection schedule for PK and ADA

Sample Times for Plasma Levels of GSK3359609
• Pre-dose on treatment visits at Weeks 1, 2, 4, 7, 10, 13, 16, 19, 25, then every 12 weeks. • End of Infusion in Weeks 1, 19 and 25 • End of Infusion +4 hours in Week 1 • Additional PK samples to be collected at every pharmacodynamic sample which is collected on the non-treatment visits
Sample Times for Serum Levels of Tremelimumab
• Pre-dose on treatment visits at Weeks 1, 2, 4, 7, 10, 13, 16, then every 12 weeks. • End of Infusion in Week 1 • End of Infusion +4 hours in Week 1 • Additional PK samples to be collected at every pharmacodynamic sample which is collected on the non-treatment visits
Samples Times for Serum Anti-Drug Antibody Samples GSK3359609
• Pre-dose on treatment visits at Weeks 1, 4, 7, 10, 13, 16, 19, 22, 25, every 12 weeks. • At the Treatment Discontinuation Visit. • On non-treatment visit days draw at any time. • For participants with a positive ADA at the last visit, draw one additional sample at 6 months after the last dose.
Samples Times for Serum Anti-Drug Antibody Samples Tremelimumab
• Pre-dose on treatment visits at Weeks 1, 4, 7, 10, 13, 16 then every 12 weeks. • At the Treatment Discontinuation Visit. • On non-treatment visit days draw at any time. • For participants with a positive ADA at the last visit, draw one additional sample at 6 months after the last dose.

8.5.2. Sample Analysis

PK analysis will be performed on samples as indicated in the SoA and Table 12. Concentrations of the study interventions will be determined using validated bioanalytical methodologies.

8.6. Pharmacodynamics

Pharmacodynamic parameters evaluated in this study are presented in Section 8.8 on biomarkers.

8.7. Genetics

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

optional. Participants who do not wish to participate in the genetic research may still participate in 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.

See Appendix 5 for information regarding genetic research. Details on processes for collection, shipment and destruction of these samples can be found in the laboratory manual/SRM.

8.8. Biomarkers

8.8.1. Blood Biomarkers

Blood samples for biomarkers will be collected as whole blood, plasma, and serum. Whole blood may be utilized to assess receptor occupancy by GSK3359609 and tremelimumab, immune cell numbers, phenotype, activation and function. Additionally, whole blood will be used to isolate PBMCs and then preserved and stored for flow cytometry of additional cell types, subsequent functional analysis or genetic analysis and their relationship to clinical responses, and changes in response to treatment. PBMCs may also be evaluated for genomic (DNA) and gene expression (RNA) or protein alterations to determine treatment-related changes in immune-related signatures. Plasma and serum samples may be used for analysis of circulating soluble factors in relation to T cell activation, cfDNA, exosomes and circulating proteins. Factors to be analyzed may include but are not limited to cytokines, chemokines, soluble receptors, cfDNA, antibodies against tumor, self-tumor mutations, gene expression; genetic analysis (DNA, RNA or protein) or viral antigens.

If predictive biomarkers are identified in the blood samples, these samples may be used for the development of a diagnostic test.

8.8.2. Tumor Tissue Biomarkers

In Part 1 and Part 2, for all participants, archival tumor tissue will be required (or a fresh biopsy if no archival is available). Fresh paired biopsies (defined as a pre-treatment sample, collected any time after end of previous therapy and prior to first dose of study intervention/SOC, and an on-treatment sample collected at Week 7) are recommended, but not mandatory, EXCEPT as noted below:

- In the PK/Pharmacodynamic cohort(s), paired biopsies are required.
- In Part 2, a minimum of 15 participants in each arm will be required to provide paired biopsies Additional participants may be requested for paired biopsies if >30% of the 15 paired tissue samples are not evaluable.

For all participants in this study, a fresh biopsy is recommended at the time of disease progression or response confirmation.

These tissues will be evaluated by immunohistochemistry (IHC) or other potential methods for expression of phenotypic and functional immune cell markers. For some participants with cancer types that may be virally mediated, for e.g., HNSCC of the oropharynx, these tissues may be utilized to assess the HPV (human papilloma virus) status either by a p16 IHC or other HPV testing methods. Additionally, tumor tissue may be utilized for DNA and/or RNA sequencing for exploratory biomarker evaluations including but not limited to T cell diversity (TCR diversity), mutational load, DNA polymorphisms (target, Fc receptor etc.), tumor antigen-specific T cell assessments as well as expression of RNA and protein changes. These samples may also be evaluated for predictive measures of response to include in the biomarker-selected population. If a predictive biomarker is identified, these tissues may be used for the development of a diagnostic test. Other biomarkers may be evaluated as determined by additional data. Details for the samples collection, processing, storage and shipment will be provided in the SRM.

8.8.3. Immunogenicity Assessments

Antibodies to GSK3359609 and tremelimumab (ADA) will be evaluated in serum samples collected from all participants according to the SoA and Table 12. The actual date and time of each blood sample collection will be recorded. The timing of ADA samples may be altered and/or ADA samples may be obtained at additional time points to ensure adequate ADA monitoring.'

Serum samples will be screened for antibodies binding to GSK3359609 and to tremelimumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to GSK3359609 and to tremelimumab and/or further characterize the immunogenicity of GSK3359609 and of tremelimumab.

The detection and characterization of antibodies to GSK3359609 and to tremelimumab will be performed using a validated assay method for each either by or under the supervision of the Sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study interventions, GSK3359609 and tremelimumab.

8.8.4. DNA/RNA Transcriptome and RNA expression Research

Samples for the assessments of blood biomarkers and tumor biomarkers are described in Section 8.8.1 and in Section 8.8.2, respectively.

8.8.5. Proteome Research

See Section 8.8.1 for information on proteome research.

8.9. Health Economics/Medical Resource Utilization and Health Economics

The PROs used in this study are presented in Section 8.1.3 and subsections.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

9.1.1. Part 1: Dose Escalation

With respect to the primary objectives and endpoints, no specific statistical hypotheses are being tested in Part 1. The primary focus will be on determining the recommended dose for further exploration, the safety profile and the PK profile.

9.1.2. Part 2: Cohort Expansion

The primary endpoint for Part 2 is OS and primary analysis is to perform Bayesian predictive probability of Phase 3 study success based on survival data.

The hypotheses about the overall survival of the study intervention (RP2D dose combination) and SOC are detailed below.

The null hypothesis is:

H_0: There is no difference in overall survival between the study intervention and the SOC

The alternative hypothesis is:

H_A: The study intervention improves overall survival over the SOC

9.2. Sample Size Determination

A maximum of 114 participants will be enrolled into the study. Up to 24 participants will be enrolled in Part 1 dose escalation and 90 participants will be enrolled in Part 2 dose expansion.

9.2.1. Part 1: Dose Escalation

The total number of participants to be enrolled in Part 1 will depend on the number of participants needed to characterize the individual dose cohorts for determination of the MTDs or MADs. With the pre-specified maximum sample size of 24 participants, simulations were conducted to determine the average sample size and percentage of times each dose would be selected under three different scenarios, assuming the bivariate CRM dose recommendations are followed, e.g., an increasing toxicity scenario, a low toxicity scenario, and a threshold toxicity scenario. For each scenario, 1000 clinical trials were simulated. The average sample sizes over the 1000 clinical trials simulated under the three scenarios were 20.2, 22.7, and 22.7, respectively. Details of the scenarios are provided in Table 14. The dose combinations in the table are the pre-selected dose combinations that are projected to be used in the study. The actual dose combinations used during the conduct of the study may be different.

For the simulations, the selected reference doses were 24 mg for GSK3359609 and 75 mg for tremelimumab. The priors for each pair of parameters (α, β) for the toxicity model for

each drug are specified via a bivariate normal distribution (as in the single drug CRM), with a separate mean and standard deviation (s.d.) for ln(α) and ln(β), and a correlation term. The parameters (s.d.) of the model are

$\ln(\alpha_1)$ -3 (10), $\ln(\beta_1)$ 1(10),

$\ln(\alpha_2)$ -3 (10), $\ln(\beta_2)$ 1(10),

ρ_1 ρ_2 0.1

where ln(α) and ln(β) for each drug are assumed to be distributed as bivariate normal with correlation ρ. The prior for the interaction term η is assumed to follow the standard normal distribution N(0,1).

In addition, the prior DLT information collected from former clinical trials of tremelimumab in combination with durvalumab and the on-going GSK3359609 monotherapy clinical trial are incorporated into the calculation of DLT probability (note: DLT information for tremelimumab monotherapy clinical trial is not available). For each dose combination, a prior observed number of DLTs and number of observations are specified in Table 13.

Table 13 Prior Observed DLTs and Number of Observations

		GSK3359609 (mg)			
		0	**8**	**24**	**80**
Tremelimumab (mg)	**225**	2/34	0/0	0/0	0/0
	75	0/57	0/0	0/0	0/0
	0	0/0	0/15	0/29	0/32

The simulation results for dose selection under various scenarios based on the priors of parameter (α, β) and prior DLT information are shown in Table 14. It is noted that the simulation results are entirely based on bivariate CRM model for every dose escalation recommendation; however, per the Part 1 design, bivariate CRM model would not be employed until the first DLT occurs.

Table 14 Simulation Results Under Various Scenarios

GSK3359609 (mg)	Tremelimumab (mg)	Scenario 1: Increasing Toxicity		Scenario 2: Little Toxicity		Scenario 3: Threshold Toxicity	
		True DLT Rate (%)	Percent of Trials Selecting Dose as MTD (%)	True DLT Rate (%)	Percent of Trials Selecting Dose as MTD (%)	True DLT Rate (%)	Percent of Trials Selecting Dose as MTD (%)
8	75	7	4	5	0	5	0.1
8	225	25	64	10	61	10	72
24	75	25	90	8	47	10	62
24	225	40	3	20	31	25	24
80	75	40	5	20	45	25	36
80	225	70	0	25	7	45	1

Notes:
1. For each scenario, entries are color-coded gray for optimal choice of dose; i.e., a dose with a DLT rate in the target toxicity interval (16%, 33%).
2. Multiple MTDs may be recommended by bivariate CRM for the specified dose escalation scheme.

9.2.2. Part 2: Cohort Expansion

In Part 2, 90 participants will be enrolled. The primary objective of the Part 2 is to evaluate and compare OS in participants treated with study intervention with those treated with SOC. Part 2 is designed to provide clinical evidence whether the study intervention will graduate to a subsequent Phase 3 study based upon clinical efficacy.

No interim analysis for futility or efficacy will be performed. Final analysis will be performed after 72 events have occurred, which is 80% of the total sample size of Part 2. Observed survival data at final analysis of this study will be used to calculate Bayesian predictive probability of success for a hypothetical Phase 3 study evaluating OS with sample size of 345 participants randomized in 2:1 ratio (230 for study intervention and 115 for the SOC). If the Bayesian predictive probability of the hypothetical future Phase 3 study success > 60% (Phase 3 success criterion), then it would be recommended to proceed to Phase 3.

The details for calculating the Bayesian predictive probability of the hypothetical Phase 3 study success are provided in Appendix 10.

The operating characteristics for the Part 2 study design are shown in Table 15. Given a sample size of 60 participants in the study intervention and 30 participants in the SOC

arm, and 345 participants (230 in the study intervention and 115 in the SOC arm) in the hypothetical Phase 3 study, if the true effect of study intervention is as expected (Figure 5), the power will be 82.5%.

Table 15 Operating Characteristics for Part 2 Design

Sample Size	Success Criterion for Phase 3	Number of Events for Final Analysis	Power	Alpha
90	> 60%	72	82.5%	0.087

If the null hypothesis is true, i.e. the OS of study intervention does not have significant difference compared with the SOC, the type I error (alpha) would be 0.087.

Note that the sample size for Part 2 may be re-evaluated upon completion of Part 1 when emerging efficacy data of Part 1are available.

Details about the simulation method for the sample size determination are provided in Appendix 10.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All participants who were screened for eligibility
Enrolled	All participants who passed screening and entered the study. Included are: Participants in Part 1 who receive at least one dose of tremelimumab or GSK3359609; Participants who are randomized for Part 2.
Intent to Treat (ITT)	All participants who are randomized in the study. This will be the primary population for Part 2 efficacy analyses.
All Treated	All participants who receive at least one dose of SOC or tremelimumab or GSK3359609. This will be the population for safety and efficacy analyses for Part 1 and safety analyses for Part 2.
PK	All participants from the All Treated population for whom a PK sample is obtained and analysed. This will be the primary population for PK analyses.
Pharmacodynamic	All participants from the All Treated population for whom a pharmacodynamic/biomarker sample is obtained and analysed. This will be the primary population for Pharmacodynamic/Biomarker analyses.

Additional analysis populations may be defined in the Reporting and Analysis Plan (RAP).

9.4. Statistical Analyses

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

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.

9.4.1. Efficacy Analyses

Lesion assessment method and timing, evaluation of disease, disease progression and response criteria will be conducted according to RECIST 1.1 [Eisenhauer, 2009] and iRECIST as outlined in Appendix 7 of the protocol. iRECIST will be used to determine treatment decisions and RECIST 1.1 will be used for the primary analysis of anticancer activity.

The ITT population will be used for anticancer activity analyses for Part 2, and All Treated Population will be used for anticancer activity analyses for Part 1. Since this is an early phase study, anticancer activity will be evaluated based on clinical evidence and response criteria. If data warrant, the response data will be summarized by part and dose level. Correlation analysis may be conducted to explore any relationship between the biomarkers and tumor response based on RECIST 1.1. Full details will be specified in the RAP.

9.4.1.1. Overall Survival (OS)

For Part 1 participants, overall survival is defined as time from the date of first dose to the date of death due to any cause. For Part 2 participants, overall survival is defined as time from the date of randomization to the date of death due to any cause. For the analysis of overall survival (OS), the last date of known contact will be used for those participants who have not died at the time of analysis; such participants will be considered censored. OS will be summarized for Part 2 using Kaplan-Meier estimates along with 2-sided 95% CI at the time of final analysis. Log-rank tests will be performed for Part 2 data to compare the overall survival between the study intervention and the SOC.

9.4.1.2. Overall Response Rate (ORR)

ORR is defined as percentage of participants with confirmed complete response or partial response at any time as per RECIST 1.1. The observed ORR and 95% exact confidence interval (CI) will be reported for final analyses.

9.4.1.3. Disease Control Rate (DCR)

DCR is defined as percentage of participants with confirmed complete response or partial response or at least 18 weeks of stable disease. DCR and 95% exact confidence interval (CI) will be reported for final analyses.

9.4.1.4. Duration of Response (DOR)

DOR is defined as time from the first documented evidence of response until the first documented sign of disease progression or death among participants who achieve a response (CR or PR). DOR will be summarized descriptively using Kaplan-Meier method.

9.4.1.5. Progression Free Survival (PFS)

For Part 1 participants, PFS duration is defined as the time from the date of first dose to first documented evidence of disease progression or death (regardless of cause of death), whichever comes first. For Part 2 participants, PFS duration is defined as the time from the date of randomization to first documented evidence of disease progression or death (regardless of cause of death), whichever comes first. PFS will be summarized using Kaplan-Meier estimates along with 2-sided 95% Cis for final analysis.

9.4.1.6. Time to Response (TTR)

TTR is defined as the time from the first dose to the first documented evidence of CR or PR for participants with a confirmed CR or PR. TTR will be summarized descriptively using Kaplan-Meier estimates along with 2-sided 95% Cis for final analysis.

9.4.1.7. Predictive Probability of Phase 3 Success

The predictive probability of Phase 3 study success with respect to OS will provide evidence whether the study will graduate into a future Phase 3 trial based on the Part 2 survival data.

The primary comparison of OS between the study intervention and SOC will be analysed by a log rank test with treatment as fixed effect. The hazard ratio (HR) will be derived based on the ratio of the hazard rates in the study intervention and SOC observed from the Part 2 overall survival data. The predictive probability of success for the hypothetical Phase 3 study will be calculated as detailed below, assuming both the data and prior follow normal distributions. By using conjugate prior, we can obtain a closed-form solution for posterior and predictive distribution of θ log(HR) at the end of Part 2 of the study.

Minimal-informative prior of θ:

$\theta \sim N(\theta_0, V_0)$, where θ_0 0 ,V_0 4.5/n_0 for a randomization ratio 2:1. N_0 is the number of events in prior and assumed to be a small value 0.1 for the noninformative prior

Posterior distribution of θ given Part 2 overall survival results X (the estimated log Hazard Ratio at the final analysis):

$\theta | X \sim N(\tilde{\theta}_m, V_{post})$,

where $\tilde{\theta}_m$ $\frac{\theta_0/V_0+X/V_{p2}}{\frac{1}{V_0}+\frac{1}{V_{p2}}}$;

V_{post} $1/(1/v_{p2}+1/v_0)$;

and V_{p2} $1/n_t+1/n_c$, where n_t and n_c are the expected number of events in the study intervention arm and SOC arm, respectively.

Then, the predictive distribution of Phase 3 log(HR) Y given Part 2 results X is:

$Y|X, \sim N(\tilde{\theta}_m, 4.5/m + V_{post})$,

where X is the estimated log Hazard Ratio from final analysis of Part 2, and Y is predictive distribution of log Hazard Ratio in the future Phase 3 study. M is the expected number of events in the future Phase 3 trial and is pre-specified as 240, which is approximately 70% of the sample size in Phase 3.

One thousand predictive distributions are sampled and the predictive probability of Phase 3 success is calculated based on the proportion of test statistics less than -1.96 (corresponding to one-sided type I error of 0.025) out of samplings drawn from the predictive distribution. The test statistic is Phase 3 signal/noise ratio of HR between the study intervention and SOC.

9.4.2. 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) will be summarized according to the scheduled, nominal visit at which they are 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.

9.4.2.1. Extent of Exposure

The number of participants administered study intervention or SOC will be summarized according to the duration of therapy.

9.4.2.2. Adverse Events

AEs will be coded using the standard MedDRA and grouped by system organ class. AEs will be graded by the Investigator according to the NCI-CTCAE (version 5.0) [NCI, 2017].

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 intervention. AEs, if listed in the NCI-CTCAE (version 5.0) 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 AEs of special interest will be summarized separately.

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

9.4.2.3. Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be summarized using frequencies and proportions according to the NCI-CTCAE (version 5.0) [NCI, 2017]. 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.

9.4.2.4. Other Safety Measures

Data for vital signs and electrocardiograms (ECGs) will be summarized based on predetermined criteria identified to be of potential clinical concern (PCI). Further details will be provided in the RAP.

9.4.3. Other Analyses

PK, pharmacodynamic, immunogenicity (ADA) and biomarker exploratory analyses will be described in the RAP. The population PK analysis and pharmacodynamic analyses may be presented separately from the main clinical study report (CSR).

9.4.3.1. Pharmacokinetic Analyses

Pharmacokinetic Parameters

PK analysis will be the responsibility of the Clinical Pharmacology Modeling and Simulation (CPMS) Department, GSK.

PK analysis of drug concentration-time data will be performed by non-compartmental methods under the direction of CPMS, Quantitative Sciences, GSK. The following PK parameters will be determined for GSK3359609 and tremelimumab separately, if data permit:

- maximum observed plasma concentration (Cmax)
- minimum observed plasma concentration (Cmin)
- area under the plasma concentration-time curve AUC(0-t) (repeat dosing).

Statistical Analysis of Pharmacokinetic Data

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

Drug concentration-time data will be listed for each participant and summarized by descriptive statistics at each time point by dose level/cohort for each part, and for GSK3359609 and tremelimumab separately.

9.4.3.2. Pharmacokinetic/Pharmacodynamic Analyses

If deemed appropriate and if data permit, exposure response relationship between GSK3359609/tremelimumab (e.g., dose, concentration, Cmax, or AUC) and clinical endpoints (e.g., antitumor response, biomarkers) may be conducted. The details of such exposure-response analysis will be outlined in the RAP.

9.4.3.3. Immunogenicity Analyses

Results of anti-drug antibodies (ADA) testing will be reported at the end of the study and will include incidence and titer. The presence or absence of antibodies to GSK3359609 and tremelimumab in dosed participants will be analysed, then be summarized descriptively and/or graphically presented, respectively. Further details will be provided in the RAP.

9.4.3.4. Translational Research Analyses

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

Further details on the translational research analyses will be addressed in the RAP or a separate biomarker RAP.

9.4.3.5. Tumor Kinetic Analyses

Exploratory analyses may be performed to evaluate the effect of study intervention on the growth kinetics of individual tumor lesions. These analyses may include tumor lesion measurements from imaging scans performed earlier in the disease course (i.e., prior to screening scans).

If deemed necessary, additional statistical analyses will be discussed in RAP.

9.5. Interim Analyses

9.5.1. Part 1: Dose Escalation

In Part 1, interim analyses will be performed to determine if a dose-escalation is appropriate and to support the dose escalation decision following the completion of each dose cohort. The primary driver for the dose- scalation decision(s) in Part 1 will be safety and tolerability of each dose cohort. The DLT information along with preliminary safety

data, including AEs, changes in laboratory values and other safety parameters, and available PK/pharmacodynamic data will be evaluated for each dose escalation cohort prior to making dose escalation decisions.

Further details regarding such analyses will be provided in the RAP.

9.5.2. Part 2: Cohort Expansion

No interim analysis for futility or efficacy will be performed in Part 2. The study team may evaluate safety, PK and Pharmacodynamic data and make the recommendation to discontinue the study at any time due to safety concerns.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. 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 ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, 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 IEC/IRB 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

10.1.2. 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.

10.1.3. 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.

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with SOP-GSKF-410. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate will not provide this separate signature.

10.1.4. 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.

10.1.5. Dissemination of Clinical Study Data

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

GSK will also provide the Investigator with the full summary of the study results. The Investigator is encouraged to share the summary results with the study participants, as appropriate.

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

GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF 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.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in Monitoring Plan.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

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 Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. 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.

10.1.7. 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 Investigator Site File.

10.1.8. 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 intervention development

10.1.9. 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.

10.2. Appendix 2: Clinical Laboratory Tests

Table 16 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	RBC Indices	WBC count with Differential		Platelets
	Hemoglobin	Neutrophils		
	Hematocrit	Lymphocytes		
	RBC count	Monocytes		
		Eosinophils		
		Basophils		
Clinical Chemistry	BUN[a]	Potassium	Bilirubin	AST (SGOT)
	Creatinine[b]	Sodium	Total protein	ALT (SGPT)
	Glucose	Calcium	Albumin	Alkaline phosphatase
				LDH
Coagulation	INR or PT			
	aPTT			
Cardiac Function	Troponin I or Troponin T			
Thyroid Function	Thyroid stimulating hormone			
	Free T4			
	Free T3 (when clinically indicated)			
Pancreatic Function	Amylase			
	Lipase			
Routine Urinalysis	Specific gravity			
	pH, glucose, protein, blood and ketones by dipstick			
Other Screening Tests	Hepatitis B (HbsAg)			
	Hepatitis C (Hep C antibody)[c]			
	Serum β-hCG Pregnancy test (for women of child bearing potential)			
	HIV testing			

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; β-hCG=beta-human chorionic gonadotropin; BUN=blood urea nitrogen; HbsAg=Hepatitis B surface antigen; RBC=red blood cells; SGOT=serum glutamic oxaloacetic transaminase; SGPT= serum glutamic pyruvic transaminase; T3= triiodothyronineT4= thyroxine; WBC = white blood cells; INR = International Normalized Ratio; PT = Prothrombin Time; aPTT = Activated Partial Thromboplastin Time

a. Required if local laboratory testing is available
b. Creatinine clearance is also required to be calculated using the formula provided in Appendix 8.
c. 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. Hepatitis C RNA Test is optional with negative Hepatitis C antibody test.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. 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 intervention/SOC, whether or not considered related to the study intervention/SOC. • 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 intervention/SOC.

Events Meeting 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 progression of 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 intervention/SOC 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 intervention/SOC 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 NOT 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.

10.3.2. 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. 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/SOC to prevent one 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.

10.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

10.3.4. Recording and Follow-Up of 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 CRF.
- 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 assign a grade according to the NCI-CTCAE v5.0 [NCI, 2017]

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention/SOC 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 intervention/SOC administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (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 one 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 medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. 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 requested to provide GSK with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The Investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • The Investigator or medically-qualified sub-Investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF. • After the study is completed at a given site, the electronic data collection tool 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, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by telephone. • Contacts for SAE reporting can be found at the beginning of this protocol and in the SRM on the Sponsor/Medical Monitor Contact Information page.

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **Medical Monitor**. • In rare circumstances and in the absence of facsimile equipment, notification by

telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found at the beginning of this protocol and in the SRM on the Sponsor/Medical Monitor Contact Information page.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definition: Woman of Childbearing Potential (WOCBP)

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

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention/SOC, additional evaluation should be considered.

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

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the 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 hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

   Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen 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.

10.4.2. Contraception Guidance

Male participants

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 5.1:

  Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

  Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 17 when having penile-vaginal intercourse with a woman of childbearing potential

Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for the duration of the study and for at least 180 days after the last dose of study treatment if receiving GSK3359609 and tremelimumab.

In addition, male participants must refrain from donating sperm for duration of study and for at least 180 days after the last dose of GSK3359609 and tremelimumab.

If the participant is randomized to SOC, then the duration of contraception after the last dose is at per the package insert and/or Institutional guidelines.

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 17.

Table 17 Highly Effective Contraceptive Methods

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency**
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner • *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
• **Highly Effective Methods[b] That Are User Dependent**

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  • oral
  • injectable

• Sexual abstinence   • *Note: 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 intervention. 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*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction)

10.4.3. Collection of Pregnancy Information:

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to male participants who receive GSK3359609 plus tremelimumab.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

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 participant and neonate, 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 intervention by the Investigator, will be reported to GSK as described in Appendix 3. 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 intervention or SOC.

10.5. Appendix 5: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention 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 GSK3359609 or in selected, advanced solid tumors and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK3359609, and in selected, advanced solid tumors. Genetic research may consist of the analysis of one 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 for 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 GSK3359609 or study interventions of this class. The results of genetic analyses may be reported in the clinical study report 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 GSK3359609 (or study interventions of this class) or in selected, advanced solid tumors continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

10.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments and Study Intervention Rechallenge Guidelines

10.6.1. Liver Chemistry Stopping and Monitoring Criteria

10.6.1.1. ALT up to 2.5xULN at Baseline

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

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**
• Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE**²** • Perform liver event follow-up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** participant with study intervention unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to language within this Appendix) • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study intervention and may continue participant in the study for any protocol specified follow-up assessments	• Viral hepatitis serology[4] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5]. • Blood sample for pharmacokinetic (PK) analysis, obtained 48 hours after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including

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 • 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	acetaminophen, herbal remedies, other over the counter medications • Record alcohol use on the liver event alcohol intake case report form **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 HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) 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 intervention 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. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

10.6.1.2. Baseline ALT up to 5xULN for Participants with Documented Liver Metastases/Tumor Infiltration

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT absolute	**Both** ALT ≥ 5xULN **and** ≥2x baseline value
ALT Increase	**Both** ALT ≥ 3xULN **and ≥** 1.5x baseline value that persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5
Cannot Monitor	**Both** ALT ≥ 3xULN **and ≥** 1.5x baseline value that cannot be monitored for 4 weeks
Symptomatic[3]	**Both** ALT ≥ 3xULN **and ≥** 1.5x baseline value associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event

Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event eCRF 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 (see **MONITORING** below) • **Do not restart/rechallenge** participant with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to guidance in this Appendix) • 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 **MONITORING:** **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24 hrs**	• 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 pharmacokinetic (PK) analysis, obtained 48 hours after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications • Record alcohol use on the liver event alcohol

• Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	intake case report form **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 HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease: complete Liver Imaging and/or Liver Biopsy CRF forms

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 which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); 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. Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

10.6.1.3. 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 GSK Medical Monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study intervention • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

10.6.2. Liver Safety Drug Restart or Re-Challenge Guidelines

If participant meets liver chemistry stopping criteria do not restart/re-challenge participant with study intervention unless all the following conditions are met:

- GSK Medical Governance approval is granted (as described below)
- IRB/IEC approval is obtained, if required
- Separate consent for treatment restart/re-challenge is signed by the participant

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

10.6.2.1. Re-challenge Following Liver Stopping Events that are Possibly Related to Study intervention

Re-challenge refers to resuming study intervention following drug-induced liver injury (DILI). Because of the risks associated with re-challenge 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 re-challenge is considered to be favorable.

Following DILI, drug re-challenge 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 re-challenge outcome include the following:

- Hypersensitivity [Andrade, 2009] with initial liver injury (e.g., fever, rash, eosinophilia)
- Jaundice or bilirubin >2 x ULN with initial liver injury (direct bilirubin >35% of total)
- Participant currently exhibits severe liver injury defined by ALT >3 x ULN, bilirubin >2 x ULN (direct bilirubin >35% of total), or INR >1.5
- SAE or fatality has been observed with drug rechallenges [Papay, 2009; Hunt, 2010]
- Evidence of drug-related preclinical liability (e.g., reactive metabolites; mitochondrial impairment) [Hunt, 2010]

Approval by GSK for re-challenge with study intervention can be considered under the following conditions:

- Investigator requests consideration of re-challenge with study intervention for a participant who is receiving compelling benefit (partial response or complete response) with study intervention that exceeds risk, and no effective alternative therapy is available
- The ALT at the time of rechallenge is <3x ULN
- The participant did not have additional risk factors for a fatal outcome following the initial injury including hypersensitivity, jaundice, bilirubin >2x ULN (direct bilirubin >35% of total bilirubin), or INR >1.5.
- IRB/IEC approval for re-challenge with study intervention must be obtained, as required.
- If the re-challenge 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 intervention 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 intervention. Documentation of informed consent must be recorded in the study chart.
- Study intervention must be administered at the dose specified by GSK.
- Participants approved by GSK Medical Governance for re-challenge with study intervention 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 intervention re-challenge, participant meets protocol-defined liver chemistry stopping criteria, study intervention must be permanently discontinued.

- GSK Medical Monitor, and the IRB/IEC as required, must be informed of the participant's outcome following study intervention re-challenge.
- GSK must be notified of any AEs as per Section 8.3.

10.6.2.2. Re-challenge Following Transient Liver Stopping Events Not Related to Study intervention

Restart refers to resuming study intervention 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, and acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study intervention should not be associated with human leukocyte antigen (HLA) markers of liver injury.

Approval by GSK for study intervention restart can be considered under the following conditions:

- Investigator requests consideration for study intervention 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 <3 x ULN).
- Possible study intervention-related 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 intervention 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 intervention-related liver injury cannot be excluded, the guidance on re-challenge in Section 10.6.2.1 will apply.
- There is no evidence of alcoholic hepatitis.
- IRB/IEC approval of study intervention restart must be obtained, as required.
- If restart of study intervention 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 intervention administration including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the study intervention restart. Documentation of informed consent must be recorded in the study chart.
- Study intervention must be administered at the dose specified by GSK.
- Participants approved by GSK Medical Governance for restarting study intervention 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 intervention restart, participant meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.

- GSK Medical Monitor, and the IRB/IEC as required, must be informed of the participant's outcome following study intervention restart.
- GSK must be notified of any AEs, as per Section 8.3.

10.7. Appendix 7: Guidelines for Assessment of Disease, Disease Progression and Response Criteria

10.7.1. Assessment Guidelines by RECIST 1.1

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 must 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 must be noted as CT on the eCRF.

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.

CT and MRI: **Contrast enhanced CT with 5mm contiguous slices is recommended.** Minimum size of a measurable baseline lesion must 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 must 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.

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.

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

10.7.2. Guidelines for Evaluation of Disease by RECIST 1.1

Measurable and Non-Measurable Definitions

Measurable lesion:

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

- ≥10 mm with MRI or CT when the scan slice thickness is no greater than 5 mm. If the slice thickness is greater than 5 mm, 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:

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

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

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

Non-Measurable only disease: The presence of only non-measurable lesions.
Note: non-measurable only disease is not allowed per protocol.

10.7.3. Evaluation of Response by iRECIST

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

Clinical stability is defined as meeting all of the following:

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

Any participant deemed **clinically unstable** may be discontinued from study intervention at site-assessed first radiologic evidence of PD. It is strongly preferred to obtain the repeat tumor imaging, when feasible, for confirmation of PD by iRECIST.

In a clinically unstable participant, if the Investigator decides to continue treatment, following consultation with the Sponsor Medical Monitor, the participant may continue to receive study intervention. The tumor assessment should be repeated at least 4 weeks and up to 8 weeks later to confirm PD by iRECIST. Images should continue to be sent in to the central imaging vendor for potential central review.

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

If a participant has confirmed radiographic progression (iCPD) as defined below, study intervention should be discontinued; however, if the participant is achieving a clinically meaningful benefit, continuation of study intervention may be considered following consultation with the Sponsor. In this case, if study intervention is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 8.1 and submitted to the central imaging vendor.

Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

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

Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological PD by RECIST 1.1 the Investigator will decide whether to continue a participant on study intervention until repeat imaging is obtained (using iRECIST for participant management (see Table 18 and Figure 4). This decision should be based on the participant's overall clinical condition. (See discussion of clinical stability in Section 1.2 above.)

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

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir

  - Note: the iRECIST publication uses the terminology “sum of measurements”, but “sum of diameters” will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

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

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

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

Assessment at the Confirmatory Imaging

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

Confirmation of Progression

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

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

- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

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

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

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

Resolution of iUPD

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

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

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

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

Management Following the Confirmatory Imaging

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

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, continuation of study intervention may be considered following consultation with the Sponsor. In this case, if study intervention is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 8.1 and submitted to the central imaging vendor.

Detection of Progression at Visits After Pseudo-Progression Resolves

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

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

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

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

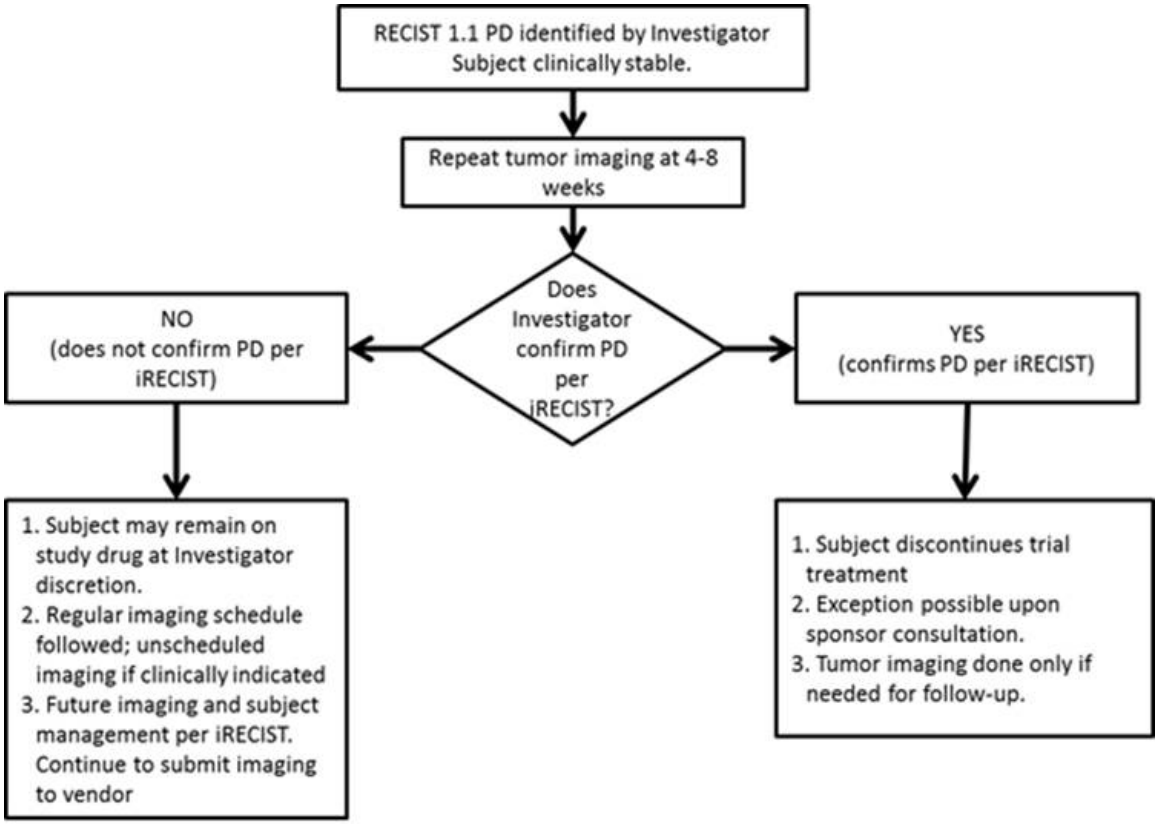
Additional details about iRECIST are provided in the iRECIST publication [Seymour, 2017].

Table 18 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study intervention at the Investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per Investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per Investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study intervention at the Investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per Investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study intervention at the Investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study intervention if condition has improved and/or clinically stable per Investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.

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

Figure 4 Imaging and Treatment for Clinically Stable Participants after First Radiologic Evidence of PD Assessed by the Investigator



10.8. Appendix 8: Creatinine Clearance Calculation Formulas

The Cockcroft-Gault Formula:

The Cockcroft-Gault formula is a commonly-used surrogate marker for actual creatinine clearance (CrCl) and employs creatinine measurements and a participant's weight (kg) to predict the clearance.

If the participant is obese *(>30% over ideal body weight*), use ideal body weight in calculation of estimate CrCl.

If the participant is *below ideal body weight*, use actual body weight in calculation of estimate CrCl.

Cockcroft-Gault Formula for serum creatinine in mmol/L

CrCl (mL/min) =	Q X (140-age [years]) X actual body weight (kg)[a] / 48816 X serum creatinine (mmol/L)
Q=0.85 for females Q=1.0 for males	
OR	
a. Calculation of Ideal Body Weight Using the Devine Formula [Devine, 1974]	
Male participants:	
	50.0 kg + (2.3 kg X each inch over 5 feet) or 50.0 kg + (0.906 kg X each cm over 152.4 cm)
Female participants:	
	45.5 kg + (2.3 kg X each inch over 5 feet) or 45.5 kg + (0.906 kg X each cm over 152.4 cm) 4 cm)

Cockcroft-Gault Formula for serum creatinine in mg/dL

CrCl (mL/min)=	Q X (140-age [years]) X actual body weight (kg)[a] / 72 X serum creatinine (mg/dL)
Q=0.85 for females Q=1.0 for males	

For example:

For a male participant with actual body weight 90.0 kg and height 68 inches, the calculation would be as follows:

Ideal body weight 50.0 + (2.3) (68-60) 68.4 kg

This participant's actual body weight is >30% over ideal body weight. In this case, the participant's ideal body weight of 68.4 kg should be used in calculating estimated creatinine clearance.

CKD-EPI Formula:

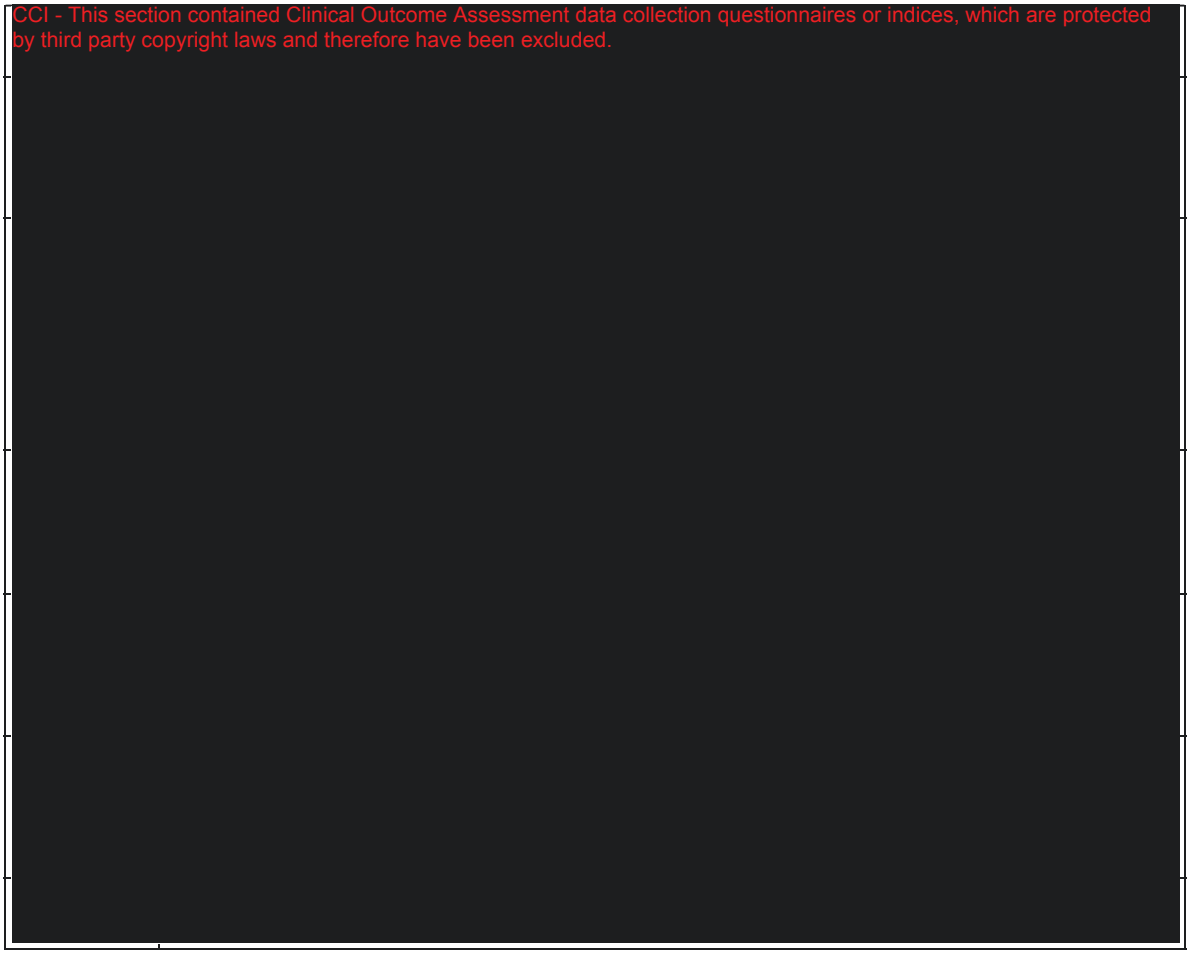
CKD stage: Kidney Disease Outcomes Quality Initiative (KDOQI) CKD stages 3/4/5 defined by eGFR using the CKD Epidemiology Collaboration (CKD-EPI) formula [Levey, 2009].

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] × 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.

10.9. Appendix 9: ECOG Performance Status

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.



Oken, 1982.

10.10. Appendix 10: Statistical Methods for Study Design

10.10.1. Bivariate CRM Method for Part 1 Dose Escalation

10.10.1.1. Description of the Bivariate Continual Reassessment Method

The bivariate CRM model-based design is a Bayesian adaptive dose escalation scheme that assumes a 5-parameter Bayesian logistic regression model [Neuenschwander, 2014] for the toxicity rate based on doses. The CRM method is fully adaptive and makes use of all DLT information, therefore is expected to locate the target dose level efficiently.

Dose escalation decisions will be held after participants within any given cohort have been observed for 28 days of DLT observation period after starting the study intervention. At the time of each dose escalation decision, the Fixed and Adaptive Clinical Trial Simulator (FACTS™ version 6.1 or higher [Tessella, Abington, United Kingdom]) will be used to obtain the posterior probabilities that the DLT rate for that dose lies in each of 4 toxicity intervals (under dosing, target dose range, excessive toxicity, and unacceptable toxicity) for each potential dose. The CRM estimates, for each potential dose combination level, the posterior probabilities that the DLT rate lies in each of four toxicity ranges:

- [0%, 16%) Under dosing
- [16%, 33%) Target toxicity
- [33%, 60%) Excessive toxicity
- [60%, 100%] Unacceptable toxicity

The recommended dose will be the dose with the highest posterior probability of having a toxicity rate in the target interval with the additional requirement that the sum of the posterior probabilities of the DLT rate in the excessive toxicity or unacceptable toxicity range is less than 25%. The use of over dose control limits the risk of exposing participants in the next cohort to an unsafe dose combination by ensuring the posterior probability of the DLT rate exceeding 33% at any dose is capped at 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 recommendations based on the bivariate CRM analysis will be used as guidance for the Safety Committee. To ensure safety of participants, additional participants may be enrolled at a current dose level at the discretion of the Safety Committee, even though a higher dose is recommended by CRM analysis.

10.10.1.2. Logistic Model for Bivariate CRM

A 5-parameter logistic model will be used for bivariate CRM analysis to guide dose selection during Part 1 dose escalation. This model will estimate the probability of observing a DLT at each combination dose in the study as DLT information becomes available.

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

$$ln\left(\frac{P_{ij}}{1-P_{ij}}\right) = \eta d_{1i}^{*} d_{2j}^{*} + ln\left(\frac{1-(1-P_{1i})(1-P_{2j})}{(1-P_{1i})(1-P_{2j})}\right)$$

$$ln\left(\frac{P_{1i}}{1-P_{1i}}\right) = \ln(\alpha_1) + \beta_1 * ln(d_{1i}^{*})$$

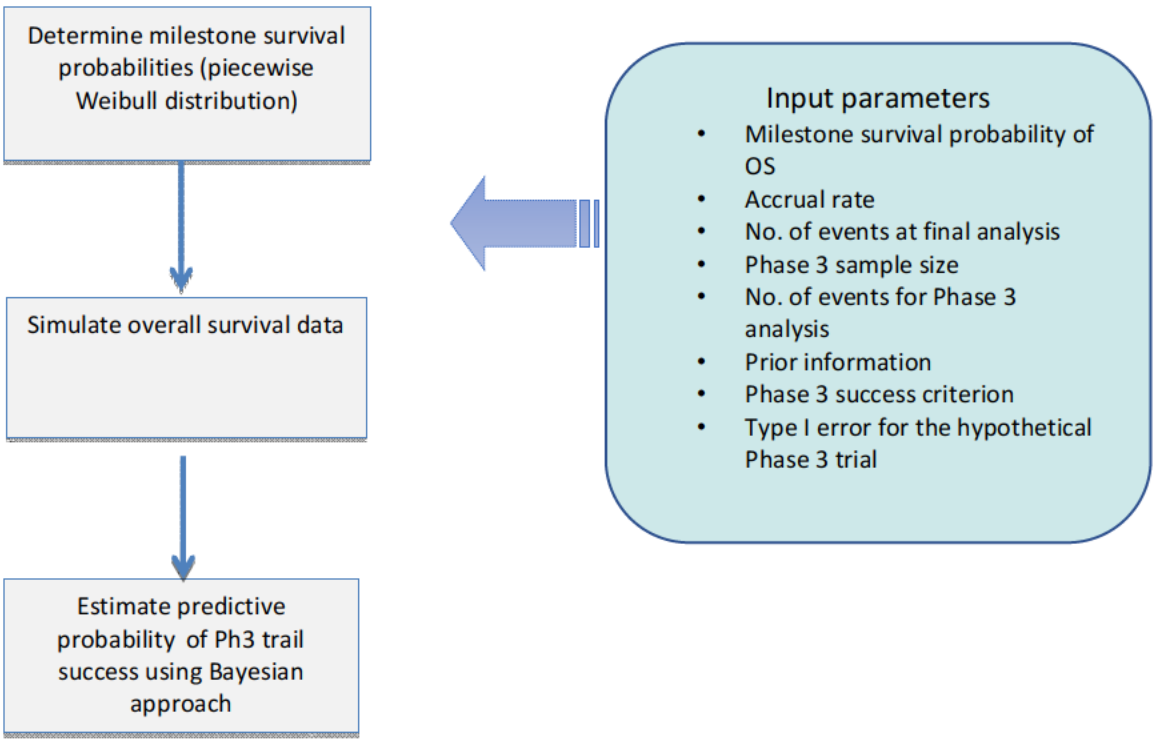
$$ln\left(\frac{P_{2j}}{1-P_{2j}}\right) = \ln(\alpha_2) + \beta_2 * ln(d_{2j}^{*})$$

where P_{ij} is the probability of DLT at dose d_{1i} (of drug 1) in combination with dose d_{2j} (of drug 2), P_{1i} is the probability of DLT if single agent drug 1 at dose d_{1i} is administered, P_{2j} is the probability of DLT if single agent drug 2 at dose d_{2j} is administered, $d_{1i}^{*} = {d_{1i}}/{d_{1s}}$, $d_{2j}^{*} = {d_{2j}}/{d_{2t}}$, and d_{1s} and d_{2t} are the reference doses for drug 1 and drug 2, respectively. H is the interaction term. A and β are Bayesian priors.

10.10.2. Simulation Method for Part 2 Sample Size Estimation

The sample size estimation for Part 2 cohort expansion is based on simulation. Figure 5 shows the flow chart of simulation.

Figure 5 Flow Chart of Simulation Approach for the Determination of Sample Size

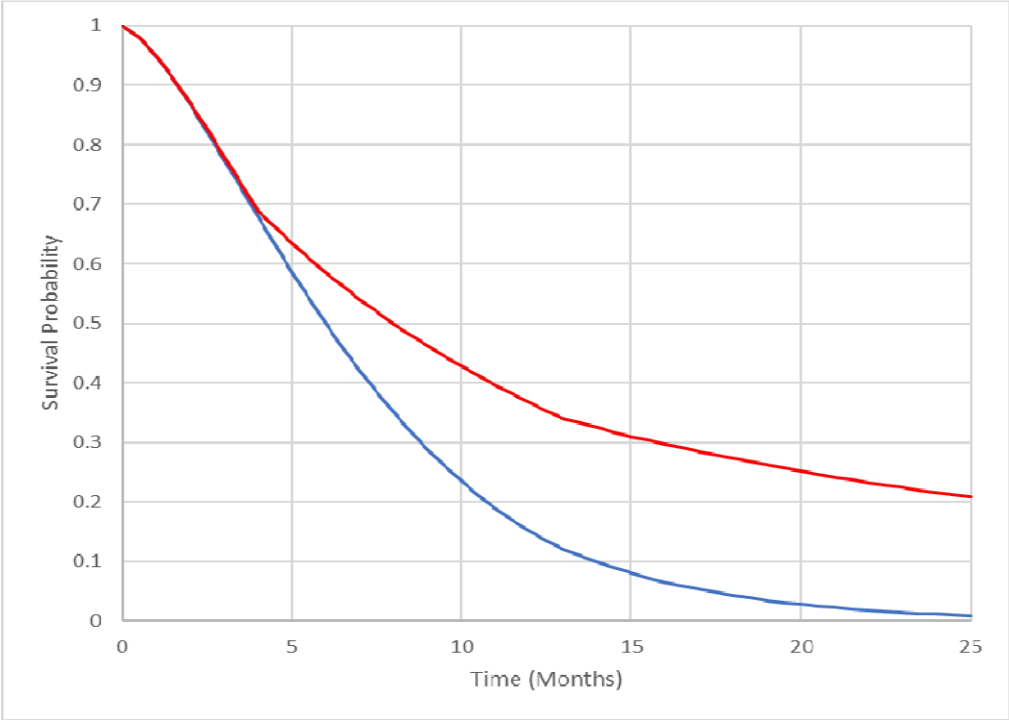


The first step of the simulation process is to simulate the overall survival curves of the study intervention and SOC arm. Both OS curves are assumed to follow piecewise Weibull distribution, one of the widely-used distributions for survival models. The two survival curves in Figure 6 were simulated based on the following assumption of milestone survival probabilities:

	1 Month	4 Month	13 Month	15 Month
Study intervention	95%	69%	34%	31%
Standard of Care (SOC)	95%	68%	12%	8%

The assumption of milestone survival probabilities of SOC are based on the publication [Ferris, 2016] and conference presentation on Phase 3 trials for recurrent HNSCC. The assumption of milestone survival probabilities of study intervention are clinically desirable outcomes. As shown in Figure 6, there is almost no separation between the two survival curves until the end of fourth months because of the anticipation of delayed effect of the study intervention.

Figure 6 Simulated overall survival for study intervention (red line) and SOC (blue line)



The key variables/parameters used for the simulation are:

Accrual rate	5 participants/Month
No. of events at final analyses	72
Hypothetical Phase 3 sample size	345
No. of events for hypothetical Phase 3 analysis	240
Prior information for log(HR)	~N (0, 45)
Success criterion at final analyses	Predictive probability of Ph3 success > 60%
Type I error for the hypothetical Phase 3 trial	0.025 (one-sided)

10.11. Appendix 11: Abbreviations and Trademarks

Abbreviations

ADA	Anti-drug antibodies
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC(0-t)	Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration)
β-hCG	Beta-human chorionic gonadotropin
ccRCC	Clear Cell Renal Cell Carcinoma
CD28	Cluster of Differentiation 28
cfDNA	cell-free DNA
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	Maximum observed concentration
Cmin	Minimum Observed Concentration;
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete Response
CrCl	Creatinine Clearance
CRM	Continual Reassessment Method
CRP	C Reactive Protein
CRPC	Castrate Resistant Prostate Cancer
CRF	Case Report Form
CRS	Cytokine Release Syndrome
CT	Computed tomography
CTFG	Clinical Trial Facilitation Group
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein 4
CV	Cardiovascular
CYP3A	Cytochrome P 3A
DCR	Disease Control Rate
DILI	Drug-induced Liver Injury
dL	Deciliter
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DoR	Duration of Response
EC	Effective Concentration
ECG	Electrocardiogram
ECHO	Echocardiography
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form

eGFR	Estimated Glomerular Filtration Rate
EORTC QLQ-C30 and H&N35	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 and Head and Neck Cancer 35 Module
FACT GP5	Functional Assessment of Cancer Therapy General Population
FACTS	Fixed and Adaptive Clinical Trial Simulator
FDG-PET	Fluorodeoxyglucose positron emission tomography
g	Gram
GCP	Good Clinical Practice
G-CSF	Granulocyte- Colony stimulating factor
GI	Gastrointestinal
GSK	GlaxoSmithKline
HPV	Human Papilloma Virus
HNSCC	Head and Neck Squamous Cell Carcinoma
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICOS	Inducible T Cell Co-Stimulator
ICOS-L-Fc	Inducible T Cell Co-Stimulator Ligand Fragment crystallizable region of an Antibody
iCPD	iRECIST confirmed progressive disease
iCR	iRECIST complete response
IEC	Independent Ethics Committees
IFNγ	Interferon, gamma
IL	Interleukin
Ig	Immunoglobulin
INR	International Normalized Ratio
iPR	iRECIST progressive disease
irAE	Immune-related Adverse Event
IRB	Institutional Review Board
IRR	Infusion-related Reactions
iRECIST	Modified RECIST 1.1 for Immune-based Therapeutics
iSD	iRECIST stable disease
iUPD	iRECIST unconfirmed progressive disease
IV	Intravenous
IVIG	IV Immunoglobulin
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KDOQI	Kidney Disease Outcomes Quality Initiative
kg	Kilogram(s)
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction
m^2	Square Meters

mAb	Monoclonal Antibody
MAD	Maximum Administered Dose
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
min	Minute
mm	Millimeters
mmHg	Millimeters of Mercury
mL	Milliliter(s)
MPM	Malignant pleural mesothelioma
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
msec	Millisecond(s)
MTD	Maximum Tolerated Dose
MUGA	Multigated Acquisition Scan
NCI-CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NSCLC	Non-small-cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival
OTC	Over the Counter
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive Disease
PD-1	Programmed death receptor protein-1
PD-L1	Programmed death-ligand 1
R/R	Relapsed/Refractory
RP2D	Recommended Phase 2 Dose
PFS	Progression-free Survival
PI	Principal Investigators
PJP	*Pneumocystis jirovecii* pneumonia
PK	Pharmacokinetics
PO	Per oral
PP	Predictive probability
PR	Partial Response
PRO-CTCAE	Patient Reported Outcomes Version of the Common Terminology Criteria for Adverse Events
PS	Performance Status
Q3W	Every 3 Weeks
Q6W	Every 6 Weeks
Q12W	Every 12 Weeks
QoL	Quality of Life
QTc	Corrected QT interval duration, corrected
QTcB	QT interval corrected by Bazett's Formula
QTcF	QT interval corrected by Fridericia's Formula
RANKL	Receptor Activator of Nuclear Factor-kappa B Ligand
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors

RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
Scr	Serum Creatinine
sCRS	Severe Cytokine Release Syndrome
SD	Stable Disease
SoA	Schedule of Activities
SOC	Standard of Care
SRM	Study Reference Manual
TCR	T Cell Receptor
TDV	Treatment Discontinuation Visit
Th1	Type 1 T helper (cells)
Th2	Type 2 T helper (cells)
Th17	T helper 17 (cells)
TNFα	Tumor Necrosis Factor, alpha
Treg	T Regulatory Cells
TTR	Time to Response
ULN	Upper Limit of Normal

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
FluMist

Trademarks not owned by the GlaxoSmithKline group of companies
FACTS

10.12. Appendix 12: Protocol Amendment History

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

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