TITLE PAGE

Division: Worldwide Development

Information Type: Protocol Amendment

Title:	A Phase I Open Label study of GSK3359609 (feladilimab) administered alone and in combination with anticancer agents in subjects with selected advanced solid tumors

Compound Number:	GSK3359609
Development Phase:	I
Effective Date:	20-AUG-2021

Protocol Amendment Number: 9

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2015N238345_00	2016-JAN-26	Original
2015N238345_01	2016-MAR-14	Amendment No. 1
Amendment 1 includes the following revisions: • Updates to the definitions of dose-limiting toxicities presented in Section 4.1.1.3, Dose-Limiting Toxicities • Inclusion of the requirement for subjects to remain under observation following completion of study treatment infusions in Section 6.1. • Clarification on the study treatment management for adverse events in subsections of Section 7 Inclusion of additional requirements for study treatment rechallenge following Grade 3 or Grade 4 infusion reactions in Section 7.12.3		
2015N238345_02	2016-NOV-14	Amendment No. 2
Amendment 2 includes the following revisions: • Updates to pembrolizumab background and dose rationale language • Requirement for the number of GSK3359609 doses during the 28-day dose escalation DLT observation period amended from two to at least one to account for delays due to reasons other than AEs. • Language allowing for the potential to investigate pembrolizumab at doses other than 200 mg deleted. • Revisions to eligibility criteria that address prior therapies or allowed concomitant medications, tumor histology, clarification on prior malignancies and required labs. Additional revisions include deleting the requirement for age of archival tumor specimen and revising pneumonitis history exclusions. • Non-serious AESI do not require 24-hour notification to GSK; introduced term events of clinical interest which do require 24 notifications. • Infusion reaction management guidelines revised to address discrepancies and simplify. • Updated language to allow MUGA in lieu of ECHO in the assessment of LVEF. General clarifications and typos were addressed, and assessment windows were added if missing.		
2015N238345_03	2017-DEC-13	Amendment No. 3
Amendment 3 included the following major revisions: • Updated subject numbers based on increase in size of the study		

- Design revised to include chemotherapy safety run-in cohort and indicate GSK3359609 (feladilimab) dosing will transition to fixed dose. In addition, included specifics on the tumor indications selected for expansion cohorts.
- Dose justification for GSK3359609 (feladilimab) fixed dosing and chemotherapy doses
- Implementation of Quality of Life and symptomatic toxicity instruments in expansion cohorts
- Update with requirement for disease assessments in subjects who discontinue study treatment due to durable CR.
- Updated Safety Management Guidelines to include myocarditis guidelines and chemotherapy guidelines
- Revised Benefit:Risk assessment to include reference to chemotherapy risks
- Revised study treatment sections and concomitant medication section with chemotherapy language
- Eligibility criteria revised to define target population for Part 1B and Part 2B cohorts. Criteria added based on chemotherapy safety run-in cohorts. Minor clarifications were also made.
- Revised Section 8.1 tables to include chemotherapy administration assessments, PK assessments and updates to GSK3359609 (feladilimab) PK sampling.
- Defined hypothesis for escalation phases and for specific expansion cohorts; sample size estimations, and futility decisions rules.

2015N238345_04	2018-OCT-30	Amendment No. 4

Amendment 4 included the following major revisions:

- Updated Nonclinical Safety to include findings from the GSK3359609 (feladilimab) (anti-ICOS agonist/GSK3174998 (anti-OX40 agonist) cytokine release assay
- Included background on OX40, GSK3174998 mechanism of action and clinical experience to support the combination with GSK3359609 (feladilimab)
- Revised design to include: combination of GSK3359609 (feladilimab) and GSK3174998; combination of fluorouracil (5-FU)/platinum with GSK3359609 (feladilimab); combination of GSK3359609 (feladilimab) with pembrolizumab and the platinum doublets.
- Included GSK3359609 (feladilimab) combination with GSK3174998 dose escalation decision using the 2D-NCRM.
- Updates to design justification and dose justifications to support the combination of GSK3359609 (feladilimab) and GSK3174998; 5-FU/platinum chemotherapy combinations
- Revised inclusion criterion 4 to define requirements for prior therapy
- Revised inclusion criterion 10 requirement for renal function using calculated creatinine clearance from the minimum of 50 to 30 mL/min
- Revised dose and safety management guidelines to include GSK3174998
- Updated study assessments (refer to Table 24 and Table 25) to include GSK3174998, 5-FU and cisplatin administration, PK sampling, and GSK3174998 immunogenicity testing

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- Updated statistical considerations and analysis to include GSK3359609 (feladilimab) combination with GSK3174998

Minor updates to include correction of typos and clarifications
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<tr><td>2015N238345_06</td><td>2019-MAR-14</td><td>Amendment No. 5</td></tr>
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Amendment 5 included the following major revisions:

- Increased the total number of subjects that will be enrolled in the study to 698 and appropriate corresponding changes were added.
- Provided detailed dose information for the HNSCC randomization cohort in the Part 2B
- Removed the eligibility requirement of absolute lymphocyte count
- Modified ALT requirement at the baseline, to allow subjects with documented liver metastases to be eligible if ALT is ≤5xULN and the liver stopping criteria for those subjects.
- Defined the subjects eligible to enroll in the Part 2A 5FU-platinum combination with GSK3359609 (feladilimab) and pembrolizumab
- Added exclusion criterion to address subjects with tumors invading major vessels due to bleeding risk

CCI [redacted]

- Updates to the Statistical Analysis Sections corresponding to the increase of the total number of subjects
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<tr><td>2015N238345_11</td><td>2020-FEB-27</td><td>Amendment No. 6</td></tr>
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- Added HNSCC combination cohort of GSK3359609 (feladilimab) and pembrolizumab for subjects with CPS <1
- Added investigation of GSK3359609 (feladilimab) and pembrolizumab Q6W as a new HNSCC randomized cohort
- Added additional information on dose expansion of combination GSK3359609 (feladilimab) (anti-ICOS agonist) and GSK3174998 (anti-OX40 agonist) at 24 mg of each agent
- Updated relevant sections including the time and events table to reflect the new cohorts that include GSK3359609 (feladilimab) Q6W dosing schedule
- Updated GSK3359609 (feladilimab) clinical experience with safety update from the GSK3359609 (feladilimab) IB.
- Added language to protocol describing retreatment option
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<tr><td>2015N238345_13</td><td>2020-APR-08</td><td>Amendment No. 7</td></tr>
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- Increased the total number of subjects that will be enrolled in the study to 873 and appropriate corresponding changes were added.
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• Added three new combination cohorts of GSK3359609 (feladilimab) plus bintrafusp alfa (M7824), GSK3359609 (feladilimab) plus dostarlimab, and GSK3359609 (feladilimab) plus dostarlimab plus cobolilmab with dose escalation and pharmacokinetic/pharmacodynamic phases in advanced solid tumors • Updated relevant sections including the time and events table to reflect the new cohorts that include the new combination agents • Updated relevant sections of biomarker cohort with additional details on screening and testing procedures and statistical analysis • Clarified difference between Adverse Event of Special Interest and Event of Clinical Interest. Included in the list of Events of Clinical Interest infection with COVID-19 • Referenced Country Specific Amendment to incorporate Japanese sites		
2015N238345_15	2020-OCT-09	Amendment No. 8
• Adjusted the total number of subjects that will be enrolled in the study to 867 and appropriate corresponding changes were added. • Updated relevant sections including the time and events table to remove dostarlimab, cobolimab, and bintrafusp alfa cohorts. • Updated relevant sections of biomarker cohort with additional details on screening and testing procedures and statistical analysis • Updated 2A cohorts to remove dostarlimab, cobolimab, and bintrafusp alfa containing arms		
TMF-11734800	2021-AUG-20	Amendment No. 9
• Reduced collection burden by eliminating pembrolizumab pharmacokinetics assay and pembrolizumab anti-drug antibody (ADA) CCI [redacted] • Eliminate second course of therapy following relapse • Clarification of End of Study and Off Study criteria • Clarification of reporting process for hepatic toxicity		

SPONSOR SIGNATORY:

Protocol Title: A Phase I Open Label study of GSK3359609 (feladilimab) administered alone and in combination with anticancer agents in subjects with selected advanced solid tumors

Protocol Number: 204691/Amendment 09

Compound Number or Name: GSK3359609

Steven Hirschfeld, MD PhD
Physician Project Lead

Date

The signed page is a separate document.

MONITOR/SPONSOR INFORMATION PAGE

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

Regulatory Agency Identifying Number(s):

Investigational New Drug Number: 126353

European Drug Regulatory Authorities Clinical Trials Number: 2016-000148-32

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 204691

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

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1. PROTOCOL SYNOPSIS FOR STUDY 204691

Rationale

GSK3359609 (feladilimab) is an anti-Inducible T cell Co-Stimulator (ICOS) receptor agonist monoclonal antibody (mAb) intended for the treatment of cancers of different histology. It is expected to differentiate from first generation immunomodulatory antibodies directed against immune checkpoint modulators by targeting a different axis in the antitumor T cell response cascade and promoting activation of a co-stimulatory receptor instead of blocking an inhibitory checkpoint receptor.

The desired pharmacology of GSK3359609 (feladilimab) is to expand the total number and increase the activity of tumor specific effector $CD4^+$ and $CD8^+$ T cell populations. Tumor specific T cells must be first primed through contact with cognate antigens and activated into effector cells in order for induction of ICOS expression to occur and GSK3359609 (feladilimab) to bind and elicit an agonist effect. Therefore, it is expected that GSK3359609 (feladilimab) will be most active in disease settings where an antitumor immune response is primed as an inherent feature of the tumor or by prior lines of therapy. Additionally, GSK3359609 (feladilimab) is expected to be active in combination with agents which prime or modulate tumor immunity. Therefore, both single agent therapy and combination therapies will be evaluated in the first-time-in-human (FTIH) clinical study.

Primary and Secondary Objective(s)/Endpoint(s)

Objectives	Endpoints
Part 1 GSK3359609 (feladilimab) (anti-ICOS mAb) Monotherapy	
Primary	
• To determine the safety, tolerability, MTD or the MAD of GSK3359609 (feladilimab)	• AEs, SAEs, DLTs, changes in safety/laboratory assessment parameters, dose modifications
Secondary	
• To determine the recommended dose of GSK3359609 (feladilimab) for further exploration • To evaluate the antitumor activity of GSK3359609 (feladilimab) • To characterize the PK properties of GSK3359609 (feladilimab) • To determine immunogenicity	• AEs, SAEs, DLTs, changes in safety/laboratory assessment parameters, dose modifications, PK, pharmacodynamic activity, antitumor activity • ORR[1], DCR[1], PFS[1], OS, TTR[1, 2], DoR[1, 2] • Plasma PK parameters such as Cmax, Ctau, AUC (0-τ) as data permit • ADA incidence by dose level/dose

Abbreviations: ADA=anti-drug antibody; AE=adverse events; AUC=area under the curve; Cmax=maximum observed concentration; Ctau=minimum observed concentration; DCR=disease control rate; DLT=dose limiting toxicity; DoR=duration of response; irRECIST=immune-related RECIST; MAD=maximum administered dose; MTD=maximum tolerated dose; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PK; pharmacokinetic; RECIST=Response Evaluation Criteria in Solid Tumors; SAE; serious adverse events; TTR=time to response

1. irRECIST is the primary measure of clinical activity for response endpoints (i.e., ORR, DCR);RECISTv1.1 guidelines are used for PFS, DoR, TTR and disease assessments.
2. CCI [redacted]

Objectives	Endpoints
Part 2 GSK3359609 (feladilimab) (anti-ICOS mAb) in Combination with Pembrolizumab (anti-PD-1 mAb) or GSK3174998 (anti-OX40 mAb)	
Primary	
• To determine the safety, tolerability, MTD or the MAD of GSK3359609 (feladilimab) in combination with pembrolizumab or GSK3174998	• AEs, SAEs, DLTs, changes in safety/laboratory assessment parameters, dose modifications
Secondary	
• To determine the recommended dose(s) and schedule of GSK3359609 (feladilimab) in combination with pembrolizumab for further exploration • To determine the recommended dose(s) of GSK3359609 (feladilimab) and GSK3174998 in combination • To evaluate the antitumor activity of GSK3359609 (feladilimab) in combination with pembrolizumab or GSK3174998	• AEs, SAEs, DLTs, changes in safety/laboratory assessment parameters, dose modifications, PK, pharmacodynamic activity, antitumor activity • ORR[1], DCR[1], PFS[1], OS, TTR[1, 2], DoR[1, 2]
• To characterize the PK properties of GSK3359609 (feladilimab), pembrolizumab, and GSK3174998 when administered in combination	• GSK3359609 (feladilimab), GSK3174998, and serum pembrolizumab PK parameters such as Cmax, Ctau, AUC (0-τ) as data permits
• To determine immunogenicity of GSK3359609 (feladilimab),	• ADA

Objectives	Endpoints
pembrolizumab or GSK3174998 when administered in combination	• incidence of each drug by dose level/dose

Abbreviations: ADA=anti-drug antibody; AE=adverse events; AUC=area under the curve; Cmax= maximum observed concentration; Ctau=minimum observed concentration; DCR=disease control rate; DLT=dose limiting toxicity; DoR=duration of response; irRECIST=immune-related RECIST; MAD=maximum administered dose; MTD=maximum tolerated dose; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PK; pharmacokinetic; RECIST=Response Evaluation Criteria in Solid Tumors; SAE; serious adverse events; TTR=time to response

1. irRECIST is the primary measure of clinical activity for response endpoints (i.e., ORR, DCR);RECISTv1.1 guidelines are used for PFS, DoR, TTR and disease assessments.
2. CCI [redacted]

Objectives	Endpoints
Part 2A3 GSK3359609 (feladilimab) (anti-ICOS mAb) Combinations with Chemotherapies (±Pembrolizumab)	
Primary	
• To determine the safety, tolerability, of GSK3359609 (feladilimab) in combination with standard of care chemotherapies	• AEs, SAEs, changes in safety/laboratory assessment parameters, dose modifications
Secondary	
• To determine the recommended dose of GSK3359609 (feladilimab) for further exploration • To characterize the PK properties of GSK3359609 (feladilimab), chemotherapies, and pembrolizumab • To determine immunogenicity of GSK3359609 (feladilimab) and pembrolizumab	• AEs, SAEs, DLTs, changes in safety/ laboratory assessment parameters, dose modifications, PK, pharmacodynamic activity, antitumor activity • Plasma PK parameters such as Cmax, and Ctau as data permit • ADA incidence by dose level/dose

Abbreviations: ADA=anti-drug antibody; AE=adverse events; Cmax= maximum observed concentration; Ctau=minimum observed concentration; DLT=dose limiting toxicity; PK; pharmacokinetic; SAE; serious adverse events

Overall Design

This is an open-label, multicenter study designed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and preliminary clinical activity of GSK3359609 (feladilimab) administered intravenously to participants with selected advanced or recurrent solid tumors. The study will be conducted in two parts with each part consisting of a dose escalation phase and expansion phase. Part 1 will evaluate GSK3359609 (feladilimab) as a monotherapy, while Part 2 will evaluate GSK3359609 (feladilimab) (anti-ICOS agonist mAb) in combination with pembrolizumab (anti-PD-1 mAb), or GSK3174998 (anti-OX40 mAb), or chemotherapy regimens; GSK3359609 (feladilimab) combinations with chemotherapies will only consist of safety run-in cohorts.

The aim of the dose escalation phases (Part 1A and 2A) is to identify recommended dose or doses of GSK3359609 (feladilimab) for further investigation either as a monotherapy or combination therapy. GSK3359609 (feladilimab) in combination with other agents is planned to be investigated in the dose escalation phase to identify recommended dose combination(s); recommended doses may be explored in the expansion phase. The recommended dose(s)/dose combination(s) will be based on the observed safety and tolerability, PK, pharmacodynamic profiles, and any preliminary anticancer activity.

The purpose of the chemotherapy safety run-in cohorts is to evaluate the safety, and preliminary efficacy, of the 24 mg and 80 mg GSK3359609 (feladilimab) doses in combination with standard of care doses of chemotherapies (±pembrolizumab); additional GSK3359609 (feladilimab) doses within the planned doses may be investigated to establish the recommended GSK3359609 (feladilimab) dose (±pembrolizumab).

In the dose expansion phases (Part 1B and 2B), the expansion cohorts include participants defined by a single tumor histology. Additionally, several expansion cohorts have been defined by a specific characteristic such as tumors exhibiting high microsatellite instability, deficiency in DNA mismatch repair processes, or viral-mediated pathology. GSK3359609 (feladilimab) monotherapy is being investigated in a biomarker defined cohort (ICOS expression); GSK3359609 (feladilimab) in combination with pembrolizumab or other agents also may be investigated in biomarker defined cohorts. Further cohorts may be defined by other features such as response to prior treatment with an immune checkpoint inhibitor, a disease characteristic, molecular/genetic alteration or pathology. The aim is to further explore the clinical activity of GSK3359609 (feladilimab) monotherapy and in combination with pembrolizumab or other agents in defined cohorts.

Treatment Arms and Duration

In Part 1 of the study, all participants will receive GSK3359609 (feladilimab) monotherapy. In Part 2 of the study, all participants will receive GSK3359609 (feladilimab) in combination with:

- Pembrolizumab

- or Standard of care chemotherapy regimens with and without pembrolizumab

  or

- GSK3174998

Participants may continue treatment until disease progression, unacceptable toxicity, or withdrawal of consent up to a maximum initial treatment duration of approximately 2 years, up to 35 cycles. For participants enrolling in HNSCC dose optimization cohort the maximum treatment duration is approximately 2 years, or up to 17 cycles for both GSK3359609 (feladilimab) and pembrolizumab. After permanent discontinuation of study treatment, the follow-up period for safety assessments will be a minimum of 90 days after the last dose of study treatment or until the start of subsequent anti-cancer treatment.

Type and Number of Participants

Overall it is estimated a total of 867 participants may be enrolled in this two-part study (Part 1 [monotherapy: Parts 1A, 1B, 1C and Part 1D] and Part 2 [combination therapy: Parts 2A, 2B, and 2C]). Approximately 166 participants are planned to be enrolled in Parts 1A and 2A [dose escalation/safety run-in], approximately 20 participants per cohort enrolled in Part 1C and Part 2C in a Japan country specific amendment, and approximately 20 participants enrolled in Part 1D in a China country specific amendment; approximately 641 participants are planned to be enrolled in Parts 1B and 2B (cohort expansion) to include approximately 60 participants in the biomarker training cohort. In many cohorts a seamless design occurs between Part 2A and Part 2B, the dose escalation and the expansion phase. Cohorts may be expanded to include additional participants to evaluate subpopulations based on parameters such as histology, genetics, or other criteria.

The Part 1B PK/pharmacodynamics cohort will enroll approximately 52 participants. The average sample size in Part 1B is 171 participants in all cohorts excluding the PK/PD/ADA cohort under the null hypothesis; the average sample size in Part 2B is 343 in all cohorts under the null hypothesis. The average sample size in Part 1B excluding the PK/PD cohort is 210 participants if two cohorts (non-biomarker) are under the alternative hypothesis; the average sample size in Part 2B is 379 participants if three cohorts are under the alternative hypothesis.

Analysis

In the GSK3359609 (feladilimab) monotherapy and pembrolizumab combination dose escalation/chemotherapy combination safety run-in phases, a modified Toxicity Probability Interval method will be used to guide dose decisions [Ji, 2010]. In the GSK3359609 (feladilimab) combination with GSK3174998 (anti-OX40) dose escalation phase, a two-dimensional continual reassessment method (2D-CRM) [Neuenschwander, 2014] will be used to guide the dose combination decisions. Dose decisions will be based primarily on dose limiting toxicities however the totality of clinical safety assessments will be considered. No formal statistical hypotheses will be tested, and analyses will be descriptive. In dose expansion phases, a Bayesian adaptive design with independent

tumor type modeling will be implemented. Additional analysis with hierarchical modeling across disease-specific participant cohorts may be explored. The design permits the trial to be frequently monitored for clinical activity with the constraint of both Type I and Type II error rates [Berry, 2013].

2. INTRODUCTION

2.1. Study Rationale

GSK3359609 (feladilimab) is intended to be a first-in-class anti-ICOS agonist antibody for the treatment of cancers of different histology. It is expected to differentiate from first generation immunomodulatory antibodies directed against Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4) and Programmed cell death protein 1 (PD-1)/PD-Ligand-1 (PD-L1) by targeting a different axis in the antitumor T cell response cascade and promoting activation of a co-stimulatory receptor instead of blocking an inhibitory checkpoint receptor. The effect of ICOS agonist activity is to promote the expansion and function of cytotoxic CD8+, and effector CD4+ T cells, resulting in improved antitumor immune responses that are durable. Due to the restricted expression of ICOS on activated T cells, it is expected that GSK3359609 (feladilimab) may result in a more favorable safety profile as compared with other antibodies that target co-stimulatory T cell receptors constitutively expressed on naïve T cells.

Nevertheless, some tumors may engage multiple mechanisms to escape immune-mediated antitumor effects thus combining an ICOS agonist with agents that target different pathways within the immune cascade may be required for achieving the desired clinical effect. Accordingly, as ICOS agonists stimulate IFNγ production which induces PD-L1 expression on tumor cells and within the tumor microenvironment [Mimura, 2018], this may facilitate the therapeutic benefit of PD-1/L1 blockade within tumors that have low levels of PDL1 expression. Several studies have underscored the co-expression of PD-1 and ICOS on tumor--infiltrating lymphocytes (TILs) and anti-PD-1-responsive peripheral T cells, as well as complementarity between inhibition of the PD-1/L1 axis and co-stimulation via the ICOS/L axis [Kamphorst, 2017; Gros, 2014; Beyrend, 2019]. Clinical studies and a series of nonclinical studies support the combination approach of an anti-ICOS agonist with immune checkpoint inhibitors or other agents that modulate the immune system distinct from ICOS biology (refer to Section 2.2, through Section 2.5).

The purpose of this FTIH, open-label study is to investigate the safety, pharmacology, PK, immunogenicity, biomarker identification, and preliminary antitumor activity in participants with selected, advanced or recurrent solid tumors with an aim to establish recommended dose(s) of GSK3359609 (feladilimab) for further exploration as a monotherapy and in combination with pembrolizumab, chemotherapy, or other agents.

2.2. Brief 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/PD-L1, have demonstrated efficacy and are proven effective as anticancer immunotherapies in a broad range of tumors including some solid tumors otherwise considered poorly immunogenic. Moreover, the PD-1 inhibitor, pembrolizumab, as a single agent in a biomarker selected NSCLC population offers patients in the first-line setting a chemotherapy-free regimen with a significant overall survival benefit [Reck, 2016].

Nevertheless, a majority of tumors are unresponsive to this class of agents as monotherapies because they 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 to improve clinical benefit. 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 with two immune checkpoint inhibitors [Wolchok, 2013; Larkin , 2015].

In some patients, however, inhibition of a select set of immune checkpoint pathways (e.g. PD-1/L1 or CTLA-4) alone may not elicit an effective antitumor response. To reinstate immunosurveillance, effective therapeutic intervention may require combinations with agents that provide co-stimulatory signals or target different processes within the immune cascade. These regimens may include chemotherapies which elicit advantageous immunological effects [Galluzzi, 2015] as evidenced by improved progression-free survival and overall survival in combination of PD-1/L1 therapies [Gandhi, 2018; Socinski, 2018]. Another approach would be to target co-stimulatory receptors (e.g. ICOS and OX40) to potentially enhance immune activation. Apart from its role in augmenting T cell activation, proliferation, and survival through direct and indirect mechanisms [Betting, 2009; Croft, 2010], OX40 signaling has been shown to block the activity of induced regulatory T (Tregs) cells, thereby further promoting T cell effector immune responses [Ito, 2006].

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.

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 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.

As evident from the clinical efficacy of anti-PD-1/L1 agents 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 as a single agent and to combine 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.

2.3. GSK3359609 (feladilimab) (Antibody with ICOS Agonist Activity)

2.3.1. Background

GSK3359609 (feladilimab) is a humanized anti-ICOS monoclonal antibody (mAb) selected for its nanomolar (nM) binding to and agonist activity in ICOS-expressing CD4+ and CD8+ effector T cells. GSK3359609 (feladilimab) 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 (feladilimab) that would result in depletion of ICOS-positive T cells through antibody-dependent or complement-dependent cellular cytotoxicity, 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.

The desired pharmacology of GSK3359609 (feladilimab) is the expansion in the total number as well as an increase in the activity of tumor specific CD4+ and CD8+ T cell populations. Tumor specific T cells must be primed and activated in order for the induction of ICOS expression to occur, and thereby for GSK3359609 (feladilimab) to bind and function. Therefore, the expectation is GSK3359609 (feladilimab) may be most active in settings where an antitumor immune response was primed by prior lines of anti-cancer therapy and/or in combination with agents that prime or modulate tumor immunity. Nevertheless, there is the potential for monotherapy activity in patients with tumors that exhibit intrinsic primed/activated effector T cells.

As indicated in Section 2.3.4 the biophysical and mechanistic properties of GSK3359609 (feladilimab) have been characterized across multiple in vitro systems. GSK3359609 (feladilimab) exhibits binding properties consistent with other successful therapeutic

antibodies. It binds with sub nanomolar affinity to human ICOS and cross-reacts with cynomolgus monkey ICOS (1.34 and 0.95 nM, respectively). GSK3359609 (feladilimab) induces activation, proliferation and cytokine production in a dose-dependent manner in activated T cells.

2.3.2. Nonclinical Pharmacokinetics

The pharmacokinetics of GSK3359609 (feladilimab) was investigated in two cynomolgus monkey IV toxicology studies (refer to Section 2.3.3.1). The large molecular size of GSK3359609 (feladilimab) (approximately 150 kilodaltons) and its composition of naturally occurring amino acids and a large molecular weight polymer preclude the requirement to perform standard distribution, metabolism and excretion studies in nonclinical species.

In the repeat dose study in cynomolgus monkeys in which two doses of GSK3359609 (feladilimab) were administered two weeks apart, systemic exposure on Day 1 generally increased proportionally as the dose increased from 0.3 to 3 milligram (mg)/kilogram (kg). However, as the dose of GSK3359609 (feladilimab) increased from 3 to 30 mg/kg, a greater than proportional increase in systemic exposure was observed. There was a decrease in plasma concentrations in monkeys given ≤3 mg/kg, typical of an immunogenicity response; all animals were confirmed to be positive for anti-drug antibody (ADA) in an ADA bridging assay.

In the second repeat dose study in which GSK3359609 (feladilimab) was administered once weekly for 4 weeks, the systemic exposure to GSK3359609 (feladilimab) increased dose-proportionally with increasing dose. Following 4 weeks of repeat dosing at both dose levels (10 mg/kg and 100 mg/kg), the increases in the gender-averaged AUC 0-168h and Cmax (maximum observed concentration) values of GSK3359609 (feladilimab) from Week 1 to Week 4 ranged from 1.6 to 2.1-fold. Instances of decreased plasma concentrations were observed in individual monkeys after the fourth dose at 10 mg/kg/week due to primate ADA formation; ADA was detected in a single female at 100 mg/kg/week.

Refer to the GSK3359609 (feladilimab) Investigator's Brochure (IB) for further details [GlaxoSmithKline Document Number RPS-CLIN-015202, 2021].

2.3.3. Nonclinical Safety

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

tissues examined including lymphoid tissues, gastrointestinal tract, liver, pancreas and testes.

The potential of immobilized GSK3359609 (feladilimab) to induce cytokine release was investigated in an in vitro assay using human peripheral blood mononuclear cells (PBMCs) from 10 healthy donors in the presence and absence of activation with immobilized anti-CD3. As expected, induction of one or more cytokines was detected in PBMCs incubated with GSK3359609 (feladilimab) in the presence of anti-CD3 which is consistent with the pharmacology of the drug. In non-activated PBMCs, weak induction of only one cytokine, interferon-gamma (IFNγ) was observed in 2 of 10 donors; and in anti-CD3 pre-stimulated PBMCs (but no anti-CD3 costimulation), weak induction of IFNγ was observed in 1 of 10 donors. In pharmacology studies, TCR engagement was required for induction of ICOS expression and for the ICOS agonist function of GSK3359609 (feladilimab). In the absence of TCR stimuli, such as anti-CD3 antibodies, there was minimal to no detectable increase in ICOS expression, GSK3359609 (feladilimab) binding to T cells, T cell activation or induction of pro-inflammatory cytokines with either immobilized or soluble form of the ICOS antibody. While the potential for GSK3359609 (feladilimab) to induce cytokine release in T cells in the absence of TCR engagement in vivo cannot be completely discharged by these in vitro assays, the weak induction of only a single cytokine and the absence of increased cytokine levels following repeat dosing in monkey studies, suggest the risk is low.

2.3.3.1. GSK3359609 (feladilimab) Monotherapy Studies

The systemic toxicity of GSK3359609 (feladilimab) after IV administration was evaluated in monkeys on repeat dose studies of 4 and 13 weeks given weekly doses of 10 and 100 mg/kg/dose. GSK33359609 was generally well tolerated with occasional transient clinical signs and mild changes in cytokine levels. There were no remarkable changes in T cell subsets, Treg cells or T cell activation markers, but decreases in monocyte count were seen in males given 100 mg/kg/week on the 13-week study. Anti-GSK3359609 (feladilimab) antibodies (ADA) were noted in some animals at both dose levels. The presence of ADA detected in 3 monkeys from each study was associated with increased GSK3359609 (feladilimab) clearance and decreased GSK3359609 (feladilimab) binding to ICOS receptors on circulating CD4+ T lymphocytes. On the 13-week study, all of the monkeys had evidence of circulating immune complexes (CIC). Adverse vascular/perivascular findings (lymphocytic infiltration and/or intimal thickening) in the heart, seminal vesicles, kidneys, cervix and vagina consistent with immune complex formation and deposition were noted in a total of 4 monkeys from both GLP toxicology studies.

One female monkey given 100 mg/kg/week on the 4-week study exhibited adverse clinical signs consistent with an acute infusion reaction and was euthanized shortly after the completion of the fourth weekly dose. This animal had microscopic changes of multi-organ inflammation associated with tissue vasculature (arteries, choroid plexus and glomerular predilection), was ADA positive, and stained positive for GSK3359609 (feladilimab), monkey IgG, IgM and/or C3 at sites of vascular injury and inflammation as well as within phagocytosed granules/globules in monocytes/macrophages in the affected tissues. On the 13-week study at 100 mg/kg/week, vascular/perivascular findings

(lymphocytic infiltration and/or intimal thickening) were observed in the heart, seminal vesicles, and kidneys in 1 male, and in the cervix and vagina in 1 female. The nature and distribution of the microscopic inflammatory lesions at known predilection sites for immune complex deposition and the presence of CIC in the affected animals are consistent with ADA-mediated immune complex disease.

One male monkey given 10 mg/kg/week for 4 weeks had microscopic evidence of minimal focal inflammation of a coronary artery which was similar to, but less severe than the lesion noted in the animal given 100 mg/kg. Although there were no detectable ADAs (possibly due to high levels of circulating drug), this lesion was consistent with immune-complex deposition because of the similarity to the lesion noted in the aforementioned animal. IHC staining did not confirm the presence of immune complex deposition since the lesion of interest was not present in subsequent heart sections.

These potential changes will be monitored in the clinic setting by assessing renal function tests, immunogenicity and electrocardiographs.

Stage-specific evaluation of spermatogenesis was not performed on testes since most male monkeys were considered to be sexually immature on both the 4-and 13-week studies. However, as GSK3359609 (feladilimab) has high-affinity binding to ICOS, which is expressed on CD4+ and CD8+ T cells which did not exhibit binding to reproductive organs. With the exception of vascular inflammation attributed to immune complex deposition, no histopathology findings in reproductive tissue parenchyma of male or female monkeys were noted.

In summary, GSK3359609 (feladilimab) was generally well tolerated in monkey toxicology studies following weekly dosing for up to 13 weeks at doses up to 100 mg/kg/week. ADAs were detected in monkeys given 10 or 100 mg/kg, however the majority of monkeys had sustained systemic exposure and CCI throughout the dosing periods indicating that the ability to determine toxicity was not compromised by ADA. Adverse infusion reactions and vascular inflammation in the heart, kidney and other organs were not considered a direct effect of test article administration but indirect toxicity attributed to ADA and based on these findings a NOAEL was not determined across the 4-and 13 week-studies.

Refer to the GSK3359609 (feladilimab) IB for further details [GlaxoSmithKline Document Number RPS-CLIN-015202, 2021].

2.3.3.2. Combination Studies

To support the combination of GSK3359609 (feladilimab) with other cancer therapies, such as pembrolizumab (anti-PD-1 mAb), and GSK3174998 (anti-OX40 mAb), the nonclinical toxicology findings with each given as single agents were reviewed. The nonclinical toxicology profiles of each agent alone are well characterized and indicate that combination toxicology studies in monkeys would not likely provide any relevant data that would inform clinical risk assessments. Risk mitigation measures for potential clinically relevant risks associated with GSK3359609 (feladilimab) combination therapy based on these nonclinical assessments or clinical safety data are described in this protocol.

2.3.3.2.1. GSK3359609 (feladilimab) Combination with Pembrolizumab

For the planned combination with pembrolizumab, review of the principal nonclinical toxicology findings in monkeys associated with pembrolizumab consisted of generalized lymphocytic infiltration consistent with its pharmacologic activity, which was not associated with clinical toxicities. In a human PBMC cytokine release assay, pembrolizumab did not cause cytokine stimulation in non-stimulated cultures but did cause increases in interleukin (IL)-2, tumor necrosis factor-alpha (TNFα), IFNγ, IL-6 and IL-17 in staphylococcal enterotoxin B stimulated cells, suggesting the potential for inappropriate cytokine release under stimulated conditions [KEYTRUDA FDA Pharmacology Toxicology Review, 2014]. The potential for cytokine release by GSK3359609 (feladilimab) in combination with pembrolizumab was evaluated in PBMC and mixed lymphocyte reaction in vitro pharmacology assays. Under stimulated conditions, T cells showed enhanced cytokine production with the combination treatment compared to the single antibody treatments alone, consistent with expected pharmacology of a co-stimulator and checkpoint inhibitor.

2.3.3.2.2. GSK3359609 (feladilimab) Combination with GSK3174998 (Anti-OX40 Agonist)

For the planned combination with GSK3174998, the principal nonclinical toxicology findings in monkeys associated with GSK3174998 single agent included detection of anti-GSK3174998 antibodies in most monkeys given ≤10 mg/kg; the ability to determine toxicity in the terminal necropsy animals was not compromised by ADAs due to the fact that robust target engagement was observed. Overall no adverse test article-related findings were noted. No infusion reactions were observed in monkeys, including those with ADA. Refer to the GSK3174998 IB for further details [GlaxoSmithKline Document Number 2014N212091_06, 2020].

The potential for cytokine release by GSK3359609 (feladilimab) and GSK3174998 (defined as test articles) in combination relative to either test article alone was evaluated in vitro in PBMCs (n=10 donors) under assay conditions with or without anti-CD3 (prestimulated or rested, respectively). During the treatment period with the combination, rested PMBCs were tested with anti-CD3 costimulation, while prestimulated PMBCs were tested with or without anti-CD3 costimulation. In rested PBMCs from 4 donors, there were IFNγ or TNFα responses (≥3X of no drug control) with GSK3359609 (feladilimab) and GSK3174998 combinations (≥0.01 μg/mL of at least one of the test articles) where no effect was observed with either test article alone at concentrations up to 10 μg/mL, or at incrementally lower concentrations of GSK3359609 (feladilimab) when combined with incrementally higher concentrations of GSK3174998. There was no evidence of a combination effect on cytokines in prestimulated PBMCs relative to the corresponding concentration of either GSK3359609 (feladilimab) or GSK3174998 alone. Refer to the GSK3359609 (feladilimab) IB for further details [GlaxoSmithKline Document Number RPS-CLIN-015202, 2021].

2.3.3.2.3. GSK3359609 (feladilimab) Combination with Chemotherapies ±Pembrolizumab

To support the combination of GSK3359609 (feladilimab) with docetaxel, or the platinum-doublets (pemetrexed/carboplatin, paclitaxel/carboplatin, gemcitabine/carboplatin, or fluorouracil (5-FU)/carboplatin or cisplatin) with and without pembrolizumab, a review of the nonclinical toxicology findings with each given as single agents indicate that a combination toxicology study in monkeys would not likely provide any relevant clinical risk assessment data due to the frank toxicities of these chemotherapeutic agents.

The nonclinical and clinical toxicity profiles of the cytotoxic chemotherapies are well characterized with extensive clinical experience for a range of oncological indications including combinations with immune checkpoint inhibitors, such as pembrolizumab, which have not identified overlapping toxicities across the two drug classes. Target organs/systems of toxicity are hematological, gastro-intestinal and reproductive; however, other systems such as cardiovascular, renal, pulmonary and nervous may exhibit findings consistent with inhibition of cellular repair and replication. These agents will be administered per approved product label.

2.3.4. Nonclinical Activity and Pharmacodynamics

2.3.4.1. GSK3359609 (feladilimab) Monotherapy

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

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

The ex vivo functional activity of GSK3359609 (feladilimab) was evaluated in isolated immune cell populations collected from healthy human donors. Isolated PBMCs were concurrently activated with anti-CD3 and treated with doses of GSK3359609 (feladilimab) in the range of 0.1 μg/ml to 100 μg/ml as an immobilized form to emulate in vivo FcγR-mediated cross-linking. GSK3359609 (feladilimab) treatment resulted in concentration-dependent induction of cytokine production in healthy human donor PBMC which included IFNγ, TNα, IL-17a, IL-10, IL-6 and to a lesser extent IL-2, IL-5 and IL-13. GSK3359609 (feladilimab) significantly increased the levels of T cell activation markers such as CD69, OX40 and CD25 in a concentration-dependent manner. GSK3359609 (feladilimab) also showed a clear concentration-dependent increase in proliferation as measured by Ki67 staining of CD4+ and CD8+ T cells. Consistent with

the ICOS expression profile and biology, a more robust response was observed in CD4+ T cells compared to CD8+ T cells. These results were consistent across healthy human donor PBMC (n=4). Studies conducted with ex vivo treated PBMCs isolated from cynomolgus monkeys were comparable to that observed with ex vivo treated human PBMC.

ICOS receptor signals through intracellular recruitment of phosphatidylinositol 3-kinase (PI3K) and via downstream activation of the mitogen activated protein kinases p38, JNK, and ERK [Chialda, 2005; Chen, 2013; Gigoux, 2014]. Treatment with GSK3359609 (feladilimab) leads to increased phosphorylation of AKT, a key protein kinase in the PI3K signaling cascade, along with other proteins downstream of AKT, such as GSK3β and ribosomal protein S6 in a concentration and time dependent manner.

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

FcγR-mediated cell-to-cell cross-linking enhanced GSK3359609 (feladilimab)-induced T cell activation, proliferation and function. GSK3359609 (feladilimab) was only able to effectively induce T cell proliferation in the presence of FcγR-expressing monocytes as a co-culture together with T cells. While an Fc blocking antibody had little or no effect on GSK3359609 (feladilimab)-induced cytokine production, it significantly inhibited GSK3359609 (feladilimab)-induced T cell proliferation further confirming that FcγR-mediated cell-to-cell cross-linking is required for optimal activity of an anti-ICOS agonist antibody.

Refer to the GSK3359609 (feladilimab) IB for further details [GlaxoSmithKline Document Number RPS-CLIN-015202, 2021].

2.3.4.2. GSK3359609 (feladilimab) Combination with anti-PD-1 or anti-CTLA-4

The T cell activating potential of GSK3359609 (feladilimab) was evaluated in multiple assay formats as a single agent and in combination with other immune checkpoint inhibitors. Ex vivo studies were conducted with PBMC isolated from healthy human donors pre-activated with anti-CD3 alone or anti-CD3/anti-CD28. Soluble GSK3359609 (feladilimab) either alone or in combination with pembrolizumab or ipilimumab demonstrated a more robust pro-inflammatory cytokine response than either single agent alone. A modified allogenic mixed lymphocyte reaction assay, where lymphocytes from one donor were mixed ex-vivo with peptide-stimulated dendritic cells differentiated from freshly isolated monocytes from another donor, was also employed to evaluate GSK3359609 (feladilimab) in combination with either pembrolizumab or ipilimumab.

Significant increases in IFNγ secretion were observed for GSK3359609 (feladilimab) combined with pembrolizumab or ipilimumab as compared to either agent alone, supporting clinical evaluation of these combinations.

In vivo experiments in different mouse models either using GSK3359609 (feladilimab)/pembrolizumab or anti-mouse ICOS in combination with an anti-PD-1 surrogate antibody demonstrated enhanced tumor growth inhibition and increased survivability of mice compared to either agent alone. Combination studies with GSK3359609 (feladilimab) and pembrolizumab in the human PBMC engrafted NSG mouse model with A2058 melanoma tumors show enhanced tumor growth inhibition and increased survivability of mice compared to either agent alone. Similar results were also observed with the anti-mouse ICOS and PD-1 surrogate antibodies in subcutaneously implanted syngeneic mouse CT26 colon carcinoma and EMT6 mammary carcinoma models, where combination treatment resulted in reduced tumor growth and 30 to 40% increased survival compared with the monotherapy groups. Furthermore, in vivo studies using ICOS-/- and ICOS-ligand (L)-/- mice demonstrated the requirement of ICOS signaling in mediating the anti-tumor activity of an anti-CTLA-4 antibody in the B16/F10 melanoma syngeneic tumor model [Fu, 2011]. Mice lacking ICOS or ICOS-L had significantly decreased survival rates compared to wild-type mice after anti-CTLA-4 antibody treatment suggesting a combination of anti-CTLA-4 treatment with an anti-ICOS agonist may provide robust anti-tumor responses. In a separate study, B16 tumors engineered to overexpress ICOS-L were found to be significantly more sensitive to anti-CTLA-4 treatment as compared to a B16/Bl6 tumor cells transduced with a control protein [Fan, 2014].

Treatment of tumor-bearing mice with anti-PD-1 antibodies upregulated ICOS on T cells. Treatment with mouse anti-PD-1 antibody in the A20 melanoma cell line model showed upregulation of ICOS+ CD4+ and CD8+ T cells in tumors as well as lymph nodes in the anti-PD-1 treated animals when compared to those treated with the vehicle or isotype control. Similarly, anti-mouse ICOS antibodies increased tumor PD-L1 expression, further support evaluating this combination. Finally, The Cancer Genome Atlas (TCGA) gene expression data demonstrates that tumors with higher ICOS expression also tend to have higher PD-L1 expression, with head and neck squamous cell carcinomas observed as having the highest ICOS expression suggesting that targeting both axes may result in greater anti-tumor immune response. Interplay between receptor induction also extended to CTLA-4. As an example, treatment with mouse anti-CTLA-4 mouse antibody induced ICOS on CD4+ and CD8+ T cells in the tumor, spleen and blood, a pattern comparable to the ipilimumab clinical response.

2.3.4.3. GSK3359609 (feladilimab) Combination with GSK3174998 (OX40)

In vivo combination studies using mouse monoclonal antibody surrogates of ICOS and OX40 agonists in multiple mouse syngeneic tumor models demonstrated enhanced activity (i.e., tumor growth inhibition and survival) of the combination in specific tumor models when compared to the single agent treated groups. In some models the combination effect was driven mainly by the OX40 mouse surrogate antibody.

Refer to the GSK3359609 (feladilimab) IB for further details on study designs and results [GlaxoSmithKline Document Number RPS-CLIN-015202, 2021].

2.3.5. GSK3359609 (feladilimab) Clinical Experience

Analysis from the dose escalation phases of GSK3359609 (feladilimab) monotherapy (Part 1A, n=22) and GSK3359609 (feladilimab) combination with pembrolizumab (Part 2A, n=36), and GSK3359609 (feladilimab) monotherapy pharmacokinetic (PK)/pharmacodynamic cohort (n=47) demonstrated GSK3359609 (feladilimab) alone and in combination with pembrolizumab was well tolerated across the 0.001–3 mg/kg dose range. Maximum tolerated dose (MTD) was not reached in Part 1A and Part 2A; maximum administered dose of GSK3359609 (feladilimab) as a monotherapy and in combination with pembrolizumab was 3 mg/kg. A range of GSK3359609 (feladilimab) doses (≥0.1-1 mg/kg) demonstrated biological and clinical activity supporting the mechanism of action of a non-depleting ICOS agonist as a clinical target [Hansen, 2018; Maio, 2019].

As of 16 March 2020, 249 participants received at least 1 dose of GSK3359609 (feladilimab) as a monotherapy, 340 participants received at least 1 dose of GSK3359609 (feladilimab) in combination with 200 mg pembrolizumab, 69 participants received at least 1 dose of GSK3359609 (feladilimab) in combination with chemotherapy (±pembrolizumab), and 19 participants received at least 1 dose of GSK3359609 (feladilimab) in combination with GSK3174998 in this current, ongoing 204691 study (refer to Section 2.3.5.2 for summary of safety). These participants are included in the preliminary safety analysis summarized below.

Refer to GSK3359609 (feladilimab) IB for updated details [GlaxoSmithKline Document Number RPS-CLIN-015202, 2021].

2.3.5.1. GSK3359609 (feladilimab) Monotherapy

Overall in the Part 1 population, 231 of 249 participants (93%) experienced at least 1 AE regardless of causality. Overall, 98 out of 249 participants (39%) experienced at least 1 AE of maximum severity ≥Grade 3. Of the 249 participants treated in Part 1, 69 participants (28%) experienced at least 1 SAE.

Anemia was the most common AE (n=56, 22%). Sixteen of 249 participants (16%) experienced maximum Grade 3 anemia, 1 participant experienced a maximum Grade 4 anemia, and no participant experienced a maximum Grade 5 anemia. Anemia occurred across dose levels, with 1 of 7 participants (14%) at 0.03 mg/kg; 7 of 25 participants (28%) at 0.1 mg/kg; 9 of 56 participants (16%) at 0.3 mg/kg; 35 of 126 participants (28%) at 1.0 mg/kg; and 2 of 24 participants (8%) at 3.0 mg/kg. Overall, 9 participants (4%) experienced at least 1 AE of maximum Grade 4 and 7 participants (3%) experienced at least 1 AE of maximum Grade 5. In order to elucidate the adverse event of special interest (AESI) profile of immune-mediated events, a very broad net of preferred terms was included in the various categories as these are potential terms that may be representative of signs/symptoms or conditions of the respective broader category; not all terms reflect true cases of immune-mediated events and should not be construed as such. Overall, in Part 1 GSK3359609 (feladilimab) monotherapy, 44 participants (18%) experienced at least 1 AESI subsumed under the AESI class of skin reactions, with pruritis as the most common event reported (20 participants [(8%]; all events were low

grade). No cases of pneumonitis were reported or identified in monotherapy. In the AESI subclass of hepatitis, no participant experienced an event of immune-mediated hepatitis, nor hepatitis, however, there was one Grade 3 event of hepatic function abnormal. Four participants experienced a Grade ≥3 event that was subsumed under the infusion-related reaction subclass: 3 participants experienced Grade 3 hypotension and 1 participant experienced a Grade 3 infusion-related reaction. One participant (<1%) experienced an event of colitis (Grade 3).

Among the dose levels of GSK3359609 (feladilimab) monotherapy investigated in the dose escalation phase (from 0.001 mg/kg to 10 mg/kg), no dose limiting toxicities (DLTs) were observed during the 28-day DLT observation period. One participant in the PK/pharmacodynamic cohort receiving 3 mg/kg GSK3359609 (feladilimab) experienced DLTs of Grade 3 or Grade 4 elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin, gamma-glutamyl transferase (GGT), impaired liver function that was considered serious, lipase and Grade 1 amylase during the 28-day observation period. Factors relevant in the assessment of these events include: the participant was receiving paracetamol as a concomitant treatment for pain and an ultrasound of the liver showed marked dilation of the biliary tract and the presence of liver lesion measuring 51 x 41 mm; the participant underwent biliary stent placement. All events were considered related to study treatment and led to treatment discontinuation.

Refer to GSK3359609 (feladilimab) IB for further details [GlaxoSmithKline Document Number RPS-CLIN-015202, 2021].

2.3.5.2. GSK3359609 (feladilimab) in Combination with Pembrolizumab

Overall in the Part 2 GSK3359609 (feladilimab) combination with pembrolizumab 200 mg, 327 of 340 participants (96%) experienced at least 1 AE regardless of causality. The most common AEs (occurring in ≥15% of participants overall regardless of GSK3359609 (feladilimab) dose level in combination with pembrolizumab 200 mg or relationship to the study treatment) were anemia (20%); nausea (19%), fatigue (18%), asthenia (17%), diarrhea (17%), dyspnea (16%), decreased appetite (16%), and cough (15%). One hundred and fifty-nine participants (47%) experienced at least 1 AE of maximum Grade ≥3.

Of the 340 participants treated in the Part 2 combination with pembrolizumab, 150 participants (44%) experienced at least 1 SAE, of which 17 participants (5%) experienced at least 1 SAE considered by the investigator as treatment related. SAEs reported in >1 participant each overall were dyspnea, pneumonitis, pneumothorax, fatigue, pneumonia, arthralgia, asthenia, general physical health deterioration, hypercalcemia, intestinal obstruction, lung infection, pain in extremity, pyelonephritis, pyrexia, tumor hemorrhage, acute kidney injury, ataxia, hyperglycemia, ileus, non-cardiac chest pain, pleural effusion, sepsis, small intestinal obstruction, and urinary tract infection.

In the Part 2 GSK3359609 (feladilimab) combination with pembrolizumab, 67 participants (20%) experienced at least 1 AESI subsumed under the AESI class of skin adverse reactions, with pruritis as the most common event reported (30 participants

[(9%]; 5 participants [1%] experienced at least 1 Grade ≥3 skin reaction event). Twelve participants (4%) experienced an event of pneumonitis; Grade ≥3 events were reported in 1 of these participants (Grade 3). In the AESI subclass of hepatitis, 2 participants (<1%) experienced an event of hepatitis (Grade 2 and Grade 3), and 1 participant (<1%) experienced an event of Grade 1 immune-mediated hepatitis. Three participants experienced a Grade ≥3 event that was subsumed under the infusion-related reaction subclass: 2 participants experienced Grade 3 hypotension and 1 participant experienced a Grade 3 rash. Two participants (<1%) experienced an event of colitis, Grade ≥3 events were reported in 1 of these participants.

In the 6 dose levels of GSK3359609 (feladilimab) (0.01, 0.03, 0.1, 0.3, 1.0, and 3.0 mg/kg) investigated in combination with 200 mg pembrolizumab in the dose escalation phase, 1 participant receiving 3 mg/kg GSK3359609 (feladilimab) in combination with 200 mg pembrolizumab experienced a DLT of Grade 3 pneumonitis that occurred 18 days after the first dose of study treatment; the event resolved within 28 days.

Refer to GSK3359609 (feladilimab) IB for further details [GlaxoSmithKline Document Number RPS-CLIN-015202, 2021].

2.3.5.2.1. GSK3359609 (feladilimab) Monotherapy and Combination with Pembrolizumab in HNSCC

The ongoing expansion phase in Study 204691 is investigating GSK3359609 (feladilimab) as a monotherapy (Part 1B) and GSK3359609 (feladilimab) in combination with pembrolizumab (Part 2B) in participants with HNSCC. At a clinical data cut-off date of 26 July 2019, 17 participants with anti-PD-1/L1 treatment experienced HNSCC received at least 1 dose of 1 mg/kg GSK3359609 (feladilimab) in Part 1B cohort. In the treated population (n=17), the median age was 56 years (range: 41-73 years); 82% were male and 82% received ≥1 prior lines of systemic therapy in the advanced/metastatic setting. Sixteen of the 17 dosed participants were considered evaluable for efficacy analysis; the overall response rate (ORR) in the evaluable population was 6% with 1 of the 16 participants achieving a partial response (PR).

In the Part 2B cohort, 34 participants with anti-PD-1/L1 naïve HNSCC received at least one cycle of 0.3 mg/kg GSK3359609 (feladilimab) in combination with 200 mg pembrolizumab. In the treated population (n=34), the median age was 62 years (range 37-77 years); 85% were male and 53% received ≥1 prior line of systemic therapy in the advanced/metastatic setting. All 34 dosed participants were considered evaluable for efficacy analyses. The ORR in the evaluable population (n=34) was 24% (95% CI: 10.7%, 41.2%) with 8 of the 34 participants achieving a complete response (n=3) or PR (n=5); disease control rate (DCR) was 65% (n=22; 95% CI: 46.5, 80.3). In addition, the majority of participants that achieved a response or stable disease had PD-L1 CPS status <20 (10/14 participants with CPS≥1 and <20, and 1 participant with CPS <1).The median progression-free survival (PFS) was 5.6 months (95% CI: 2.4, 7.4) [Rischin, 2019].

2.3.5.3. GSK3359609 (feladilimab) Combination with Chemotherapy ± Pembrolizumab

In Part 2 combination with chemotherapy ± pembrolizumab, 69 of 69 participants (100%) experienced at least 1 AE. The most common AEs (occurring in ≥20% of participants overall for GSK3359609 (feladilimab) in combination with chemotherapy ± pembrolizumab regardless of relationship) were nausea in 36 of 69 participants (52%), anemia in 25 of 69 participants (36%), neutropenia in 22 of 69 participants (32%), diarrhea in 21 of 69 participants (30%), and fatigue in 18 of 69 participants (26%). Overall, in Part 2 combination with chemotherapy ± pembrolizumab, 55 of 69 participants (80%) experienced at least 1 AE of maximum Grade ≥3; Grade 3 (39 participants, 57%), Grade 4 (13 participants, 19%), or Grade 5 (3 participants, 4%). Grade 5 AEs were considered by the investigator as not related to study treatment.

In Part 2 combination with chemotherapy ± pembrolizumab, treatment-related AEs were experienced by 68 of 69 participants (99%) in the overall Part 2 combination with chemotherapy ± pembrolizumab. The most common treatment-related AE was nausea (45%). Most treatment-related AEs were Grade 3 and Grade 4 (45 participants, 65%). No participant experienced at least 1 treatment-related AE of maximum Grade 5.

Of the 69 participants treated in Part 2 combination with chemotherapy ± pembrolizumab, 30 participants (43%) experienced at least 1 SAE of which 13 participants (19%) experienced at least 1 SAE considered by the investigator as related to study treatment. SAEs reported in >1 participant were febrile neutropenia, dyspnea, colitis, diarrhea, fatigue, pneumonia, pneumonia aspiration, syncope, and tumor hemorrhage. The most common SAE, in 5 of 69 participants (7%), was febrile neutropenia. Overall, 29 participants (42%) experienced at least 1 SAE of maximum Grade ≥3. Grade 3 (22 participants, 32%); Grade 4 (4 participants, 6%); Grade 5 (3 participants, 4%).

In the GSK3359609 (feladilimab)/docetaxel safety cohort (n=10) 1 participant (10%) experienced at least 1 treatment-related SAE of maximum Grade ≥3: Grade 3: fatigue. In the GSK3359609 (feladilimab)/5FU/cisplatin safety cohort (n=5) 3 participants (60%) experienced at least 1 treatment-related SAE of maximum Grade ≥3:
Grade 3: pancytopenia, stomatitis, intestinal ischemia, blood creatinine increased, and neutrophil count decreased. Grade 4: mucosal inflammation, hypernatremia, and sepsis. In the GSK3359609 (feladilimab)/pemetrexed/carboplatin/pembrolizumab safety cohort (n=4) 1 participant (25%) experienced at least 1 treatment-related SAE of maximum Grade ≥3: Grade 3: myocarditis. In the GSK3359609 (feladilimab)/paclitaxel/carboplatin/pembrolizumab safety cohort (n=3) 2 participants (67%) experienced at least 1 treatment-related SAE of maximum Grade ≥3: Grade 3: rash maculo-papular, febrile neutropenia. In the GSK3359609 (feladilimab)/5FU/cisplatin/pembrolizumab safety cohort (n=8) 4 participants (50%) experienced at least 1 treatment-related SAE of maximum Grade ≥3: Grade 3: febrile neutropenia, diarrhea. Grade 4: febrile neutropenia. In the GSK3359609 (feladilimab)/5FU/carboplatin/pembrolizumab safety cohort (n=11), 2 participants (18%) experienced at least 1 treatment-related SAE of maximum Grade ≥3. Grade 3: colitis, febrile neutropenia, pneumonia, dyspnea.

Thirteen participants experienced a least 1 AE leading to permanent discontinuation of study treatment in the Part 2 combination with chemotherapy ± pembrolizumab. Events of pneumonia aspiration and an event of lower respiratory infection in 1 participant each had a fatal outcome; neither event was considered by the investigator as related to study treatment. All remaining events leading to permanent discontinuation of study treatment were considered by the investigator as related to study treatment.

Refer to GSK3359609 (feladilimab) IB for further details [GlaxoSmithKline Document Number RPS-CLIN-015202, 2021].

2.4. Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to pembrolizumab IB [Merck Sharp & Dohme Corp, Pembrolizumab IB, 2021] and approved labelling.

The most common reported AEs (≥20% of patients) with pembrolizumab single agent include fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain and abdominal pain [KEYTRUDA FDA Pharmacology Toxicology Review, 2014]. Serious and fatal AEs associated with treatment include immune-mediated adverse reactions, which consisted of pneumonitis, colitis, endocrinopathies (i.e., hypophysitis, thyroid disorders, and Type1 diabetes mellitus), hepatitis, nephritis, infusion reactions, and skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis.

2.5. GSK3174998 (Anti-OX40 Agonist)

GSK3174998 is a humanized wild-type, IgG1 anti-OX40 agonist mAb. GSK3174998 possesses mechanisms of action specific to the established functions of OX40 on T cells which include:

- Transduction of a costimulatory signal following T cell priming and activation thus augmenting T cell activation, proliferation and survival through direct and indirect (e.g., cytokine release) mechanisms.

- Inhibition of regulatory T cell (Treg) activity by blocking the release of the inhibitory cytokine IL-10 and the suppressive function of natural Tregs (nTregs); thereby further stimulating the nascent immune response.

Additionally, as GSK3174998 is a wild-type, IgG1 mAb, its fragment crystallizable (Fc) domain binds to the Fc receptor (FcR) on innate immune cell populations which is anticipated to augment OX40 signaling via this cross-linking. GSK3174998 has the

potential to possess an antibody dependent cell- mediated cytotoxicity mechanism based on its inherent structure.

Detailed information on the biology, pharmacology, pharmacokinetic, and nonclinical safety characteristics can be found in the GSK3174998 IB [GlaxoSmithKline Document Number 2014N212091_06, 2020 refer to Section 2.3.3.2.2 for summary of nonclinical safety].

2.5.1. GSK3174998 (Anti-OX40) Clinical Experience

Details on the preliminary clinical findings and information regarding warnings, precautions, contraindications, warnings and other pertinent information can be found in GSK3174998 IB [GlaxoSmithKline Document Number 2014N212091_06, 2020].

Overall in Study 204691, in Part 2 combination with GSK3174998, (regardless of GSK3359609 (feladilimab) dose level in combination with GSK3174988), 4 of 19 participants (21%) experienced at least 1 treatment-related AE. No participant experienced at least 1 treatment-related AE of maximum Grade ≥3. Three of 19 participants (16%) experienced at least 1 treatment -related AE of maximum Grade 1 (fatigue [2 events], decreased appetite, and neutrophil count increased). One participant (5%) experienced at least 1 treatment related AE of maximum Grade 2 (infusion-related reaction). Participants who received GSK3359609 (feladilimab) 8 mg + GSK3174998 24 mg: 1 event each (25%) of decreased appetite and fatigue; GSK3359609 (feladilimab) 24 mg + GSK3174998 24 mg: 1 event (10%) of infusion-related reaction of Grade 2; GSK3359609 (feladilimab) 80 mg + GSK3174998 24 mg: 1 event (25%) of neutrophil count increased and 1 event (25%) of fatigue.

Of the 19 participants treated in Part 2 combination with GSK3174998, 7 participants (37%) experienced at least 1 SAE. SAEs reported in 3 participants (16%) were dyspnea, and in 1 participant (5%) each of abdominal pain, bronchitis, confusional state, dysphagia, hypotension, infusion related reaction, metapneumovirus infection, and metastases to central nervous system. Six participants experienced at least 1 SAE of maximum Grade ≥3. SAEs of maximum Grade 3 (dyspnea, abdominal pain, bronchitis, confusional state, dysphagia, hypotension, metapneumovirus infection), Grade 4 (dyspnea), or Grade 5 (dyspnea) were experienced by 4 (21%), and 1 (5%), and 1 (5%) of 19 participants, respectively.

No participant in Part 2 combination with GSK3174998 experienced at least 1 SAE of maximum Grade ≥3 considered by the investigator as related to treatment.

No participant in Part 2 combination with GSK3174998 experienced an AE leading to permanent discontinuation of study treatment.

Refer to GSK3359609 (feladilimab) IB for further details [GlaxoSmithKline Document Number RPS-CLIN-015202, 2021].

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Part 1 GSK3359609 (feladilimab) Monotherapy	
Primary	
• To determine the safety, tolerability, MTD or the MAD of GSK3359609 (feladilimab)	• AEs, SAEs, DLTs, changes in safety/laboratory assessment parameters, dose modifications
Secondary	
• To determine the recommended dose of GSK3359609 (feladilimab) for further exploration	• AEs, SAEs, DLTs, changes in safety/laboratory assessment parameters, dose modifications, PK, pharmacodynamic activity, antitumor activity
• To evaluate the antitumor activity of GSK3359609 (feladilimab) • To characterize the PK properties of GSK3359609 (feladilimab)	• ORR[1], DCR[1], PFS[1], OS, TTR[1, 2,] DoR[1,2] • Plasma PK parameters such as Cmax, Ctau, AUC (0-τ) as data permit
• To determine immunogenicity	• ADA incidence by dose level/dose
Exploratory	
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

Abbreviations: ADA=anti-drug antibody; AE=adverse events; AUC=area under the curve; Cmax= maximum observed concentration; Ctau=minimum observed concentration; DCR=disease control rate; DLT=dose limiting toxicity; DNA=deoxyribonucleic acid; DoR=duration of response; CCI [redacted] IHC=immunohistochemistry; irRECIST=immune-related RECIST; MAD=maximum administered dose; MTD=maximum tolerated dose; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PK; pharmacokinetic; ; CCI [redacted] RECIST=Response Evaluation Criteria in Solid Tumors; RNA=ribonucleic acid; SAE; serious adverse events; TTR=time to response

1. irRECIST is the primary measure of clinical activity for response endpoints and PFS; RECISTv1.1 guidelines are used for disease assessments.
2. TTR and DoR will be evaluated if data permit; refer to Section 10.7.2.1 for further details on the possible analysis of antitumor activity in the dose escalation cohorts.

Objectives	Endpoints
Part 2 GSK3359609 (feladilimab) (ICOS) in Combination with Pembrolizumab or GSK3174998 (anti-OX40)	
• **Primary**	
• To determine the safety, tolerability, MTD or the MAD of GSK3359609 (feladilimab) in combination with pembrolizumab or GSK3174998 (anti-OX40)	• AEs, SAEs, DLTs, changes in safety/laboratory assessment parameters, dose modifications

Objectives	Endpoints
• **Secondary**	
• To determine the recommended dose(s) and schedule of GSK3359609 (feladilimab) in combination with pembrolizumab or GSK3174998 for further exploration • To determine the recommended dose(s) of GSK3359609 (feladilimab) and GSK3174998 in combination	• AEs, SAEs, DLTs, changes in safety/laboratory assessment parameters, dose modifications, PK, pharmacodynamic activity, antitumor activity
• To evaluate the antitumor activity of GSK3359609 (feladilimab) in combination with pembrolizumab or GSK3174998	• ORR[1], DCR[1], PFS[1], OS, TTR[1, 2,] DoR[1]
• To characterize the PK properties of GSK3359609 (feladilimab), pembrolizumab, and GSK3174998 when administered in combination	• GSK3359609 (feladilimab), GSK3174998, and pembrolizumab PK parameters such as Cmax, Ctau, AUC (0-τ) as data permit
• To determine immunogenicity of GSK3359609 (feladilimab), pembrolizumab, orGSK3174998, when administered in combination	• ADA incidence of each drug by dose level/ dose
• **Exploratory**	
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

Abbreviations: ADA=anti-drug antibody; AE=adverse events; AUC=area under the curve; Cmax= maximum observed concentration; Ctau=minimum observed concentration; CPS=combined positive score; DCR=disease control rate; DLT=dose limiting toxicity; DNA=deoxyribonucleic acid; DoR=duration of response; CCI [redacted] HNSCC=head and neck squamous cell carcinoma; IHC=immunohistochemistry; irRECIST=immune –related RECIST; MAD=maximum administered dose; MTD=maximum tolerated dose; ORR=overall response rate; OS=overall survival; PD-L1= programmed cell death receptor 1-ligand 1; PFS=progression-free survival; PK; pharmacokinetic; CCI [redacted] RECIST=Response Evaluation Criteria in Solid Tumors; RNA=ribonucleic acid; SAE; serious adverse events; TTR=time to response

1. irRECIST is the primary measure of clinical activity for response endpoints (i.e., ORR, DCR);RECISTv1.1 guidelines are used for PFS, DoR, TTR and disease assessments.
2. CCI [redacted]

Objectives	Endpoints
Part 2A GSK3359609 (feladilimab) Combination with Chemotherapies (+Pembrolizumab)	
Primary	
• To determine the safety, tolerability, of GSK3359609 (feladilimab) in combination with standard of care chemotherapies ± pembrolizumab	• AEs, SAEs, changes in safety/laboratory assessment parameters, dose modifications
Secondary	
• To determine the recommended dose of GSK3359609 (feladilimab) for further exploration • To characterize the PK properties of GSK3359609 (feladilimab), chemotherapies, and pembrolizumab • To determine immunogenicity of GSK3359609 (feladilimab) and pembrolizumab	• AEs, SAEs, DLTs, changes in safety/laboratory assessment parameters, dose modifications, PK, pharmacodynamic activity, antitumor activity • Plasma PK parameters such as Cmax, and Ctau as data permit • ADA incidence by dose level/dose
• **Exploratory**	
CCI [redacted]	

Abbreviations: ADA=anti-drug antibody; AE=adverse events; Cmax= maximum observed concentration; Ctau=minimum observed concentration; DCR=disease control rate; DLT=dose limiting toxicity; DNA=deoxyribonucleic acid; DoR=duration of response; irRECIST=immune –related RECIST; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PK; pharmacokinetic;; RECIST=Response Evaluation Criteria in Solid Tumors; RNA=ribonucleic acid; SAE; serious adverse events; TTR=time to response

1. irRECIST is the primary measure of clinical activity for response endpoints (i.e., ORR, DCR);RECISTv1.1 guidelines are used for PFS, DoR, TTR and disease assessments
2. TTR and DoR will be evaluated if data permit; refer to Section 10.7.2.1 for further details.

4. STUDY DESIGN

4.1. Overall Design

This is a FTIH, open-label, multicenter study designed to investigate the safety, tolerability, pharmacology, PK, preliminary clinical activity, and establish a recommended dose of GSK3359609 (feladilimab) for further exploration.

As illustrated in Figure 1, the study will be conducted in two parts (Part 1 GSK3359609 (feladilimab) monotherapy and Part 2 GSK3359609 (feladilimab) combination therapy) whereby each part consists of a dose escalation/safety run-in phase followed by a cohort expansion phase. GSK3359609 (feladilimab) combinations with chemotherapy with or without pembrolizumab will only consist of safety run-in cohorts (Part 2A only).

Part 1A dose escalation phase will evaluate escalating weight-based dose levels of monotherapy GSK33596069 administered intravenously once every three weeks (Q3W) to participants with selected relapsed and/or refractory solid tumors. Based on safety and tolerability, and the pharmacokinetic/pharmacodynamic characteristics of the molecule, recommended monotherapy dose level or dose levels may be further investigated in expansion cohorts (Part 1B).

Part 2A pembrolizumab combination dose escalation phase will be initiated when a monotherapy dose level of GSK3359609 (feladilimab) has been deemed safe and has demonstrated consistent, dose-responsive pharmacodynamic activity; two dose levels below this dose level will become the starting dose investigated in combination with a 200 mg fixed dose of pembrolizumab (refer to Section 4.5.7 for dose rationale).

GSK3359609 (feladilimab) dosage will be investigated at fixed doses with GSK3174998 and the chemotherapy combinations in Part 2A (Refer to Section 4.5.9 for the fixed-dose rationale).

Part 2A GSK3174998 combination dose escalation phase will initiate at starting doses of 8 mg for GSK3359609 (feladilimab) and GSK3174998 (refer to Table 2). RP2 combination doses selected will consider safety and tolerability, clinical activity, and the PK/pharmacodynamic characteristics.

The starting GSK3359609 (feladilimab) dose of 24 mg or 80 mg will be combined with standard doses of chemotherapy (refer to Section 4.5.3 and Section 4.5.8 for dose rationales) and pembrolizumab (200 mg); lower doses of GSK3359609 (feladilimab) that have been investigated in other cohorts may also be evaluated in combination with chemotherapy.

As depicted in Figure 2, seamless design will be implemented to combine dose escalation with dose expansion, based on toxicity and efficacy [Pan, 2013]. In both Part 1 and Part 2, the dose expansion phase may start before the dose escalation phase is completed. All

available safety and tolerability data from participants in dose expansion will be incorporated into dose escalation decision making. The basis of the decision to initiate expansion of a dose level/dose will consider the following graduation rules:

1. Established safety and tolerability;
2. Preliminary PK/pharmacodynamic characteristics (i.e., measures of target engagement and functional effects [redacted]) and/or
3. Preliminary antitumor activity.

Once a dose level(s) passes the graduation rules (refer to Figure 2) the selected dose(s) may enter into the expansion phase for further investigation following approval by active study investigators. Alternate GSK3359609 (feladilimab) schedules are being investigated (GSK3359609 (feladilimab) Q6W in combination with pembrolizumab Q6W); drug sequencing may be investigated in the expansion phase. In addition, dose levels under investigation in the ongoing monotherapy dose escalation phase may incorporate information, such as safety data, from participants who were accrued to the expansion phase. Randomization and/or futility rules may be incorporated if appropriate in expansion phase to optimize the dose allocation based on evaluations of safety and antitumor activity. The details of randomization schema for expansion cohorts will be documented before the initiation of expansion cohort; details of the futility rules will be documented in the reporting and analysis plan (RAP)before initiation of interim analyses [Pan, 2013].

The overall study will enroll approximately 867 participants diagnosed with solid tumor malignancies.

- In the dose escalation phases of the study, and in the PK/pharmacodynamic, and ADA expansion cohorts the solid tumor types selected for inclusion include bladder/urothelial cancer, cervical cancer, colorectal cancer (CRC), esophageal cancer with squamous cell histology, head and neck (HN) cancer, melanoma, malignant pleural mesothelioma (MPM), non-small-cell lung cancer (NSCLC), and prostate cancer.
    - PK/Pharmacodynamic expansion cohorts (Part 1C, Part 2C, and Part 1D) are restricted to enrollment from sites located in Japan and China; these cohorts are active by country-specific amendments to the 204691 protocol.
- In the cohort expansion phases of the study (Part 1B and Part 2B), several expansion cohorts have been defined by tumor histology or by a specific characteristic such as tumors exhibiting high microsatellite instability (MSI-H), deficiency in DNA mismatch repair (dMMR) processes, or viral-mediated pathology; enrollment in these cohorts is not limited to the tumor types/histologies in the aforementioned list (defined as tumor agnostic). A Part 2B HNSCC cohort will investigate GSK3359609 (feladilimab) at an alternative dosing schedule of once every 6 weeks (Q6W); participants will be randomly

assigned to GSK3359609 (feladilimab) doses of 48 mg or 160 mg Q6W in combination with pembrolizumab 400 mg administered at the schedule of Q6W.

  - A Part 2B expansion cohort will enroll approximately 30 participants with PD-1/L1 treatment naïve HNSCC that is PD-L1 CPS <1

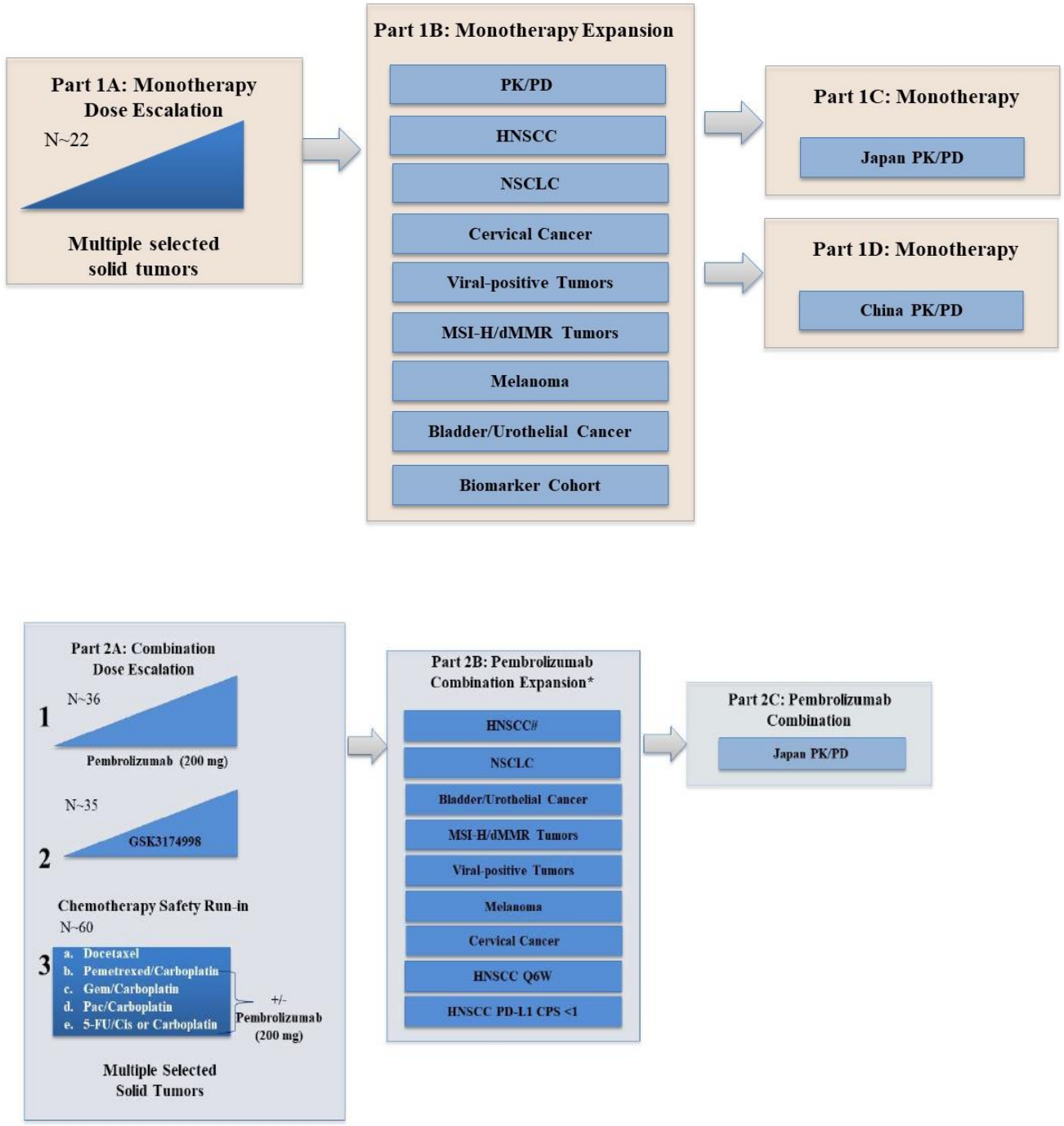
- Additional expansion cohorts may enroll participants with a specific tumor type selected from the aforementioned list or from a tumor type/histology not protocol-defined; the basis for the selection will be evidence-based and by an amendment to the protocol to define the cohorts.

GSK3359609 (feladilimab) monotherapy and in combination with pembrolizumab or other anti-cancer agents may be investigated in biomarker defined cohorts to evaluate the effect/interaction of the status of the biomarker on the activity of the regimens. Additionally, cohorts may be defined based on other features such as prior response with an immune checkpoint inhibitor, disease characteristic, molecular/genetic alterations or pathology.

The overall study size may extend beyond 867 by a protocol amendment if data from expansion phases support extended enrollment or additional combinations are investigated.

Assessment of disease status will be performed by the Investigator in accordance with Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 and Immune Related (ir) RECIST. A decision to discontinue treatment due to disease progression will be based upon irRECIST; primary efficacy response endpoint analysis will use irRECIST. Scans will be collected centrally and stored to allow for the option of central review.

Figure 1 Study Design



Abbreviations: 5-FU=fluorouracil; Cis=cisplatin; dMMR= deficient mismatch repair; Gem=gemcitabine; IHC=immunohistochemistry; MSI-H= microsatellite instability-high; NSCLC=non-small cell lung cancer; Pac=paclitaxel; PD-L1=programmed death; HNSCC= head and neck squamous cell cancer

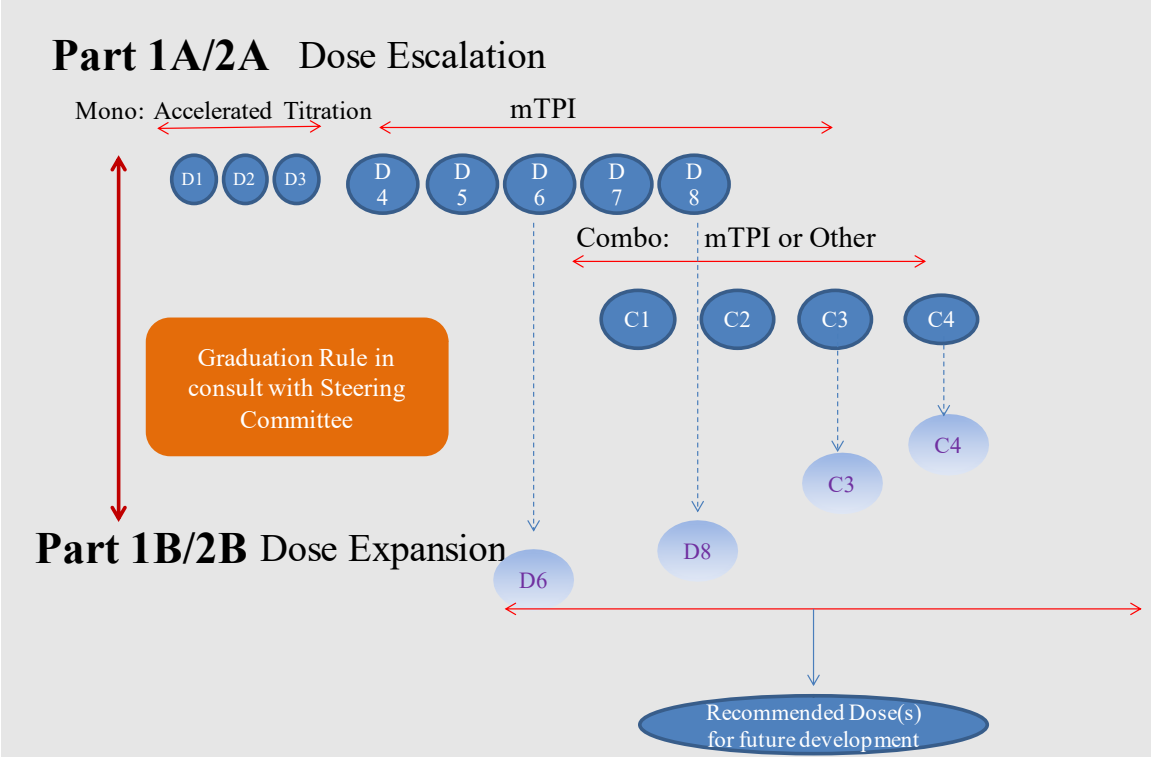
#: a subset of HNSCC participants will be randomly assigned to one of 3 doses of GSK3359609 (feladilimab) (refer to Table 6) in combination with 200mg of pembrolizumab

*Participants enrolled in the Part 2B cohorts (GSK3359609 (feladilimab)/pembrolizumab combination) may be stratified by PD-L1 IHC status and prior PD-1/L1 treatment

1. The number of participants allocated to any Part is an estimate.

2. The number of cohorts indicated in any Part is an estimate.
3. Expansion cohorts may increase enrollment following outcome of interim analyses (refer to Section 10.6 for details); enrollment in the overall population will not exceed the approximate number of 867 participants except by an amendment.
4. Participants enrolled in Part 1 (GSK3359609 (feladilimab) monotherapy) upon disease progression may be permitted to receive GSK3359609 (feladilimab) in combination with pembrolizumab (defined as crossover); refer to Section 5.4 for further details.

Figure 2 Study Phase Progression Chart



1. Figure 2 illustrates an example scenario; exact dose graduation will depend on data emerging from dose escalation
2. Graduation rule for monotherapy and combination therapy may be different; graduation rules will be based on safety and efficacy in combination with exploratory PK/pharmacodynamic modeling
3. Multiple tumor types may be enrolled in dose expansion phases

4.1.1. Dose Escalation Phase

Decisions to escalate to subsequent dose levels in Part 1A monotherapy and Part 2A combination therapy will be according to the dose selection design put into practice. The underlying principle behind dose selection designs used in this study is that selection of each subsequent dose level/dose considers the number of participants presenting with a dose limiting toxicity (DLT) event relative to the number of participants enrolled at the corresponding dose level/dose under evaluation.

Additionally, the decision to escalate to the next dose level/dose will take into account the cumulative safety, available PK, and pharmacodynamic data from all participants in the current dose level as well as those from prior dose levels.

Dose escalation may proceed until the maximum tolerated dose (MTD) or maximum administered dose (MAD), otherwise defined as the highest dose administered in the absence of reaching MTD, of the monotherapy and individual combination regimens are identified.

4.1.1.1. Part 1A Monotherapy Dose Escalation

In the monotherapy dose escalation phase of the study, two rule-based designs will be in use. For the first three dose levels (refer to Table 1), an accelerated titration design is planned with one participant enrolled at each of these dose levels. Each participant must receive at least one dose of GSK3359609 (feladilimab), complete the 28-day DLT evaluation period and the available safety data must be reviewed before a decision to escalate to the next dose level is made (i.e., the dose level is cleared). If the single participant experiences DLT or drug-related ≥Grade 2 toxicity, this event will trigger the implementation of the modified Toxicity Probability Interval (mTPI) design [Ji, 2010] at that dose level and at subsequent dose levels as shown in Figure 3. 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 to achieve the three-participant required minimum.

In the dose levels under evaluation by the mTPI design, a minimum of three participants will be accrued to each dose level. In the first dose level fully accrued under the mTPI design and in all subsequent dose levels, treatment will be administered at least one week apart between the first two participants enrolled; the third and any subsequent participants will be administered treatment at a minimum of one day 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. Evaluation of the available safety data over the first 28 days of treatment for each participant enrolled in that dose level is required from at least 3 participants before a decision is made to enroll participants at the next higher dose level. The maximum number of participants assigned to any single dose level will be at the discretion of the Sponsor in consultation with the investigators.

Dose escalation for GSK3359609 (feladilimab) monotherapy will begin with a starting dose of 0.001 mg/kg administered Q3W; refer to Section 4.5 for justification of starting dose and schedule. Table 1 presents the maximum dose that may be selected for each dose level increase based on a maximum fold increase of 3.3. The predetermined maximum dose level of GSK3359609 (feladilimab) to be evaluated is 3.0 mg/kg administrated Q3W; if subsequent analyses of PK and pharmacodynamic properties and emerging clinical safety profile support the exploration of higher dose levels, escalations to dose levels greater than 3.0 mg/kg will follow the same deciding principles applied to the preceding dose levels. Dose levels intermediate to those presented in Table 1 or schedules other than once every three weeks may be explored if exposure is significantly higher than predicted, excessive toxicity is observed, or if further evaluation of PK and pharmacodynamic markers to inform on dose selection is warranted.

4.1.1.2. Japan PK/pharmacodynamic Cohort (Part 1C and Part 2C, Japan only)

In order to evaluate safety, tolerability, PK/pharmacodynamic and preliminary anti-cancer activity of GSK3359609 (feladilimab) monotherapy or GSK3359609 (feladilimab)

+ pembrolizumab in Japanese participants with selected advanced solid tumors, the Part C (Japan PK/pharmacodynamic Cohort) was added in a country specific amendment. Briefly, a total of up to 20 Japanese participants in each cohort will be enrolled with at least 3 participants at each dose level based on the mTPI design rule (Section 4.1.1.2.1). Based on the mTPI design rule, a lower dose level of 0.1 mg/kg may be added, and additional participants may be added to further evaluate PK/pharmacodynamic and safety of GSK3359609 (feladilimab) as a monotherapy or combination with pembrolizumab at the optimized dose range in the main study (0.3mg/kg ~ 3.0mg/kg). All study related information such as study design, study assessments and data analyses are described in the Japan country specific protocol amendment 5.

Participants enrolled in Part 1C will not be tolerated for transition to GSK3359609 (feladilimab) and pembrolizumab combination therapy. Japan can also participate in any other enrolling cohorts for Part 2A and Part 2B after completing the evaluation of the GSK3359609 (feladilimab) dose/dose level under investigation in Part 2A and Part 2B as a monotherapy (Part 1C) and/or in combination with pembrolizumab (Part 2C).

Table 1 Part 1A Maximum Dose Levels

Dose Level	GSK3359609 (feladilimab) (mg/kg)	Dose Selection Design
1	0.001	Accelerated Titration
2	0.003	Accelerated Titration
3	0.01	Accelerated Titration
4	0.03	mTPI
5	0.1	mTPI
6	0.3	mTPI
7	1.0	mTPI
8	3.0	mTPI
9	10.0	mTPI

4.1.1.2.1. Modified Toxicity Probability Interval

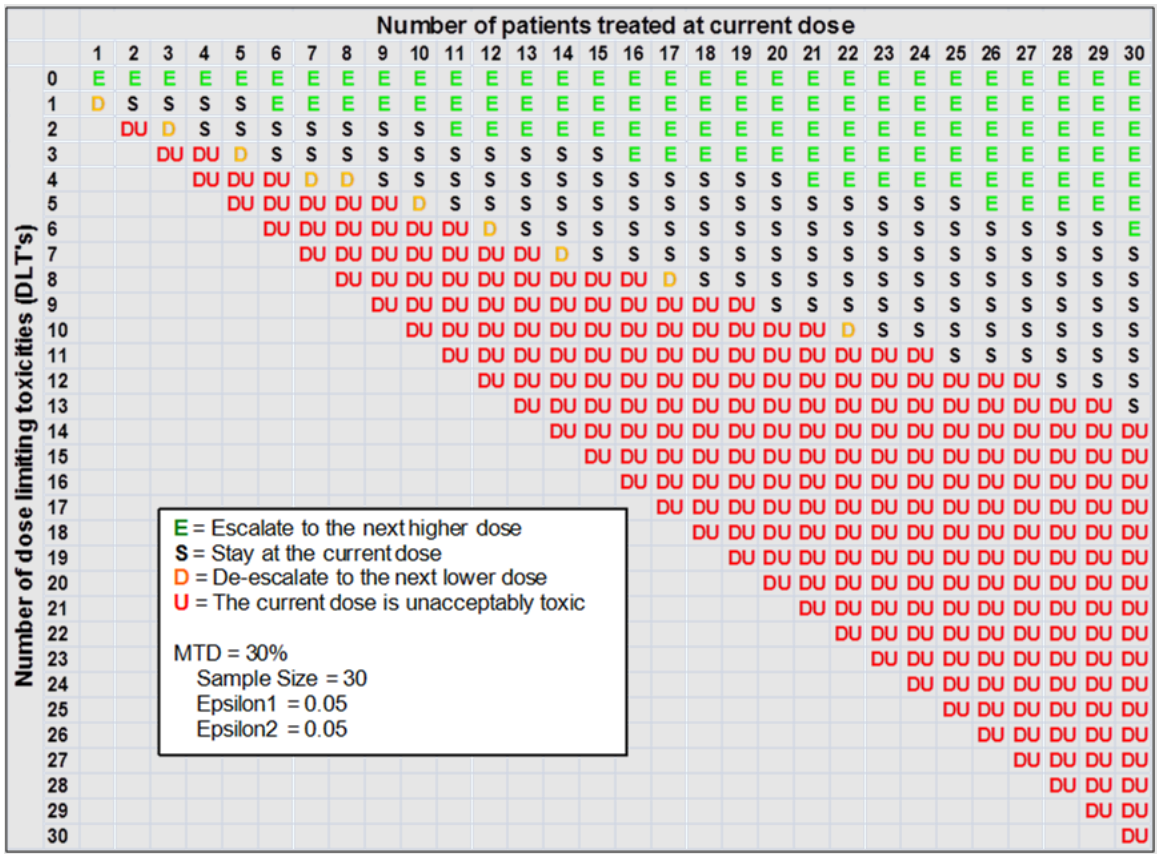
The mTPI design assumptions include the following:

(i) A maximum of 30 participants will complete the DLT evaluation period at any given dose;
(ii) The true underlying toxicity rate for GSK3359609 (feladilimab) falls within the range from 25% to 35% and centers at 30%.

The monitoring rules guiding dose escalation are provided in Figure 3. Columns provide the numbers of participants treated at a dose level, and rows provide the corresponding numbers of participants experiencing DLT. The entries in the table are dose-finding decisions (i.e., E, S, and D) representing escalating the dose, staying at the same dose, and de-escalating the dose, respectively. In addition, decision U indicates that the current dose level is unacceptable because of high toxicity and should be excluded from further investigation in the study. As an example, if one of three participants experience a DLT, the decision is located in row 1 and column 3, which indicates S, that is to stay at the current dose level. Consequently, an additional three participants will be treated at the

same dose level currently being investigated. If none of these three participants experience DLT, the decision is at row 1 and column 6, which is E, that is to escalate to the next dose level. Thus, the next cohort of participants will be treated at the next-higher dose level. If at this dose level three of three participants experience DLTs, the decision is DU, that is to dose de-escalate to the preceding lower dose level and subsequently exclude the current dose from the study because of unacceptable toxicity.

Figure 3 Modified TPI Dose Decision Rules



As presented in Figure 3, the dose-finding decisions using the mTPI method were generated based on a beta/binomial model and pre-calculated before study initiation. The letters in different colors are computed based on the decision rules under the mTPI method and represent different dose-finding actions. In addition to actions that include de-escalate the dose (D), stay at the same dose (S), and escalate the dose (E), the table includes action unacceptable toxicity (U), which is defined as the execution of the dose-exclusion rule in mTPI.

4.1.1.3. Part 2A Combination Therapy Dose Escalation/Safety Run-in

4.1.1.3.1. GSK3359609 (feladilimab) Combination with Pembrolizumab

Dose escalation for GSK3359609 (feladilimab) plus

- pembrolizumab combination therapy will begin with a fixed dose of 200 mg pembrolizumab administered intravenously Q3W

A starting dose level of GSK3359609 (feladilimab) in combination with pembrolizumab will be two dose levels below the Part 1A monotherapy dose that was deemed safe and had demonstrated pharmacodynamic activity. Dose decision rules will follow the mTPI method with Figure 3 depicting the dose-finding actions escalation decisions based on DLT observed within a cohort. Safety, tolerability, PK, pharmacodynamic measures, and antitumor activity will be considered in determining recommended phase 2 dose (RP2D) of GSK3359609 (feladilimab) in combination. If the combination doses in the starting dose cohort of Part 2A are not tolerable, lower doses of GSK3359609 (feladilimab) may be evaluated.

4.1.1.3.2. GSK3359609 (feladilimab) Combination with Chemotherapy (± pembrolizumab)

The dose of GSK3359609 (feladilimab) in each chemotherapy combination will be 24 mg based upon current evidence of activity in other cohorts at 0.3 mg/kg and comparability of exposure at 24 mg. The passage below describes the initial dose escalation design:

GSK3359609 (feladilimab) in combination with docetaxel or platinum-based chemotherapy doublets (± 200 mg pembrolizumab) consist of safety run-in cohorts only (refer to Figure 1). The mTPI design will guide dose escalation/de-escalation decisions to support determining the GSK3359609 (feladilimab) RP2 dose in combination with standard doses of chemotherapy (refer to Section 4.1.1.2.1 for mTPI details). An initial three participants will receive 80 mg of GSK3359609 (feladilimab) in combination with chemotherapy; if no DLTs are observed (refer to Section 4.1.1.4), an additional 6 to 9 participants may receive this dose or de-escalate/escalate to a lower/higher dose in combination with chemotherapy (± pembrolizumab).

A minimum of nine participants will receive GSK3359609 (feladilimab) at the dose recommended in combination with each chemotherapy regimen (± pembrolizumab). Safety, tolerability, PK, pharmacodynamic measures, and antitumor activity will be considered in determining RP2D of GSK3359609 (feladilimab) for each chemotherapy combination.

4.1.1.3.3. GSK3359609 (feladilimab) Combination with GSK3174998 (Anti-OX40)

GSK3174998 (anti-OX40)

As presented in Table 2, dose escalation will initiate with 8 mg of GSK3359609 (feladilimab) in combination with 8 mg of GSK3174998 with one participant enrolled in this combination dose cohort (Dose Cohort 1). This single participant will be evaluated for DLT. If the first participant becomes unevaluable for DLT due to reasons other than toxicity, another participant will be enrolled Cohort 1. If the single participant in Dose

Cohort 1 experiences a DLT or treatment-related ≥ Grade 2 AE during the 28-day DLT observation period, then additional participants will enroll in Dose Cohort 1 and the two-dimensional continual reassessment method (2D-CRM) will guide dose escalation decisions [Neuenschwander, 2014].

Starting with Dose Cohort 2 (if no occurrence of DLTs or ≥,Grade 2 treatment-related AEs) at least three participants will be enrolled and the two-dimensional continual reassessment method (2D-CRM) [Neuenschwander, 2014] will guide dose escalation decisions according to dose combinations presented in Table 2.

In the first dose level fully accrued under the 2D-CRM design and in all subsequent dose levels, treatment will be administered at least 3 days apart between the first two participants enrolled; the third and any subsequent participants will be administered treatment at a minimum of one day apart (Refer to Section 4.1.1.1 for rationale of the staggered approach). Evaluation of the available safety data over the first 28 days of treatment for each participant enrolled in that dose level is required from at least 3 participants before a decision is made to enroll additional participants at the next higher dose level. The maximum number of participants assigned to any single dose level will be at the discretion of the Sponsor in consultation with the investigators.

Additional dose combinations (doses that have been evaluated as monotherapies; refer to GSK3359609 (feladilimab) IB [GlaxoSmithKline Document Number RPS-CLIN-015202, 2021] and GSK3174998 IB [GlaxoSmithKline Document Number 2014N212091_06, 2020]) and schedules may be explored based on emerging data (i.e., safety, PK, and PD).

Table 2 Planned Dose Escalation Levels for GSK3359609 (feladilimab) and GSK3174998

Dose Combination Level Cohort	GSK3359609 (feladilimab) (mg)	GSk3174998 (mg)	Dose Escalation Design
1	8	8	Run-in: if no occurrence of a DLT or drug-related ≥ Grade 2 AE in the DLT observation period
			Run-in and implement 2D-CRM: if occurrence of a DLT or drug-related ≥ Grade 2 AE in the DLT observation period
2	8	24	2D-CRM
3	24	24	2D-CRM
4	80	24	2D-CRM
5	80	80	2D-CRM

If the starting dose combination level of GSK3359609 (feladilimab) in combination of GSK3174998 is not tolerable, lower doses of GSK3359609 (feladilimab) and/or GSK3174998 may be evaluated.

Safety, tolerability, PK, pharmacodynamic measures, and antitumor activity will be considered in determining RP2D of GSK3359609 (feladilimab) in combination with GSK3174998. A minimum of 10 additional participants may be enrolled at RP2D to further explore GSK3359609 (feladilimab) in combination with GSK3174998; in these participants, tumor biopsy at Screening will be required (refer to Table 28 for further details). Initially 4 participants will be enrolled to obtain further safety information; if no DLTs arise that prohibit further enrollment at the RP2D, an additional 6 participants will be enrolled at the RP2D.

Description of the Two-Dimensional Continual Reassessment Method

For each cohort under the 2D-CRM design, a dosing recommendation to the next dose level will be made using the 2D-CRM method. The 2D-CRM design makes use of a 5-parameter Bayesian logistic regression model relating dose and dose limiting toxicity. The model is expected to locate the MTD efficiently while minimizing the number of participants exposed to pharmacologically inactive or unsafe dose combination levels. Further details on the model are provided in Section 10.2.2.

All available data, including safety, PK and PD data from current and prior cohorts will be reviewed at the dose escalation meeting. Although the 2D-CRM will be used to recommend the next dosing level, clinical judgment by the Medical Monitor, internal dose-escalation committee and in consultation with the investigators can halt dose escalation or reduce the recommended dose of each agent in the combination as deemed appropriate at any time during the trial.

The MTD will be defined as that dose combination that has the highest posterior probability of having a DLT rate within the Target Toxicity range and for which the posterior probability that the DLT rate lies within the Excessive Toxicity or the Unacceptable Toxicity range is less than 25%.

The 2D-CRM estimates for each potential dose combination and the posterior probabilities that the DLT rate lies in each of four toxicity ranges are provided below:

- A dose falls in the **Underdosing** range if the probability of a DLT at the dose is [0%, 16%)
- A dose falls in the **Target** Toxicity range if the probability of a DLT at the dose is [16%, 33%)
- A dose falls in the **Excessive** Toxicity range if the probability of a DLT at the dose is [33%, 60%)
- A dose falls in the **Unacceptable** Toxicity range if the probability of a DLT at the dose is [60%, 100%]

At the time of each dose-escalation decision, the dose combination with the highest posterior probability of lying in the Target Toxicity range will be the model-recommended dose combination level for the next cohort. Additionally, the following constraints for the recommended dose combination level will be maintained:

- The posterior probability of the DLT rate lying in the Excessive Toxicity or Unacceptable Toxicity range is less than 25%.
- The recommended dose is no more than 3.4 times that of the previous dose.

Note that de-escalation as well as escalation is possible using this method.

An updated posterior estimate of the dose-toxicity curve will also be provided at the time of the dose-escalation meeting.

Dose escalation will continue until:

i. An MTD is found:

   At least 9 participants (only applicable to combination treatment with GSK3174998) have been treated at the current target dose combination

   AND

   The posterior probability that the DLT rate for the current dose combination lies in either the excessive toxicity or unacceptable toxicity range is less than 25%

   AND

   The posterior probability that the DLT rate for the next higher dose lies in either the excessive toxicity or unacceptable toxicity range is greater than or equal to 25%.

OR

ii. All dose combination levels are cleared: The MAD has been reached and at least 9 participants (only applicable to combination treatment with GSK3174998) have been dosed at that dose combination level.

OR

iii. No dose combination level is cleared (i.e. all doses have a posterior probability of lying in either the excessive toxicity or unacceptable toxicity range of greater than or equal to 25%)

   AND

   At least two DLTs have been observed.

Bayesian Prior

The 2D-CRM methodology requires that a Bayesian prior distribution for the dose-toxicity curve be pre-specified. A bivariate normal distribution for the prior of each pair of single-agent parameters $(ln(\alpha), ln(\beta))^T$ and a normal distribution for the prior of the interaction log-odds multiplier η are assumed. Table 3 shows the parameters of prior distributions with reference dose levels $d_1^* = 80$ mg for GSK3359609 (feladilimab), and $d_2^* = 24$ mg (GSK3174998). The prior and reference dose levels may be updated based on the emerging data in which case details will be documented in the reporting and analysis plan (RAP).

Table 3 Parameters of Prior Distributions

Treatment/Term	Parameter	Mean	Standard Deviation	Correlation
GSK3359609 (feladilimab)	$ln(\alpha_1), ln(\beta_1)$	-3.5, -1	5, 1	0
GSK3174998	$ln(\alpha_2), ln(\beta_2)$	-3, -1	5, 1	0
Interaction	η	0	1.121	N/A

The DLT information based on available monotherapy data from GSK3359609 (feladilimab) in study 204691 and GSK3174998 in study 202102 are incorporated into the DLT prior distribution calculation. Table 4 shows the DLT profile r/n at each dose combination for GSK3174998, where r is the number of DLTs and n is the number of participants of a given dose combination; these table present possible dose combinations based on the monotherapy doses evaluated for each single agent however it does not imply that all dose combinations will be studied.

Table 4 Prior Monotherapy DLT Profile for GSK3359609 (feladilimab) and GSK3174998

		GSK3359609 (feladilimab) Dose Level (mg)								
		0	**0.08**	**0.24**	**0.8**	**2.4**	**8**	**24**	**80**	**240**
GSK3174998 Dose Level (mg)	**800**	0/4								
	240	0/7								
	80	0/4								
	24	0/10								
	8	0/10								
	2.4	0/8								
	0.8	0/1								
	0.24	0/1								
	0		0/1	0/1	0/2	0/8	0/15	0/17	0/24	1/11

* No a priori (i.e. 0/0) in shaded area.

4.1.1.4. Dose Limiting Toxicity

The severity of all toxicities will be graded using National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 4.0) [NCI, 2010]. The DLT observation period is 28 days in length and begins on the day GSK3359609 (feladilimab) is first administrated to the participant.

A DLT is defined as an AE that meets at least one of the criteria listed in Table 5 and is considered by the investigator to be clinically relevant and attributed (probably, or possibly) to the study treatment during the 28-day DLT observation period. An AE considered related to the underlying disease under study it is not defined as a DLT.

For Part 2 pembrolizumab combination, Grade 3 or Grade 4 toxicities that are known to occur with pembrolizumab therapy and are controlled within two weeks using the recommended supportive measures (refer to Section 7) may not be considered dose-

limiting (refer to Table 5 for DLT definitions). These known toxicities will be evaluated during dose escalation decisions to assess for parameters that include increases in frequency or severity.

Table 5 Dose-Limiting Toxicity Criteria

Toxicity	DLT Definition
Hematologic	• Febrile neutropenia as defined by CTCAE v4 • Grade 4 neutropenia of >7 days in duration or requiring G-CSF • Grade 4 anemia of any duration • Grade 4 thrombocytopenia of any duration or Grade 3 thrombocytopenia with bleeding
Non-hematologic	• Grade 4 toxicity • Grade 3 pneumonitis of any duration • 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 • Following events are not considered DLTs o Grade 3 and Grade 4 asymptomatic electrolyte abnormalities that are corrected within 24 hours without clinical sequelae o Grade 3 nausea, vomiting, or fatigue that resolves to ≤Grade 1 within 7 days with optimal supportive care o Grade 3 and Grade 4 infusion reactions in participants not receiving prophylaxis for IRRs (refer to Section 7.12.3 for details on IRR management)
Other	• Toxicity that results in permanent discontinuation of GSK3359609 (feladilimab) monotherapy or GSK3359609 (feladilimab) and agent in combination during the first four weeks of treatment • Grade 3/Grade 4 toxicity that results in a participant not receiving the expected doses of a regimen in Cycle 1, defined by 21 days • Any other toxicity considered to be dose-limiting that occurs beyond four weeks will be considered in the selection of the dose to recommend for expansion cohorts • Any other event which in the judgment of the investigator and GSK Medical Monitor is considered to be a DLT

a. Abbreviations: CTCAE=Common Toxicity Criteria for Adverse Events; DLT = Dose-limiting toxicity; G-CSF =Granulocyte colony-stimulating factor; GSK =GlaxoSmithKline; IRR=infusion related reaction

b. Suggested toxicity management guidelines as described in Section 7 may include systemic corticosteroids for immune-related toxicities; if systemic corticosteroids use delays administration of the second dose of study treatment 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 provided the toxicity did not meet study treatment discontinuation criteria and following approval by the Sponsor.

Toxicity management and dose modification guidelines provided in sub-Sections of Section 7 are directed for those AEs of special interest that, although not observed in nonclinical studies, may be expected with the administration of immune directed therapies such as GSK3359609 (feladilimab). Additionally, Table 13 provides general guidance for the management of non-hematologic AEs.

Guidance for the identification, evaluation, and the established algorithms for the treatment management of immune-related adverse events (irAEs) including dose modification algorithms are provided in Section 7.1 and Section 7.2. These guidelines are based on the experience of irAE management following the development of immune check-point inhibitors such pembrolizumab. Guidelines are also provided for hepatotoxicity (Section 7.4); gastrointestinal events (Section 7.5); renal toxicity (Section 7.6); skin toxicity (Section 7.7); endocrine events (Section 7.8); pneumonitis (Section 7.9); hematologic events (Section 7.10); uveitis/iritis (Section 7.11), and infusion reactions or severe cytokine release (Section 7.12).

If there is a delay in administration of study treatment, refer to Section 7.18 for guidance on planning of subsequent study visits.

4.1.1.5. Intra-Participant Dose Escalation

For Part 1A, Part 2A, and expansion phases (i.e., PK/pharmacodynamic Cohort), intra-participant dose escalations may be considered on a case-by-case basis provided the participant has completed at least one treatment cycle without the occurrence of drug-related ≥Grade 2 AE or SAEs of any severity Grade in the first 28 days of treatment. For the expansion phases in which Week 6 on-treatment biopsy was mandatory, approval for intra-participant escalation also requires acquisition of this biopsy. Approval for intra-participant dose escalations requires the approval of the GSK Medical Monitor. Additionally, all participants at the next higher dose level/levels must have completed the DLT observation period with MTD not reached. Participants may dose-escalate to the highest cleared dose. Individual participants may dose-escalate multiple times provided that the above criteria are met at each intra-participant dose escalation step. Cumulative safety data from these participants will be included in the overall determination of MTD and RP2D.

Additional safety assessments or PK sampling may be specified at the time of dose escalation or schedule modification based on the safety profile in previous participants at the higher dose level. Intra-participant dose escalations or schedule modification will be discussed with investigators and approved by the GSK Medical Monitor and safety monitoring required will be specified in writing.

4.1.1.6. Determination of RP2D

A GSK3359609 (feladilimab) RP2D/doses will be determined from Part 1A and Part 2A combination with 200 mg pembrolizumab and may be further refined in Part 1B and Part 2B; the RP2 doses of GSK3359609 (feladilimab) and GSK3174998 in combination will be determined from Part 2A. Dose escalation in Part 1A GSK3359609 (feladilimab) monotherapy is expected to be completed when approximately 22 participants are enrolled and complete the DLT observation period. For Part 2A combination studies the

target enrolment varies for each cohort, depending upon the number of dose levels being tested. For the cohorts with pembrolizumab and GSK3174998, enrolment is expected to be completed when approximately 36 and 35 participants, respectively, are enrolled in the dose determination stage have completed the DLT evaluation period. In both dose escalation phases of study, the RP2D may be the MTD, the MAD, or a lower dose that provides adequate PK properties and clinical activity with acceptable tolerability. The identification of MTD may not occur if a RP2D is established prior to reaching the MTD. More than one dose of GSK3359609 (feladilimab) may be recommended for further exploration in Part 1B and Part 2B or other studies. A final determination of RP2D(s) will consider the mTPI suggested dose level(s) (Part 1A/Part 2A pembrolizumab combination) and the 2D-CRM suggested dose level(s) (Part 2A GSK3359609 (feladilimab) in combination with GSK3174998); available data from expansion cohorts, a clinically active dose (e.g., tumor response), the safety profile, and available PK and pharmacodynamic data generated from all enrolled participants.

A GSK3359609 (feladilimab) RP2D in combination with standard doses of chemotherapy (± pembrolizumab) will be determined using mTPI for dose decision in Part 2A only.

Alternate schedules or dose levels may be explored if data emerge supporting their investigation even after a RP2D is defined. Moreover, GSK3359609 (feladilimab) fixed doses may be investigated in the expansion phases of Part 1 and Part 2 and will be used in Part 2 combinations with chemotherapy (± pembrolizumab) and GSK3174998.

4.1.2. Dose Expansion Phase

Any dose level(s)/doses in the dose escalation phases (Part1A and Part 2A) may be selected for expansion in Part 1B and Part 2B of the study in order to collect additional data on safety, PK, pharmacodynamic activity, and preliminary clinical activity.

Each expansion cohort will include participants defined by a single tumor type as indicated in Figure 1 or characterized by other features such as prior treatment with an immune checkpoint inhibitor, a molecular/genetic alteration (MSI-H/dMMR), or pathology. Participants enrolled in Part 1B and Part 2B, may be stratified by prior PD-1/L1 treatment history (i.e., naïve or experienced; best response). The details of these subgroups will be presented in the reporting and analysis plan (RAP).

In addition, participants enrolled to the Part 2B (GSK3359609 (feladilimab)/pembrolizumab combination) NSCLC cohort may be grouped by PD-L1 expression status (Tumor Proportion Score [TPS] ≥50% versus TPS <1-49%) as determined by IHC thus approximately 40 participants were allocated to this cohort to ensure sufficient representation of PD-L1 expression categories reported in a case series of 2222 patients [Herbst, 2016]; enrollment to this cohort may require further enrichment of participants based on PD-L1 status. Participants enrolled in Part 2B HNSCC may be grouped by PD-L1 expression status, by other features such as HPV status and prior treatment history. In the Part 2B HNSCC Randomization Cohort and Part 2B HNSCC Every 6 Week (Q6W) Cohort, participants will be randomly assigned to one dose level of GSK3359609 (feladilimab) in combination with either pembrolizumab 200 mg (Table 6)

or pembrolizumab 400 mg (Table 7), respectively. The Part 2B HNSCC cohort may target approximately 20 participants per dose level. Based on the interim analysis, a dose level in the randomized cohort(s) may be dropped and the randomization ratio may be changed.

Table 6 GSK3359609 (feladilimab) Dose Levels for HNSCC Randomization Cohort

Randomization Cohort	GSK3359609 (feladilimab) (mg/kg)	Pembrolizumab (mg)
1	0.1 Q3W	200 Q3W
2	1.0 Q3W	200 Q3W
3	3.0 Q3W	200 Q3W

Table 7 GSK3359609 (feladilimab) Dose for HNSCC Every 6 Week (Q6W) Schedule Cohort

Randomization Cohort	GSK3359609 (feladilimab) (mg)	Pembrolizumab (mg)
1	48 Q6W	400 Q6W
2	160 Q6W	400 Q6W

Other Part 2B cohorts may also group participants by PD-L1 IHC status using an expression scoring system and interpretation of score according to the 22C3 pharmDx package insert. Participants enrolled in Part 2B will also be grouped by prior PD-1/L1 treatment history (i.e., naïve or experienced) or other features that emerge as relevant to evaluation of study treatment activity. A minimum of 10 participants per subgroup will be required to be enrolled, receive treatment and be evaluable for response for the interim analysis.

GSK3359609 (feladilimab) as a monotherapy or in combination with pembrolizumab may be evaluated in biomarker defined cohorts in which participants may be selected based on ICOS expression on specific T cell populations or by some other biomarker; approximately 20 participants initially may be enrolled in each of those cohorts. In both Part 1B and Part 2B, the selection of indications will be evidence based either in part on data generated in Part 1A and Part 2A, respectively, as well as emerging nonclinical data or external clinical data. Appropriate adaptive randomization and futility rules may be incorporated in the expansion phase to optimize the dose allocation based on evaluations of safety and antitumor activities; an alternative GSK3359609 (feladilimab) schedule or drug sequencing approach may be investigated in the expansion phase. If any expansion cohort would support a single arm strategy, the expansion cohort could be further

increased in size to enable a pivotal study which would be the participant of a protocol amendment.

As indicated in Section 11.7, the Steering Committee will review the totality of data available for Study 204691 to inform on the dose level indications for any of the expansion cohorts. Criteria that may be considered in the determination of which dose level(s) to expand and which tumor types to select for cohort expansion may include:

- Safety and Tolerability parameters such as frequency of DLT, AEs of special interest (AESI), and the extent of dose modifications for either GSK3359609 (feladilimab) or pembrolizumab.
- Target engagement and/or pharmacodynamic activity measures CCI [redacted]
- Clinical activity parameters such as tumor response (i.e., complete response [CR], partial response [PR]) and stable disease (SD) with duration of 18 weeks allowing for a one-week window per Table 27.

After approximately10 participants at any dose level have been enrolled in a given monotherapy expansion cohort with available unconfirmed overall response data, an analysis for futility may be conducted using a Bayesian model approach (refer to Section 10.3). Based on the output from the model, the Steering Committee may recommend continued accrual to that expansion cohort or to the other expansion cohorts, or termination of accrual to any or all the cohorts. The Steering Committee could also recommend exploration of a different dose level on the basis of emerging data. The interim analysis based on the initial 10 participants may trigger an increase in sample size to approximately 30 participants for defined population that may be enriched by dose or another characteristic. These futility rules serve as guidance for further expansion; with expansion decisions informed by all available clinical data.

For any of the expansion cohorts tested, if observed clinical benefit appears to be associated with specific disease characteristics and/or biomarkers, a new cohort may be opened for further investigation with participants enriched with these specific characteristics and/or biomarkers.

The selection of dose level(s)/doses and tumor types/characteristics selected for cohort expansion will be communicated to the sites in writing.

4.1.2.1. PK/Pharmacodynamic Dose Expansion Cohorts

Any dose level or levels may be expanded beyond the expected 3 participants enrolled in dose escalation phase in order to collect additional data on safety, PK, pharmacodynamic activity, and preliminary efficacy. Participants can only be enrolled at previously cleared dose levels. Participants enrolled in PK/pharmacodynamic cohorts may have the dose escalated to a higher cleared dose level (i.e., not exceeding the MTD) once the necessary PK/pharmacodynamic procedures have been completed. Model-based designs may be employed for each PK/pharmacodynamic dose expansion cohort in order to sufficiently explore parameters critical (i.e., safety, tolerability, and efficacy) in establishing the

biologically optimal GSK 3359609 monotherapy dose and the biologically optimal doses of the two agents in combination.

4.2. Study Treatment and Duration

The study is comprised of two primary parts, each composed of two phases:

1. Part 1: GSK3359609 (feladilimab) monotherapy
    a. Part 1A: dose escalation
    b. Part 1B: dose expansion

2. Part 2: GSK3359609 (feladilimab) combination therapy
    a. Part 2A: dose escalation/safety run-in
    b. Part 2B: dose expansion

Each part and phase of the study includes a screening period, a treatment period, and a follow-up period. For participants who meet all eligibility criteria and register into the study, the maximum duration of treatment with GSK3359609 (feladilimab) is expected to be approximately two years, up to 35 cycles; in those participants who receive combination therapy Q3W, the maximum duration of treatment with GSK3359609 (feladilimab) in combination with pembrolizumab (± chemotherapy) or GSK3174998 is expected to be two years, up to 35 cycles. The maximum treatment duration for participants enrolled in HNSCC Q6W dosing cohort is expected to be approximately 2 years, up to 18 cycles for both GSK3359609 (feladilimab) and pembrolizumab. The duration of chemotherapy treatment will be according to institutional practice but should be a minimum of 4 cycles (cycle=21 days); the maximum duration of GSK3359609 (feladilimab) and pembrolizumab treatment is expected to be two years; thus, if the course of chemotherapy treatment is completed after a minimum of four cycles or discontinued prior to completion of a minimum of 4 cycles, GSK3359609 (feladilimab) and pembrolizumab treatment may continue. The maximum duration of other agents in combination with GSK3359609 (feladilimab) will be up to 35 cycles, in which 1 cycle is defined as 21 days, or approximately 2 years. The maximum follow-up period for safety assessments will be 90 days from the date of the last dose of study treatment. The expected maximum follow-up period for survival and subsequent anti-cancer therapy will be two years from the date of the last dose of study treatment. Participants who discontinue study treatment due to achieving confirmed CR (refer to Section 5.4 for additional requirements) will be followed for progression (refer to Section 5.4 for details on the frequency of these assessments).

Participants participating in Part 1A or Part 1B will receive GSK3359609 (feladilimab) as an IV infusion administered once every three weeks at a dose level dependent on to which dose level the participant is accrued (Part 1A) or what dose level(s) was chosen for further exploration in dose expansion cohorts (Part 1B).

Participants participating in Part 2A (pembrolizumab or GSK3174998 combination will receive GSK3359609 (feladilimab) as an IV infusion administered once every three weeks (refer to Table 1 and Table 2) in combination with 200 mg of pembrolizumab as

an IV infusion administered once Q3W for part 2A1 or with GSK3174998 as an IV infusion administered once every three weeks at doses ranging from 8 mg to 80 mg (refer to Table 2) for Part 2A2. The dose/doses of GSK3359609 (feladilimab) in Part 2B (pembrolizumab combination) will be defined based on the review of the outcome measures for Part 1A and Part 2A.

Participants participating in Part 2A3 chemotherapy combination cohorts will receive GSK3359609 (feladilimab) 24 mg or 80 mg dose (refer to Table 8 for fixed doses) in combination with chemotherapy at doses and schedules based on standard of care practice (refer to Table 12); pembrolizumab 200 mg dose will be administered as an IV infusion administered once Q3W.

4.3. Study Population

The number of dose levels and the level at which the MTD or MAD is reached in Part 1A and Part 2A cannot be predetermined. An adequate number of participants will be enrolled into the study to establish the recommended dose(s) for further investigation. Overall it is estimated that a total of approximately 867 participants may be enrolled in this two-part study (approximately 166 participants in Parts 1A and 2A [dose escalation/safety run-in],approximately 40 participants in the Part 1C and Part 2C PK/pharmacodynamic cohorts (Japan only) in a Japan country specific amendment and 20 participants in the Part1D PK/pharmacodynamic cohort (China only) in a China country specific amendment; approximately 641 participants in Parts 1B and 2B [cohort expansion]). The study population in Part 1A/Part 1B and Part 2A (dose escalation and GSK3359609 (feladilimab) plus chemotherapy safety cohorts) will be adults with advanced/recurrent solid tumor malignancies, who either:

- have disease that has progressed on prior systemic therapy
- are not candidates for standard of care therapy, or
- have disease for which no further standard of care therapy exists.

In the Part 2A GSK3359609 (feladilimab)/pembrolizumab plus chemotherapy safety cohorts and Part 2B combination with pembrolizumab the expansion cohort populations may be comprised of participants with advanced/recurrent solid tumors who have not received treatment for advanced disease.

In Part 1A and Part 2A, if at any dose level a participant prematurely discontinues study treatment before the completion of the 28-day DLT observation period for reasons other than a DLT, a replacement participant may be enrolled and assigned to the same dose level if <3 participants complete the DLT observation period at that dose level.

In those Part 1A dose levels that have a single participant enrolled, a replacement participant will be enrolled if <1 participant prematurely discontinues study treatment before the completion of the 28-day DLT period.

Participants will not be replaced in Parts 1B and 2B of the study.

4.4. Design Justification

In the GSK3359609 (feladilimab) monotherapy and combination dose escalation phases of the study, safety, tolerability, pharmacology, and preliminary efficacy will be evaluated utilizing designs that account for the starting dose level, greater precision around the true toxicity rate, and for Part 2A, the agents under investigation as combination therapy.

Part 1A includes an accelerated titration design planned for the first three dose levels in order to minimize the number of participants enrolled at sub-optimal doses followed by the mTPI approach, a well-validated method to identify the MTD/RP2D of a given agent.

Part 2A combinations of GSK3359609 (feladilimab) and pembrolizumab, or chemotherapy (± pembrolizumab) will employ the mTPI method where the dose of GSK3359609 (feladilimab) may be adjusted based on the DLT rate observed or by emerging evidence supporting a selected dose while in combination with a standard of care dose of pembrolizumab fixed at 200 mg and standard of care doses of chemotherapies (refer to Table 12). The Part 2A combination of GSK3359609 (feladilimab) and GSK3174998 will employ a run-in design for the starting combination dose level (Dose Cohort 1) as the 2 lowest doses of both agents were selected based on the findings from a cytokine release assay (refer to Section 2.3.3.2.2 for details). The use of the 2D-CRM design for combination with GSK3174998 provides estimations of the target probability of dose-limiting toxicity at the recommended combination doses for phase II trials without treating too many participants at suboptimal doses.

The solid tumor types selected for dose escalation include bladder/urothelial carcinoma, carcinoma of HN, cervical carcinoma, CRC, esophageal carcinoma of squamous histology, prostate carcinoma, melanoma, MPM and NSCLC. The selection of these solid tumors was based on evidence of prior response to immune checkpoint therapies [Swaika, 2015; Zamarin, 2015] and/or 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; Goodman, 2017; Hellmann, 2018].

The dose expansion phases of the study may commence while dose escalation phases are ongoing. GSK3359609 (feladilimab) dose levels cleared for safety (refer to Section 4.1.1.1) may be investigated as expansion cohorts defined by specific solid tumor histology or perhaps by a specific characteristic, agnostic of tumor type, such as prior response to immunotherapy, biomarker phenotype that is evidenced-based (i.e., optimal immune features such as tumor mutation burden, and/or ICOS expression), or other features such as mismatch repair deficiencies which is suggestive of a greater likelihood to respond to anti-ICOS agonist monotherapy or as combination therapy with pembrolizumab [Le, 2017]. An alternate dosing schedule of GSK3359609 (feladilimab) Q6W will be explored in combination with pembrolizumab 400 mg Q6W in participants with HNSCC to evaluate safety, pharmacodynamic, PK and preliminary clinical activity (refer to Section 4.5.5).

The inclusion of GSK3359609 (feladilimab) combinations with pembrolizumab, GSK3174998, and chemotherapy (± pembrolizumab) in the FTIH study setting is based on the rationale that targeting more than one axis in the cancer immunity cycle or targeting immunosuppressive mechanisms may result in improved, sustained efficacy

which potentially may be identified early in development. Although GSK3359609 (feladilimab) is expected to have meaningful clinical activity as a monotherapy, the full potential of the molecule in certain indications is likely to be discovered in combination with other agents, particularly other immune checkpoint modulators.

Clinical evidence from immune checkpoint modulators indicates the emergence of objective responses to these agents that activate antitumor immune responses may follow delayed kinetics of weeks or months [Wolchok, 2009]. The potential delay in tumor regression can be preceded by an initial apparent progression with the appearance of new lesions or increase in some lesions while certain lesions are regressing thereby producing an overall "mixed response". While overall disease assessment of disease status will be in accordance with RECIST v1.1 and irRECIST, the decision to discontinue treatment due to disease progression will be based upon irRECIST to account for the unique biological mechanisms of immunotherapies.

4.5. Dose Justification

4.5.1. Part 1A: GSK3359609 (feladilimab) (ICOS) Monotherapy Dose Rationale

The minimally anticipated biologic effect level (MABEL) approach was used as the basis for the 0.001 mg/kg starting dose of GSK3359609 (feladilimab) monotherapy in the dose escalation phase of the study. The basis of the approach is in consideration of the International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) S9 guidance on selection of starting dose for a biopharmaceutical with immune agonistic properties. The projected human GSK3359609 (feladilimab) exposure predicted by cynomolgus monkey PK and GSK3359609 (feladilimab) pharmacology factored into the selection of the starting dose implemented in study 204691.

The PK of GSK3359609 (feladilimab) was assessed in two cynomolgus monkey studies, with single and repeat doses ranging from 0.3 mg/kg to 100 mg/kg; GSK3359609 (feladilimab) exposure was approximately dose-proportional (refer to Section 2.3.2). Across the dose levels tested, PK profiles did not demonstrate any evidence of target-mediated disposition. These results suggest that allometric methods are appropriate to predict human PK; furthermore, human PK of GSK3359609 (feladilimab) is expected to be similar to the PK of mAbs of the same isotype (IgG4). Allometric scaling predicted a Cmax value of 0.028 μg/mL at 0.001 mg/kg.

The MABEL assessment was based on measures of CCI [redacted] and functional effects (such as cytokine production and activation/ proliferation of T cell populations) as characterized by in vitro binding experiments using ex vivo CD3/CD28 stimulated primary human peripheral blood mononuclear cells from healthy donors. The use of RO as a surrogate for biological activity was deemed appropriate as RO provides a general characterization of GSK3359609 (feladilimab) signaling in target cells and since individual biological effects of GSK3359609 (feladilimab) are not yet prioritized in terms of their impact on participant safety. The functional effect of GSK3359609 (feladilimab) was also characterized in several experiments yielding different activity coefficients depending on cell type, co-stimulation status, and cytokines analyzed.

A RO of 10% or binding effective concentration (EC)10 based on predicted Cmax was evaluated to guide selection of the starting dose. The binding EC10 (μg/mL) of GSK3359609 (feladilimab) in CD4+ T cells ranged from 0.059 – 0.666 with a median value of 0.154; in CD8+ T cells the binding EC10 ranged from 0.055 - 0.842 with a median value of 0.144. The calculated starting dose based on the median EC10 values projected a starting dose of 0.005 mg/kg. Of note, RO calculations assumed that the difference between GSK3359609 (feladilimab) bound to protein and free GSK3359609 (feladilimab) is negligible (RO = Cmax/ (EC50 + Cmax)). This approach will yield higher RO and as such more conservative dose estimates than the approach which assumes a specific level of target expression. In addition, using activated T cells, as was applied in the binding experiments summarized above, would produce a greater response than without T cell activation, in which case ICOS receptors are detectable in a small percentage of T cells (<5%).

An EC10 threshold for the functional assays was also evaluated to guide starting dose selection. In the cytokine release immunoassay, TNFα was the most sensitive of the five cytokines analyzed, the EC10 (μg/mL) values of GSK3359609 (feladilimab) at the 24-hour time-point were 0.006 and 0.028 with a median of 0.017. Percent increase in OX40+CD4+ T cells was the most sensitive measure of T cell activation status as measured by flow cytometry, the EC10 (μg/mL) of GSK3359609 (feladilimab) at the 48-hour time-point ranged from 0.002 to 0.186, with a median value of 0.029. The calculated starting dose based on the median EC10 values from both measures of functional effect projected a starting dose of 0.001 mg/kg; at the starting dose of 0.001 mg/kg, the RO as estimated from the binding assay would be 3%.

The EC50 values of IFNγ as the cytokine purported to be relevant for immune antitumor activity [Ikeda, 2002] were analyzed to project a GSK3359609 (feladilimab) dose that may achieve relevant pharmacology. The projected 0.01 mg/kg dose of GSK3359609 (feladilimab) would result in Cmax concentrations near the EC50 value of IFNγ. A dose of 0.05 mg/kg would result in Cmax concentrations near the EC50 value for binding of activated T cells.

Refer to GSK3359609 (feladilimab) IB [GlaxoSmithKline Document Number RPS-CLIN-015202, 2021] and Section 2.3.4 for further details.

4.5.2. Part 2A: GSK3359609 (feladilimab) (ICOS) Starting Dose in Combination with Pembrolizumab

No drug-drug interaction affecting the PK for the combination of GSK3359609 (feladilimab) and pembrolizumab is expected. As a checkpoint inhibitor, rather than a direct immune-stimulator, pembrolizumab is not expected to substantially increase the potential for excessive cytokine release in response to GSK3359609 (feladilimab), but specific synergies cannot be excluded a priori. The starting dose of GSK3359609 (feladilimab) for Part 2A (combination dose escalation phase) will be two dose levels below a dose that was shown to be tolerated and at which a pharmacodynamic effect was observed during the monotherapy dose escalation.

Refer to GSK3359609 (feladilimab) IB [GlaxoSmithKline Document Number RPS-CLIN-015202, 2021] and Section 2.3.4 for further details.

4.5.3. Part 2A: GSK3359609 (feladilimab) (ICOS) Starting Dose in Combination with Chemotherapy ±Pembrolizumab

No drug-drug interaction affecting the PK profiles is expected for the combinations of GSK3359609 (feladilimab) and docetaxel or carboplatin/cisplatin-based chemotherapies; including when GSK3359609 (feladilimab) and chemotherapies are in combination with pembrolizumab. The safety profiles of the defined chemotherapies are well established and expected to be unique to the potential immune-mediated toxicities identified as risks for GSK3359609 (feladilimab) (refer to Section 4.6.2) and known for pembrolizumab (refer to the pembrolizumab IB [Merck Sharp & Dohme Corp, Pembrolizumab IB, 2021]) except for infusion related reactions which can occur with specific chemotherapies. Refer to infusion related reaction management guidelines in Section 7.12.3.

The starting dose of GSK3359609 (feladilimab) in the chemotherapy safety run-in cohorts will be 80 mg, as the dose level equivalent of 1mg/kg is one of the dose levels under investigation in the PK/PD cohorts and a dose level to be investigated in other expansion cohorts. The fixed dose of GSK3359609 (feladilimab) is expected to provide similar and adequate control of exposure variability compared to body-weight based dosing (refer to Section 4.5.6 for details on fixed dose justification).

4.5.4. Part 2A: GSK3359609 (feladilimab) (ICOS) Starting Doses in Combination with GSK3174998 (OX40)

Based on the preliminary data from this FTIH study, 204691, no dose-limiting toxicities were observed in the dose escalation cohorts over the range of GSK3359609 (feladilimab) dose levels (0.001 mg/kg [~0.08 mg] to 3 mg/kg [~240 mg]) evaluated in advanced cancer participants receiving GSK3359609 (feladilimab) as a monotherapy; one participant in the PK/pharmacodynamic cohort receivingGSK3359609 (feladilimab) at 3 mg/kg experienced liver function test elevations that were considered DLTs. Additionally, there were no cases of cytokine release syndrome reported. Refer to GSK3359609 (feladilimab) IB for further details on the preliminary safety and PK results reported from the 204691 study [GlaxoSmithKline Document Number RPS-CLIN-015202, 2021].

The lower starting dose of 8 mg (~0.1 mg/kg) is 1/30 of the top dose of GSK3359609 (feladilimab) that was evaluated and was chosen based on the findings from the CRA that showed under specific experimental conditions increases in IFNγ or TNFα responses (refer to Section 2.3.3.2.2 for further details). The GSK3359609 (feladilimab) doses of 24mg and 80mg were selected based on the preliminary ICOS CCI [redacted] pharmacodynamic analysis in the periphery which showed high CCI [redacted] levels on CD4 and CD8 T cells over the 21-day dosing cycle starting at 0.3 m/kg (~24 mg); close to total receptor saturation was observed at 1mg/kg (~80 mg) dose level.

4.5.5. GSK3359609 (feladilimab) Dosing Frequency

Guided by GSK3359609 (feladilimab) pharmacodynamic activity and the expectation of standard IgG4 mAb PK terminal elimination half-life longer than 2 weeks, a dosing frequency of Q3W was initially selected for GSK3359609 (feladilimab), which is consistent with the population PK estimated median disposition half-life of ~3 weeks. Also, this dosing frequency schedule increases participant convenience for administration with planned combination partners also dosed Q3W (e.g. pembrolizumab).

Since select partner agents may be dosed less frequently than every three weeks, alternative extended dosing schedules would provide additional convenience and flexibility to participants and clinicians beyond a Q3W option. Hence, a six-weekly (Q6W) dosing schedule for GSK3359609 (feladilimab) will be explored, specifically in randomized schedule optimization cohorts for participants with PD-1/L1 Naive HNSCC. Two doses for initial Q6W schedule exploration, 48 and 160 mg, are selected to provide matching cumulative exposures corresponding to respective Q3W regimens in the Q3W HNSCC dose-randomized cohorts (0.3 and 1 mg/kg). Preliminary PK simulations suggest a doubling of dose and interval for GSK3359609 (feladilimab) (e.g. 0.3 mg/kg Q3W to 48 mg Q6W) is expected to provide similar cumulative AUC with an approximate doubling of end-of-infusion Cmax and marginally lower end-of-cycle trough concentrations (~43% at steady-state). The typical Cmax for 160 mg Q6W will be maintained below thresholds established with the Q3W regimens.

4.5.6. GSK3359609 (feladilimab) Fixed Dose Rationale

In Part 1A (monotherapy) and Part 2A (combination with pembrolizumab) GSK3359609 (feladilimab) was administered on body weight-based dosing. Fixed doses may be tested in the expansion cohorts, in the safety run-in phase with chemotherapy combinations, assuming a typical median weight of 80 kg.

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 in the simulations were based on the observed distribution 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 (feladilimab) exposures higher than these increases have been evaluated in the current Phase 1 study 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 Cmax 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, shorten preparation time, and improve ease of administration. Thus, switching to a fixed dose based on a reference body weight of 80 kg is reasonable and appropriate.

The fixed dose equivalents of the weight-based GSK3359609 (feladilimab) dose levels using 80 kg weight are presented in Table 8.

Table 8 GSK3359609 (feladilimab) Fixed Dose Calculations

Dose Level	GSK3359609 (feladilimab) mg/kg	GSK3359609 (feladilimab) mg
1	0.001	0.08
2	0.003	0.24
3	0.01	0.8
4	0,03	2.4
5	0.1	8.0
6	0.3	24.0
7	0.6	48.0
8	1.0	80.0
9	2.0	160.0
10	3.0	240.0

4.5.7. Part 2: Pembrolizumab Dose Rationale

The dose of pembrolizumab planned is 200 mg Q3W. The dose recently approved in the United States and several other countries for treatment of melanoma participants is 2 mg/kg Q3W. The rationale for selecting 200 mg Q3W is summarized below.

In KEYNOTE-001, an open-label Phase I study conducted to evaluate the safety, tolerability, PK and pharmacodynamics, and anti-tumor activity of pembrolizumab when administered as monotherapy. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg and 10 mg/kg, administered every 2 weeks (Q2W) and dose expansion cohorts evaluated 2 mg/kg Q3W and 10 mg/kg Q3W in participants with advanced solid tumors. All dose levels were well tolerated and no dose-limiting toxicities were observed. This first-in-human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. No MTD had been identified. In addition, two randomized cohort evaluations of melanoma participants receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed, and one randomized cohort evaluating 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of important differences in efficacy or safety profile across doses [Merck Sharp & Dohme Corp, Pembrolizumab IB, 2021].

An integrated body of evidence suggests that 200 mg Q3W is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety was found in participants with melanoma in the range of doses between 2 mg/kg and 10 mg/kg.

Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with 2 mg/kg Q3W dose.

A population PK model, which characterized the influence of body weight and other participant covariates on exposure, has been developed. The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. The distribution of exposures from the 200-mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose and importantly will maintain individual participant exposures within the exposure range established in melanoma as associated with maximal clinical response. PK properties of pembrolizumab, and specifically the weight-dependency in clearance and volume of distribution are consistent with the conclusion there is no meaningful advantage to weight-based dosing relative to fixed dosing [Merck Sharp & Dohme Corp, Pembrolizumab IB, 2021].

In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in participants with melanoma can be expected, as the anti-tumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in participants with melanoma, NSCLC, and other tumor types support a lack of meaningful difference in PK exposures obtained from the doses tested among the various tumor types. Thus the 200 mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other tumor indications.

Moreover, a fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. The existing data suggest 200 mg Q3W as the appropriate dose for pembrolizumab.

For the 2B HNSCC dose optimization cohort, the planned dose of pembrolizumab is 400 mg every 6 weeks (Q6W). A 400 mg Q6W dosing regimen of pembrolizumab is expected to have a similar benefit-risk profile as 200 mg Q3W, in all treatment setting in which 200 mg Q3W pembrolizumab is currently approved [Lala, 2018; Geiger, 2019]. Specifically, the dosing regimen of 400 mg Q6W for pembrolizumab is considered adequate based on modelling and simulation (M&S) analyses, given the following rationale:

- The proposed schedule is intended solely for an investigational study
- Pharmacokinetic (PK) simulation demonstrating that in terms of pembrolizumab exposures-
    - Average concentration over the dosing interval (C_{avg}) (or area under the curve [AUC]) at 400 mg Q6W is similar to that at the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.
    - Trough concentrations (Ctau) at 400 mg Q6W are generally within the range of those achieved with 2 mg/kg or 200 mg Q3W in the majority (>99%) of participants.

- Peak concentrations (C_{max}) at 400 mg Q6W are well below the C_{max} for the highest clinically tested dose of 10 mg/kg Q2W, supporting that the safety profile for 400 mg Q6W should be comparable to the established safety profile of pembrolizumab.

- Exposure-response (E-R) for pembrolizumab has been demonstrated to be flat across indications, and OS predictions in melanoma and NSCLC demonstrate that efficacy at 400 mg Q6W is expected to be similar to that at 200 mg or 2 mg/kg Q3W, given the similar exposures; thus 400 mg Q6W is expected to be efficacious across indications.

4.5.8. Part 2: Chemotherapy Dose Rationale

Docetaxel is a semisynthetic taxane approved in different tumor indications. The dosage of docetaxel as a single-agent and in combination for several tumor indications, including NSCLC and HNSCC, is 75mg/m^2, every three weeks; thus, this dose and schedule was selected in combination with GSK3359609 (feladilimab).

The carboplatin chemotherapy doublets will calculate the dose of carboplatin according to Calvert formula using the target AUC of 4-6 mg/ml per min as per local standard of care in combination with:

1. Pemetrexed at 500 mg/m^2
2. Gemcitabine at 1250 mg/m^2
3. Paclitaxel at 200 mg/m^2

The doses selected in combination are according to Category 1 recommendations in National Comprehensive Cancer Network treatment guidelines.

Carboplatin (AUC 5) or cisplatin at 100 mg/m^2 (per GSK assignment) will be combined with 5-FU at 1000 mg/m^2 (Refer to Table 12 further details). The doses selected were in accordance with standard doses given for first-line treatment of recurrent or metastatic HNSCC [Vermorken, 2008].

4.5.9. Part 2: GSK3174998 (OX40) Dose Rationale

In the GSK3174998 FTIH study, 201212, no DLTs or cases of CRS were observed over the GSK3174998 dose range evaluated (0.003 mg/kg [~0.24 mg] to 10 mg/kg [~800 mg]) in participants with advanced cancer. The OX40 CCI [redacted] pharmacodynamic analysis in the periphery showed high CCI [redacted] levels on T cells over the 21-day dosing cycle starting with the 0.3 m/kg (~24 mg) dose of GSK3174998 [GlaxoSmithKline Document Number 2014N212091_06, 2020].

The lower starting dose of 8 mg (~0.1 mg/kg) is 1/100 of the top dose of GSK3174998 evaluated and was chosen based on the findings from the CRA that showed, under specific experimental conditions, increases in IFNγ or TNFα responses (refer to Section 2.3.3.2.2 for further details). Nevertheless, the potential for CRS is expected to be low based on the ICOS and OX40 co-stimulatory receptor biology. Based on the totality of data, including CCI [redacted], clinical activity, and safety, doses of 8 mg, 24 mg

and 80 mg GSK3174998 were selected for testing in the combination with GSK3359609 (feladilimab).

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK3359609 (feladilimab) [GlaxoSmithKline Document Number RPS-CLIN-015202, 2021], pembrolizumab [Merck Sharp & Dohme Corp, Pembrolizumab IB, 2021], and GSK3174998 [GlaxoSmithKline Document Number 2014N212091_06, 2020] can be found in the respective IBs. Refer to the chemotherapy approved product labels for information on contraindications, warnings and precautions.

The following sub sections outline the risk assessment and mitigation strategy for GSK3359609 (feladilimab) in this protocol.

This is an open-label, first time in human study of this agent to be conducted in participants with select advanced solid tumors that are relapsed/refractory to standard therapies. GSK3359609 (feladilimab) has preclinical activity; preliminary clinical activity has been reported with GSK3359609 (feladilimab) as a monotherapy in metastatic melanoma and in HNSCC as well as GSK3359609 (feladilimab) in combination with pembrolizumab in HNSCC (refer to Section 2.3.5.1 and Section 2.3.5.2.1). Furthermore, there is evidence of durable tumor response or a prolongation of tumor control rate relative to historic expectations in urothelial cancer, NSCLC, and cervical cancer. However, Study 204691 is non-randomized; moreover, it is unknown whether GSK3359609 (feladilimab) will have clinical activity as a monotherapy or in combination with pembrolizumab, GSK3174998, or chemotherapy across the other tumor types under investigation. Thus, any potential beneficial effect for an individual participant attributable to GSK3359609 (feladilimab) as a monotherapy or as part of combination therapy is possible using the basis of the preliminary clinical activity observed in Study 204691. For other tumor types there is insufficient experience to come to any conclusions. Furthermore, MTD was not reached and the dose ranges proposed in the combination studies are documented to result in meaningful CCI that correlates with durable clinical responses in several tumor types. Data obtained in this study may help identify individuals more likely to benefit or have side-effects from GSK3359609 (feladilimab). Study participants may benefit from the medical tests and screening performed during the study.

The doses or dose ranges selected for the other compounds used in the combinations are all associated with tumor responses in several types of advanced solid malignancies as documented in the respective product package insert or Investigator's Brochure.

Finally, preliminary experience to date with pembrolizumab and conventional chemotherapy combinations shows no added toxicity by adding GSK3359609 (feladilimab) to any of these agents. The observed toxicities are those previously documented with the respective agent qualitatively and quantitatively.

4.6.1. Risk Assessment

The following sub sections outline the risk assessment and mitigation strategy for this protocol. Refer to the individual chemotherapy agent's approved product label for the information on contraindications, warnings, and precautions.

Table 9 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-stimulatory mechanism of action of these agents.	• Participants with the following medical history are ineligible for this study o Toxicity (Grade 3) related to prior immunotherapy leading to study treatment discontinuation o Active autoimmune disease (refer to Section 5.2 exclusion criterion 8) o Severe hypersensitivity to another mAb • Established management algorithms for irAEs • Refer to Section 7 for further details on the identification, evaluation, and management of toxicities with a potential immune etiology.
Infusion and hypersensitivity reactions and potential severe Cytokine Release Syndrome (CRS)	• Risk for infusion reactions and hypersensitivity is inherent to many mAbs [Brennan, 2010] • The overall rate of IRRs with ICOS is low and there have been no cases of CRS observed across the clinical program of GSK3359609 (feladilimab) [GlaxoSmithKline Document RPS-CLIN-015202, 2021].	• 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 7.12.3 for further details on management of infusion reactions and details on CRS management.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Immune complex disease	• Immune complex formation and deposition findings in nonclinical safety studies (refer to Section 2.3.3.1 and the GSK3359609 (feladilimab) IB)	• 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

4.6.2. Overall Benefit:Risk Conclusion

Current data from GSK3359609 (feladilimab) preclinical studies indicate a potential for anti-tumor activity through effects resulting from stimulation of ICOS. Current preliminary clinical data using GSK3359609 (feladilimab) as monotherapy or in combination demonstrate benefit in several advanced solid tumor malignancies. Considering the measures taken to minimize risks to participants participating in the Phase I clinical trial, the potential risks identified in association with GSK3359609 (feladilimab) as a monotherapy or combination therapy are justified by the anticipated benefits that may be afforded to participants with relapsed/refractory solid tumors. In particular, in the setting of previously treated metastatic melanoma.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

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

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

5.1. Inclusion Criteria

For a participant to be eligible for inclusion in this study all the following criteria must be fulfilled:

1. Capable of giving signed, written informed consent
2. Male or female, age ≥18 years (at the time consent is obtained).

3. 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:

    - Bladder/urothelial cancer of the upper and lower urinary tract
    - Cervical
    - Colorectal (includes appendix)
    - Esophagus, squamous cell
    - Head and Neck Carcinoma
    - Melanoma/Cutaneous Melanoma (non-uveal) required in Part 1B Melanoma Biomarker Cohort
    - MPM
    - NSCLC
    - Prostate
    - MSI-H/dMMR tumor (Part 1B and Part 2B)
    - HPV-positive or EBV-positive tumor (Part 1B and Part 2B)

Note:
In Part 2A chemotherapy safety cohort for 5-FU/platinum combination with GSK3359609 (feladilimab) and pembrolizumab, only participants with HNSCC that was diagnosed as recurrent or metastatic and considered incurable by local therapies, are eligible.

4. 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; exceptions are in these tumor types in which pembrolizumab single agent may be a standard: NSCLC, HN squamous cell cancer (HNSCC), bladder/urothelial cancer, MSI-H/dMMR cancers, melanoma and cervical cancer (refer to the country-specific pembrolizumab/anti-PD-1/L1 package inserts for the indications). In these Part 2B pembrolizumab combination expansion cohorts, prior treatment with anti-PD-1/L1 may not be required.

    - Participants must not have received more than 5 prior lines of therapy for advanced disease including both standards of care and investigational therapies.
        - Participants in the biomarker cohort are required to have received prior anti-PD-1/L1 and anti-CTLA-4 therapy (either concurrently or sequentially)
        - Participants with BRAF mutation positive melanoma are required to have received prior BRAF targeted therapy; as well as prior anti-PD-1/L1 and anti-CTLA-4 therapy (either concurrently or sequentially)
    - Participants who received prior anti-PD-1/L1 therapy must fulfill the following requirements (Part 1B [except PK/PD cohort)/ Part 2B):
        - Have achieved a CR, PR or SD and subsequently had disease progression while still on PD 1/L1 therapy
        - Have received at least 2 doses of an approved PD-1/L1 inhibitor (by any regulatory authority)

    - Have demonstrated disease progression as defined by RECIST v1.1 within 18 weeks from the last dose of the PD-1/L1 inhibitor. The initial evidence of disease progression is to be confirmed by a second assessment no less than four weeks from the date of the first documented PD (the confirmatory scan could be the baseline eligibility scan for this study)
- In Part 2A 5-FU/platinum combination with GSK3359609 (feladilimab) and pembrolizumab cohort, participants must not have received prior systemic therapy administered in the recurrent or metastatic setting (with the exception of systemic therapy given as part of multimodal treatment for locally advanced disease).

5. Archival tumor tissue obtained at any time from the initial diagnosis to study entry; a fresh tumor biopsy using a procedure that is safe for the participant on a lesion not previously irradiated unless lesion progressed will be required if archival tissue is unavailable (refer to Table 28).
6. Agree to undergo a pre-treatment and on-treatment biopsy and have disease amenable to biopsy required in PK/pharmacodynamic Cohort (Part 1B), dose randomized HNSCC, HNSCC CPS<1, Melanoma dose expansion cohorts, Biomarker cohort, and PK/PD phase of Part 2A combination cohorts.
7. Measurable disease per RECIST version 1.1 (refer to Appendix 6). 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) 0-1 (refer to Appendix 7).
9. Life expectancy of at least 12 weeks.
10. Adequate organ function as defined in Table 10:

Table 10 Definitions for Adequate Organ Function

System[a]	Laboratory Values
Hematologic[b]	
ANC	≥1.5x10^9/L
Hemoglobin	≥9 g/dL
Platelets	≥100x10^9/L
Hepatic	
Total bilirubin *For participants with Gilbert's Syndrome (only if direct bilirubin ≤35%)*	≤1.5xULN *≤3.0xULN*
ALT	≤2.5xULN; or ≤5xULN for participants with documented liver metastases
Renal	
Calculated CrCl[c]	≥30 mL/min
Cardiac	
Ejection fraction	≥ 50% by echocardiogram[d]

Abbreviations: ANC = Absolute neutrophil count; ALT = alanine aminotransferase; CrCl = creatinine clearance; TSH = thyroid-stimulating hormone; ULN = upper limit of normal; WNL = within normal limits

a. Participant eligibility for the GSK3359609 (feladilimab) chemotherapy combinations requires laboratory values fulfilling the warnings/precautions requirements indicated in the approved product label (i.e., CrCl requirements for cisplatin)
b. Absolute Lymphocyte Count will be included in the baseline assessment, but no range limit requirement for the eligibility.
c. Estimated CrCl should be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (refer to Appendix 10)
d. Multigated acquisition scan (MUGA) is acceptable if ECHO is not available (refer to Section 8.4.7)

11. QT duration corrected for heart rate by Fridericia's formula (QTcF) <450 milliseconds (msec) or QTcF <480 msec for participants with bundle branch block.

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

12. A female participant is eligible to participate if she is not pregnant (as confirmed by a negative serum beta-human chorionic gonadotrophin [β-hCG] test in females of reproductive potential) and not lactating, or at least one of the following conditions applies:

    - Non-reproductive potential defined as:
      - Pre-menopausal females with one of the following:
        - Documented tubal ligation
        - Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
        - Hysterectomy

- Documented Bilateral Oophorectomy
- Postmenopausal defined as 12 months of spontaneous amenorrhea. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.

a. Reproductive potential and agrees to follow one of the options listed in Appendix 3 from 30 days prior to the first dose of study medication and until 120 days after the last dose of study treatment.

13. Male participants with female partners of child bearing potential must agree to use one of the methods of contraception specified in Appendix 3 from time of first dose of study treatment until 120 days after the last dose of study treatment.
14. In France, a participant will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.
15. Documented Human Papilloma Virus (HPV)/ Epstein-Barr (EBV)-positive tumor as determined by a local laboratory for Part 1B and Part 2B pembrolizumab combination viral-positive expansion cohorts only
16. Documented MSI-H or dMMR-positive tumor as determined by local laboratory for Part 1B and Part 2B pembrolizumab combination MSI-H/dMMR expansion cohorts only.
17. ICOS expression result using an analytically validated IHC assay by central laboratory for Part 1B Biomarker Cohort only. Participants may be required to have a defined ICOS expression score for eligibility; refer to Section 8.2 for details.
18. Gene expression (GEX) result using an analytically validated method by central laboratory may also be required for Part 1B Biomarker Cohort only. Participants may be required to have a defined GEX result for eligibility; refer to Section 8.2 for details.
19. PD-L1 CPS <1 using the FDA approved PD-L1 IHC 22C3 pharmDx assay by central laboratory testing for Part 2B HNSCC PD-L1 CPS <1 Cohort. Documented test result of CPS<1 from FDA approved PD-L1 IHC 22C3 pharmDx assay in local laboratory, if available, may be accepted in lieu of the central laboratory test result.

5.2. Exclusion Criteria

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

1. Prior treatment with the following therapies:
    - Anticancer therapy within 30 days or 5 half-lives of the drug, whichever is shorter. At least 14 days must have elapsed between the last dose of prior anticancer agent and the first dose of study drug is administered.

- Part 2B (GSK3359609 (feladilimab)/pembrolizumab combination): prior pembrolizumab washout is not required

- Prior radiation therapy: permissible if at least one non-irradiated measurable lesion is available for assessment according to RECIST version 1.1 or if a solitary measurable lesion was irradiated, objective progression is documented. A wash out of at least two weeks before start of study drug for radiation of any intended use to the extremities for bone metastases and 4 weeks for radiation to the chest, brain, or visceral organs is required.
  - Radiation therapy to the lung that is >30 Gy requires a greater than 6 month washout from first dose of study treatment.
- Investigational therapy within 30 days or 5 half-lives of the investigational product (whichever is shorter). At least 14 days must have elapsed between the last dose of investigational agent and the first dose of study drug is administered.

2. Prior allogeneic tissue or other solid organ transplantation.
3. Toxicity from previous anticancer treatment that includes:
   - ≥Grade 3 toxicity considered related to prior immunotherapy and that led to treatment discontinuation.
   - Toxicity related to prior treatment that has not resolved to ≤Grade 1 (except alopecia, endocrinopathy managed with replacement therapy, and peripheral neuropathy which must be ≤Grade 2).
4. Invasive malignancy or history of invasive malignancy other than disease under study within the last two years, except as noted below:
   - Any other invasive malignancy for which the participant was definitively treated, has been disease-free for ≤2 years and in the opinion of the principal investigator and GSK Medical Monitor will not affect the evaluation of the effects of the study treatment on the currently targeted malignancy, may be included in this clinical trial.
   - Curatively treated non-melanoma skin cancer
5. Central nervous system (CNS) metastases, with the following exception:
   - Participants who have previously-treated CNS metastases, are asymptomatic, and have no requirement for steroids at least 14 days prior to first dose of study drug.

   Note: Participants with carcinomatous meningitis or leptomeningeal spread are excluded regardless of clinical stability.
6. Received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor, recombinant erythropoietin) within 14 days prior to the first dose of GSK3359609 (feladilimab).

7. Major surgery ≤4 weeks before the first dose of study treatment. Participants must have also fully recovered from any surgery (major or minor) and/or its complications before initiating study treatment.
8. Active autoimmune disease (refer to Appendix 2) that has required systemic treatment within the last two years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs).

a. Note: Replacement therapy (e.g., thyroxine or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

9. Concurrent medical condition requiring the use of systemic immunosuppressive medications within 7 days before the first dose of study treatment. Physiologic doses of corticosteroids for treatment of endocrinopathies or steroids with minimal systemic absorption, including topical, inhaled, or intranasal corticosteroids may be continued if the participant is on a stable dose.
10. Condition requiring treatment with strong inhibitors/inducers of cytochrome p450 (CYP) 3A4 within 7 days prior to first dose of chemotherapy (Note: requirement applies to participants enrolled to Part 2 chemotherapy combination with docetaxel)
11. Active infection requiring systemic therapy, known human immunodeficiency virus infection, or positive test for hepatitis B active infection or hepatitis C active infection (refer to Table 27 for details).
12. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver metastases, or otherwise stable chronic liver disease per investigator assessment).

    NOTE: Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis.

13. Recent history (within the past 6 months) of acute diverticulitis, inflammatory bowel disease, intra-abdominal abscess, or gastrointestinal obstruction that required surgery
14. Receipt of any live vaccine within 4 weeks prior to first dose of study treatment.
15. Recent history of allergen desensitization therapy within 4 weeks of starting study treatment.
16. History of severe hypersensitivity to monoclonal antibodies or to the chemotherapies under investigation including any ingredient used in the formulation.
17. History or evidence of cardiac abnormalities including any of the following:

    - Recent (within the past 6 months) history of serious uncontrolled cardiac arrhythmia or clinically significant electrocardiogram abnormalities including second degree (Type II) or third degree atrioventricular block.
    - Cardiomyopathy, myocardial infarction, acute coronary syndromes (including unstable angina pectoris), coronary angioplasty, stenting, or bypass grafting within the past 6 months before enrollment.

- Congestive heart failure (Class II, III, or IV) as defined by the New York Heart Association functional classification system (Refer to Appendix 5).
- Recent (within the past 6 months) history of symptomatic pericarditis.

18. History (current and past) of idiopathic pulmonary fibrosis, pneumonitis (for past pneumonitis exclusion only if steroids were required for treatment), interstitial lung disease, or organizing pneumonia. Note: post-radiation changes in the lung related to prior radiotherapy and/or asymptomatic radiation-induced pneumonitis not requiring treatment may be permitted if agreed by the investigator and Medical Monitor.
19. Recent history (within 6 months) of uncontrolled symptomatic ascites or pleural effusions.
20. Any serious and/or unstable pre-existing medical, psychiatric disorder, or other condition that could interfere with the participant's safety, obtaining informed consent, or compliance to the study procedures.
21. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial, unless prospective IRB approval (by chair or designee) is given allowing exception to this criterion for a specific participant.

5.3. Screening/Baseline/Run-in Failures

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

5.4. Withdrawal/Stopping Criteria

Participants will receive study treatment for the scheduled time period, if applicable, unless one of the following events occurs earlier: disease progression (as determined by irRECIST), death, or unacceptable toxicity, including meeting stopping criteria for liver chemistry (refer to Section 5.4.1), or other criteria are met as defined in Section 5.4.2 and in Section 7, and all subsections. Participants with infusion delays >21 days due to toxicity should consider discontinuing study drug(s) unless the treating investigator and Sponsor/Medical Monitor agree there is strong evidence supporting continued treatment.

Participants enrolled in Part 2 combination with pembrolizumab or GSK3174998 who require permanent discontinuation of one of the study agents in a given treatment combination due to toxicity must permanently discontinue both agents in that combination, unless continued treatment with the remaining agent is agreed upon by the treating investigator and Sponsor/Medical Monitor. Participants enrolled in Part 2 combination with chemotherapy who require permanent discontinuation of chemotherapy should continue treatment with GSK3359609 (feladilimab) and/or pembrolizumab unless toxicity ensues or otherwise indicated in Section 7 and associated subsections; if

GSK3359609 (feladilimab) and/or pembrolizumab is required to be permanently discontinued, then chemotherapy will be discontinued.

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

a. Deviation(s) from the protocol
b. Request of the participant or proxy
c. Discretion of the investigator
d. Participant is lost to follow-up
e. Closure or termination of the study

The primary reason for discontinuation must be recorded in the participant's medical records and electronic case report form (eCRF).

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

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

The assessments required at the treatment discontinuation visit (TDV) must be completed within 30 days of the decision to permanently discontinue study drug(s) and prior to the start of subsequent anti-cancer therapy.

All participants who discontinue from study treatment (early or permanent) for any reason will have safety assessments at the time of discontinuation and during post study treatment follow-up as specified in Time and Events Tables (refer to Section 8.1).

Participants with a CR or PR require confirmation of response via imaging at least 4 weeks after the first imaging showed a CR or PR.

Early discontinuation of GSK3359609 (feladilimab) and/or pembrolizumab or chemotherapy (early discontinuation of study treatment will not per se constitute permanent discontinuation) was considered for participants who have attained a confirmed complete response per RECIST 1.1 and who received study treatment for at least 24 weeks and had at least two treatments beyond the date when the initial CR was declared; these participants will undergo disease assessments at a frequency of 12 weeks (refer to Table 27 for details). These participants were permitted to resume study treatment upon disease progression; this retreatment was defined as a Second Course. In addition, participants with RECISTv1.1 confirmed SD, PR, or CR who complete the 35 cycles of study treatment and study treatment is discontinued for this reason and not for other reasons such as disease progression or intolerability will undergo disease assessments at a frequency of 12 weeks (refer to Table 27); these participants were able to receive a second course of study treatment upon disease progression. For those participants to be eligible for a second course of study treatment, all following requirements were met:

- Experienced an investigator-determined radiographic disease progression by RECIST 1.1 after discontinuing the initial course of study treatment
- No subsequent/ new anticancer treatment was administered after the last dose of study treatment
- Fulfilled all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria
- Study 204691 is ongoing

If study treatment was restarted, participants were required to resume assessments outlined in Table 27; in addition, limited PK and immunogenicity sampling is required.

Participants receiving GSK3359609 (feladilimab) monotherapy administered Q3W (Part 1) were allowed to crossover to receive GSK3359609 (feladilimab) in combination with pembrolizumab Q3W provided the participant has documented objective progression (i.e., radiologic and not clinical deterioration only) and has not experienced any drug-related AEs ≥Grade 3 or SAEs of any Grade; additionally, the GSK medical monitor must be consulted and approve the decision before crossover is permitted.

All participants who permanently discontinue study treatment for any reason will be followed for survival a every 12 weeks until death or until the last participant discontinues treatment and has had their last follow up for safety. 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.).

All participants who permanently discontinue study treatment for reasons other than disease progression or consent withdrawal will be followed for progression or until the start of anti-cancer therapy whichever comes first. Refer to Table 27 for the frequency of assessments.

5.4.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the Food and Drug Administration (FDA) premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

If any of the following criteria are met, all study drugs must be discontinued and hepatotoxicity events must be reported to GSK within 24 hours. Complete liver event eCRF forms and SAE forms if the event also meets the criteria for SAE reporting. The eCRF liver event form does not appear automatically, but must be manually activated.

If treatment is held or discontinued do not restart/rechallenge the participant with study treatment unless all the requirements described in this section have been met, including clearance from the sponsor. Liver chemistry stopping criteria are provided below.

:

Liver Chemistry Stopping Criteria –Liver Stopping Event for the participants with ALT ≤ 2.5 ULN at the baseline value	
ALT-Increase	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[a, b]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[b]	ALT ≥ 3xULN **and** INR>1.5
Cannot Monitor	ALT ≥ 3xULN but <5xULN **and** cannot be monitored weekly for ≥4 weeks
Symptomatic[c]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Abbreviations: ALT= alanine aminotransferase; INR=international normalized ratio; ULN=upper limit of normal

a. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment 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.
b. 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)**; INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants.
c. 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).

Liver Chemistry Stopping Criteria –Liver Stopping Event for Participants with ALT >2.5 or ≤ 5 x ULN at Baseline Value	
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

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, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR 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).

Refer to Section 7.4 for additional guidance on the management of hepatotoxicity.

5.4.1.1. Study Treatment Restart/Rechallenge

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

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

Refer to Appendix 4 for full guidance.

5.4.2. Stopping Rules for Clinical Deterioration

As indicated in Section 4.4, 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 irRECIST 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 treatment.

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 treatment or managed by supportive care (e.g., bisphosphonates and/or bone directed radiotherapy, thoracentesis, or paracentesis for accumulating effusions), study treatment should be discontinued. 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:

- ECOG PS worsening of at least 2 points from baseline
- Skeletal related events defined by the following:
  - pathologic bone fracture in the region of cancer involvement
  - cancer related surgery to bone, and/or
  - spinal cord or nerve root compression
- Development of new CNS metastases
- Any setting where the initiation of new antineoplastic therapy has been deemed beneficial to the participant even in the absence of any such documented clinical event.

5.5. Participant and Study Completion

For Part 1A and Part 2A combinations with pembrolizumab or GSK3174998 the dose escalation phases of the study, participants will be considered as completing the study if they complete screening assessments, receive at least two doses of study treatment or receive one dose but experience a DLT, are observed during the 28 day DLT observation period, and complete the treatment discontinuation visit and the follow-up visit for safety or have died while receiving study treatment or during post-study treatment follow-up period for safety.

For Part 2A combinations with chemotherapy (± pembrolizumab), participants will be considered as completing the study if they complete the screening assessments, receive at least two doses of study treatment or receive one dose but experience a DLT that leads to study treatment discontinuation, are observed during the 28 day DLT observation period, and complete the treatment discontinuation visit and the safety follow-up visit or have died while receiving study treatment or during the post-study treatment safety follow-up period.

For Part 1B and 2B, the expansion phases of the study, participants will be considered as completing the study if they complete screening assessments, receive at least one dose of study treatment, discontinue study treatment for reasons other than lost to follow-up or non-compliance, and complete the study treatment discontinuation visit and safety follow-up visits or have died while receiving study treatment or during post-treatment follow-up period.

In the event the Sponsor decides to close the study, participants receiving ongoing study treatment will be considered as completing the study.

The end of the study is defined as the completion of the last participant's required visits post study treatment discontinuation.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe GSK3359609 (feladilimab) administered as a monotherapy or as combination therapy to participants as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

GSK3359609 (feladilimab) will be administered intravenously to participants at each study site under medical supervision of an investigator or designee. When administered in combination in Part 2 of the study, GSK3359609 (feladilimab) will be administered first. The date and time of administration will be documented in the source documents and reported in the eCRF.

In Part 2, pembrolizumab and GSK3174998 (refer to Table 11) will be administered intravenously to participants starting at least 30 minutes and no more than one hour following the end of the GSK3359609 (feladilimab) infusion under medical supervision

of an investigator or designee. The date and time of administration will be documented in the source documents and reported in the eCRF.

In Part 2 combinations with chemotherapy (refer to Figure 1), chemotherapy regimens will be administered to participants starting at least 30 minutes and no more than one hour following the end of the GSK3359609 (feladilimab) infusion. For the combinations of GSK3359609 (feladilimab) with chemotherapy and pembrolizumab, pembrolizumab will be administered intravenously to participants starting at least 30 minutes and no more than one hour following the end of the GSK3359609 (feladilimab) infusion then chemotherapy will be administered at least 30 minutes to one hour following the end of the pembrolizumab infusion under medical supervision of an investigator or designee. The sequence in which chemotherapy doublets are administered is per standard practice. The date and time of administration will be documented in the source documents and reported in the eCRF. Participants should receive the indicated premedication regimens and supplementation according to the approved product label or standard practice (i.e., corticosteroids, folic acid, vitamin B12, and diphenhydramine). Chemotherapy premedication indicated on the day of dosing should be administered after GSK3359609 (feladilimab) EOI.

All participants are required to remain under observation at the study site for at least 1.5 hours post-infusion of the last study drug administered for the first two study treatment dosing visits. At subsequent study treatment dosing visits, for participants who experience infusion-related reactions, the post-infusion observation time should remain as at least 1.5 hours; for participants who do not experience infusion reactions, these participants should remain under observation at the study site post-study treatment infusion for at least 30 minutes or as per the judgement of the investigator or as per institutional guidelines. Refer to Section 7.12.3 for details on the management of participants experiencing infusion reactions.

For drug administered by an investigator or designee, the dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. The specific time of study treatment administration (e.g., time of the week for first administration; time of the day for each administration) should take into consideration PK sampling time points, study visit procedures, and the post-infusion observation time interval. Infusions may be administered up to 72 hours before or after the planned date of treatment for administrative reasons only (e.g., scheduling an infusion around a holiday).

The study reference manual (SRM) contains details on product administration and specific instructions for the calculation of GSK3359609 (feladilimab) dose, and for the preparation of GSK3359609 (feladilimab) and pembrolizumab and administration of these infusions.

The details on the chemotherapy product characteristics and instructions for preparation and administration are according to the individual package inserts.

Refer to Section 4.2 for information on the duration of study treatment.

Table 11 GSK3359609 (feladilimab) and Combination Study Products Description and Administration

	Study Treatment		
Product Name:	GSK3359609 (feladilimab)	Pembrolizumab	GSK3174998
Product Description	Humanized anti-ICOS IgG4 mAb	Humanized anti-PD-1 IgG4 mAb	Humanized anti-OX40 IgG1 mAb
Dosage form /strength:	10 mg/mL solution	100 mg/4 mL solution/25 mg/mL	Lyophilized powder for reconstitution
Planned dosage level(s):	Refer to Table 1 (0.001 to 3 mg/kg)	200 mg	8 mg, 24 mg, 80 mg
Route of Administration	IV infusion	IV infusion	IV Infusion
Dosing instructions/ Frequency:	Administer diluted product /once Q3W or Q6W (refer to SRM for infusion time)	Administer diluted product /once Q3W or Q6W (refer to SRM for infusion time)	Administer diluted product/once Q3W (refer to SRM for infusion time)
Part of Study	1 and 2	2	2
Manufacturer	GSK	Merck	GSK

Table 12 Chemotherapy Description and Administration

Chemotherapy[1]							
Name	Docetaxel	Carboplatin	Pemetrexed	Paclitaxel	Gemcitabine	Cisplatin	5-FU
Description	Microtubule stabilizer/ small molecule	DNA cross-linker/small molecule	Folate analog/ small molecule	Microtubule stabilizer/ small molecule	Nucleoside analog/ small molecule	DNA cross-linker/small molecule	Nucleoside analog/ small molecule
Dosage form/strength	Refer to package insert	Refer to package insert	Refer to package insert	Refer to package insert	Refer to package insert	Refer to package insert	Refer to package insert
Dosage	75mg/m^2	AUC 4-6 mg/ml per min	500 mg/m^2	200 mg/m^2	1250 mg/m^2	100 mg/m^2	1000 mg/m^2/day
Route of administration	IV infusion	IV infusion	IV infusion	IV infusion	IV infusion	IV infusion	IV infusion
Dosing instructions / frequency	Administer diluted product/ once Q3W	Administer diluted product/once Q3W	Administer diluted product/once Q3W	Administer diluted product/once Q3W	Administer diluted product on Day 1 and Day 8 of every 21-day cycle (Q3W)	Administer diluted product/once Q3W	Administer diluted product continuous on Day 1 through Day 4 of every 21-day cycle (Q3W)

Abbreviations: AUC=area under the curve; FU= Fluorouracil; IV=intravenous; Q3W= every three weeks

1. Chemotherapies will be sourced locally from commercial stock, except in countries where Regulatory Authorities mandate that the sponsor supply all study treatment(s) required for the conduct of a clinical trial.

6.2. Treatment Assignment

Participants enrolled in Part 1 of the study will be assigned to receive GSK3359609 (feladilimab) monotherapy in an open-label fashion; in the Part 1B melanoma cohort, participants will be randomly assigned to a GSK3359609 (feladilimab) dose level of 0.3 mg/kg or 1.0 mg/kg in a 1:1 allocation ratio. Participants enrolled in Part 2 of the study will be assigned to a combination treatment in an open-label fashion and according to the combination treatment cohorts open for accrual. In the Part 2B melanoma cohort, participants will be randomly assigned to a GSK3359609 (feladilimab) dose level of 0.3 mg/kg or 1.0 mg/kg in combination with 200 mg of pembrolizumab in a 1:1 allocation ratio. In the Part 2B HNSCC randomization cohort, participants will be randomly assigned to a GSK3359609 (feladilimab) dose level of 0.1 mg/kg or 1 mg/kg or 3.0 mg/kg in combination with 200 mg of pembrolizumab in a 1:1:1 ratio (refer to Table 6). Other expansion cohorts may investigate more than one dose level of GSK3359609 (feladilimab); if implemented, participants in this cohort will be randomly assigned to the selected dose levels.

6.3. Blinding

This is an open-label study.

6.4. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.5. Preparation/Handling/Storage/Accountability

6.5.1. Preparation

Refer to the SRM for instructions on the preparation of GSK3359609 (feladilimab), pembrolizumab, and GSK3174998. Refer to chemotherapy package inserts for preparation instructions.

6.5.2. Handling

Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor, and/or GSK study contact.

Material Safety Data Sheets (MSDS)/equivalent documents 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.

6.5.3. Storage

All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

Refer to the SRM for storage condition specifications and temperature monitoring requirements.

6.5.4. Accountability

- Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM.

6.6. Compliance with Study Treatment Administration

All study treatments will be intravenously administered to participants at the site. Administration will be documented in the source documents and reported in the eCRF.

6.7. Treatment of Study Treatment Overdose

6.7.1. GSK3359609 (feladilimab) (ICOS) or GSK3174998 (OX40) Overdose

An overdose is defined as administration of a dose that is at least 50% greater than the intended dose. In the event of an overdose the investigator must:

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

An overdose event that is not associated with clinical symptoms or abnormal laboratory results is defined as an event of clinical interest (ECI); refer to Appendix 8 for details on the expedited reporting requirements for ECI.

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 GSK3359609 (feladilimab). In the event of a suspected overdose, it is recommended that the appropriate supportive clinical care be instituted as dictated by the participant's clinical status.

6.7.2. Pembrolizumab Overdose

An overdose of pembrolizumab will be defined as ≥1000 mg (5 times the dose) of pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant must be observed closely for signs of toxicity. Contact the Medical Monitor immediately and closely monitor the participant for AEs/SAEs and laboratory abnormalities. Appropriate supportive treatment should be provided if clinically indicated. An overdose event that is not associated with clinical symptoms or abnormal laboratory results is defined as an ECI; refer to Appendix 8 for details on the expedited reporting requirements for ECI.

6.7.3. Chemotherapy Overdose

Refer to the instructions in the approved product labels in the event of an overdose of docetaxel; carboplatin; pemetrexed; paclitaxel, gemcitabine, cisplatin, or 5-FU. Contact the Medical Monitor immediately and closely monitor the participant for AEs/SAEs.

6.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after permanent discontinuation of study treatment. The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition. Refer to Section 5.4 and Section 8.1 for details on the follow-up assessments required for participants who have permanently discontinued study treatment.

6.9. Concomitant Medications and Non-Drug Therapies

Participants will be instructed to inform the investigator prior to starting any new medications from the time of first dose of study treatment until discontinuation of study treatment. 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 the GSK for clarification.

If future changes are made to the list of permitted/prohibited medications, formal documentation will be provided by GSK and stored in the study file. Any such changes will be communicated to the investigative sites in the form of a letter. Refer to the drug interaction information in the chemotherapy product package inserts for precautions and prohibited concomitant medications.

6.9.1. Permitted Medications and Non-Drug Therapies

Participants enrolled in chemotherapy-containing cohorts (Part 2A) should receive premedication/supplementation regimens according to the approved product label or standard practice. 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, that is, 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 GSK3359609 (feladilimab). 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 treatment, unless clinically indicated for toxicity management and agreed upon by the investigator and the GSK Medical Monitor.
c. Steroids: refer to Section 7 and the associated sub-sections for acceptable use while participant in on study treatment. 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 GSK3359609 (feladilimab); refer to exclusion criterion 9 in Section 5.2 for further requirements. Steroids used for chemotherapy premedication are permitted.

6.9.2. Prohibited Medications and Non-Drug Therapies

The following medications are prohibited before the first dose of study treatment (refer to Section 5.2 for specific time requirements) and while on treatment in this study:

a. Anticancer therapies other than those referred to as Study Treatment 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 6.9.1)
b. Any investigational drug (s) other than those referred to as Study Treatment
c. Live vaccines such as intra-nasal flu vaccine
d. Strong CYP3A4 inhibitors and inducers in participants enrolled in the docetaxel-containing cohorts (use as premedication is permitted)

7. DOSE AND SAFETY MANAGEMENT GUIDELINES

Distinct safety management guidelines, including dose modification algorithms, are provided in this section for participants treated with:

- GSK3359609 (feladilimab)
- Pembrolizumab
- GSK3174998
- Chemotherapies

Please note: In instances where the investigator is directed to permanently discontinue study treatment, the instructions are mandatory as described in Section 5.4.

An overview of general dose modification guidelines for GSK3359609 (feladilimab) and pembrolizumab is presented in Table 13.

All AEs are to be graded according to NCI-CTCAE (version 4.0) [NCI, 2010]. All dose modifications and the reason(s) for the dose modification must be documented in the eCRF.

Table 13 General Dose Modification and Management Guidelines for Drug-related or Immune-Related Non-Hematologic Adverse Events Not Otherwise Specified

Severity	Management	Follow-up
Grade 1	• Continue study drug(s)[a] • Administer symptomatic treatment as appropriate	***Symptoms resolve to baseline within 7 days:*** • Provide close follow-up to evaluate for increased severity ***Symptoms ongoing >7 days*:** • Consider following algorithm for Grade 2 events
Grade 2	• Continue study drug(s)[a] • Administer symptomatic treatment • Investigate etiology • Consider consulting subspecialist, biopsy, and/or diagnostic procedure • Discuss with Sponsor/Medical Monitor	***Symptoms ongoing >7 days or worsening:*** • Consider holding study drug(s)[a] • Consider starting moderate dose systemic corticosteroids (e.g., 0.5 mg/kg/day of prednisone or equivalent) if considered GSK3359609 (feladilimab), pembrolizumab and/or GSK3174998- related ○ Continue steroids until improvement to ≤Grade 1 or resolution; taper steroids as medically appropriate • Resume study drug(s) at the same dose if symptoms have improved to Grade 1 and if applicable steroid dose is 10 mg prednisone/day or less • If symptoms continue or worsen to Grade 3 to Grade 4, see below
Grade 3/Grade 4	• Hold study drug(s)[a] • **Note:** events that require discontinuation of study drug(s)[a] include Guillain-Barre Syndrome, encephalitis • Consult subspecialist • Administer 1-2 mg/kg/day IV methylprednisolone if considered GSK3359609 (feladilimab) pembrolizumab and/or GSK3174998 related • Discuss with Sponsor/Medical Monitor	***Symptoms improve to ≤ Grade 2:*** • Continue steroids until improvement to ≤Grade 1 or baseline; taper steroids over at least 1 month, then if symptoms have improved to ≤Grade 1 within 12 weeks of last dose and steroid dose is ≤10 mg prednisone or equivalent per day within 12 weeks, consider resuming study drug(s) ***Symptoms ongoing:*** • Discuss further management with consultant and Sponsor/Medical Monitor • Consider alternative immunosuppressive therapy

Severity	Management	Follow-up
Grade 4 or recurrent Grade 3	• Permanently discontinue study drug(s)[a] • Consult subspecialists • •Administer 1-2 mg/kg/day IV methylprednisolone • Discuss with Sponsor/Medical Monitor	

a. If >1 study drug is administered per protocol (e.g. GSK3359609 (feladilimab) in combination with pembrolizumab, GSK3174998, or chemotherapy) guidance applies to all study drugs; discuss management on a case-by-case basis with the Sponsor/Medical Monitor. Refer to Section 7.18 for guidance on chemotherapy dose modifications. In cases where treatment with study drug(s) was held for Grade 2 AEs, permanently discontinue study drug(s) if Grade 2 AE does not resolve to ≤Grade 1 within 12 weeks of the last dose.

7.1. General Guidelines for Immune-Related Adverse Events

An irAE is defined as a clinically significant AE of any organ that is associated with study treatment exposure to GSK3359609 (feladilimab) or pembrolizumab is of unknown etiology and is consistent with an immune-related mechanism. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

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

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

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

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

Before administration of study treatment, investigators are to review a participant's AEs, concomitant medications, and clinical evaluation results e.g., vital signs, lab results, ECGs, ECOG PS, physical exam findings, responses, etc. as outlined in the Time and Events Table (Section 8.1, Table 27) to monitor for new or worsening irAEs and ensure continued dosing is appropriate.

AESI are defined as events of potential immunologic etiology. 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.

7.3. General Guidelines for Clinically Significant Toxicities Not Otherwise Specified

While specific guidance is provided for AESI, it is possible that other clinically significant drug-related toxicities that are not specifically described may occur and warrant dose modification.

Investigators must contact the GSK Medical Monitor for all Grade 3 or greater clinically significant non-hematological drug-related toxicities where permanent discontinuation of study treatment may be warranted according to the guidelines provided in Section 7. Otherwise, investigators are encouraged to contact the GSK Medical Monitor as needed to discuss any case that warrants separate discussion outside of the scope of current guidelines.

In the event the toxicity does not resolve to ≤Grade 1 or baseline within 12 weeks after the last infusion, study treatment must be permanently discontinued after consultation with the Sponsor. With investigator and Sponsor agreement, participants with a laboratory AE still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled.

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

7.4. Management of Hepatotoxicity

In the event of treatment-emergent hepatotoxicity, potential contributing factors such as concomitant medications, viral hepatitis and other infectious causes, choledocholithiasis, and hepatic metastases, and myositis should be investigated. Concomitant medications known to be hepatotoxic which may be contributing to liver dysfunction should be discontinued or replaced with alternative medications to allow for recovery of liver function. As generally understood, aspartate aminotransferase (AST) or alanine

aminotransferase (ALT) >3 x upper limit of normal (ULN) and concomitant bilirubin ≥2.0 x ULN (>35% direct bilirubin), in the absence of elevated alkaline phosphatase or biliary injury, suggests significant liver injury and which constitutes an ECI (refer to Appendix 8). Record alcohol use on the liver event alcohol intake form in the eCRF. Liver dysfunction must be fully evaluated even if clinical signs and symptoms indicate progression of liver tumor lesions. Imaging studies must be obtained to document potential progression of malignancy. Guidelines for management of emergent hepatotoxicity are shown in Table 14.

Hepatotoxicity events must be reported to GSK within 24 hours. Complete liver event eCRF forms and SAE forms if the event also meets the criteria for SAE reporting. The eCRF liver event form does not appear automatically, but must be manually activated.

If treatment is held or discontinued do not restart/rechallenge the participant with study treatment unless all the requirements described in Section 5.4.1.1 have been met, including clearance from the sponsor. Liver chemistry stopping criteria are provided in Section 5.4.1.

Table 14 Guidelines for Dose Modification and Management of Drug-related Hepatotoxicity

Severity	Management	Follow-up
Grade1 ALT > ULN to 3x ULN OR Total bilirubin > ULN to 1.5x ULN	**MONITOR** • Assess liver function at least weekly	Monitor the participant at least weekly until liver chemistries resolve, stabilize, or return to within baseline ***Hepatotoxicity improves to ≤ Grade 1 or baseline or remains stable*:** • Provide close follow-up to evaluate for increased severity. ***Hepatotoxicity worsens to ≥ Grade 2:*** • See below
Grade 2 ALT >3-5x ULN OR Total bilirubin >1.5-3xULN	• Hold study drug(s)[a] • Assess for infection and liver metastases • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments **within 24-72 hours** (see below) • Assess liver function at least twice weekly • Discuss with Sponsor/Medical Monitor • Consider consultation with a hepatologist	Monitor the participant at least twice weekly until liver chemistries resolve, stabilize, or return to within baseline ***Hepatotoxicity improves to ≤ Grade 1 or baseline within 7 days*:** • Resume study drug(s) (note: requirements specified in Section 5.4.1.1 must be met before treatment can restart) • Provide close follow-up to evaluate for recurrence ***Hepatotoxicity ongoing > 7 days*:** • Start systemic steroids (e.g., 0.5 mg/kg/day prednisone or equivalent), if considered

Severity	Management	Follow-up
		GSK3359609 (feladilimab) and/or pembrolizumab related • Continue steroids until improvement to ≤ Grade 1; taper steroids over at least one month • Resume study drug(s) if hepatotoxicity resolves to ≤ Grade 1, and if applicable, steroid dose is ≤10 mg prednisone or equivalent per day within 12 weeks of last dose. (note: requirements specified in Section 5.4.1.1 must be met before treatment can restart) • Provide close follow-up to evaluate for recurrence **Discontinue study treatment if:** • Hepatotoxicity continues or worsens to ALT >5x ULN or total bilirubin to >3x ULN (follow instructions below) • ALT ≥ 3xULN but <5xULN persists for ≥4 weeks • ALT ≥ 3xULN but <5xULN **and** cannot be monitored weekly for ≥4 weeks • Unable to reduce steroid dose to ≤10 mg prednisone or equivalent per day within 12 weeks, if applicable **Recurrence after rechallenge:** • **Discontinue** study drug(s) permanently • Monitor participant closely for clinical signs and symptoms • Perform full panel LFTs a weekly or more frequently if clinically indicated until ALT decreases to ≤ Grade 1 • At the time of the recurrence, complete the eCRF liver event forms.

Severity	Management	Follow-up

Grade 3
ALT >5 x ULN-20 x ULN
OR
Total bilirubin >3x ULN-10 x ULN
	• Immediately discontinue study drug(s)[a]
	• Assess for infection and liver metastases
	• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessment **within 24 hours** (see below)
	• Assess liver function at least twice weekly
	• Consider administration of 1-2 mg/kg/day IV methylprednisolone, if considered GSK3359609 (feladilimab) and/or pembrolizumab related
	• Discuss with Sponsor/Medical Monitor within 24 hours
	• Consider consultation with a hepatologist
		Monitor the participant at least twice weekly until liver chemistries resolve, stabilize, or return to within baseline
		
		• If ALT or bilirubin have not decreased within 72 hours in the absence of other etiologies, and if applicable, steroid treatment has not been administered, initiate treatment with 1-2 mg/kg/day IV methylprednisolone:
		  • Continue steroids until improvement to ≤ Grade 1 or baseline or resolution; taper steroids over at least one month
		  • If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity.

Severity	Management	Follow-up
Grade 4 ALT >20 x ULN OR Total bilirubin >10x ULN **Additional Stopping Criteria:** ALT ≥3x ULN **AND** Total bilirubin ≥2x ULN (>35% direct bilirubin)[b] ALT≥3xULN and INR>1.5, if INR measured[c] ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity[d]	• Immediately discontinue study drug(s)[a] • Assess for infection and liver metastases • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessment **within 24 hours** (see below) • Assess liver function at least twice weekly • Administer 1-2 mg/kg/day IV methylprednisolone, if considered GSK3359609 (feladilimab) pembrolizumab and/or GSK3174997 related • Discuss with Sponsor/Medical Monitor within 24 hours • Consider consultation with a hepatologist	Monitor the participant at least twice weekly until liver chemistries resolve, stabilize, or return to within baseline • Continue steroids, if applicable, until improvement to ≤ Grade 1 or baseline or resolution; taper steroids over at least one month • If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity.

Abbreviations: ALT = Alanine aminotransferase; ULN = Upper limit of normal; AST = Aspartate aminotransferase; IV = Intravenous LFT = liver function tests; INR = International Normalized Ratio

a. If >1 study drug is administered per protocol (e.g. GSK3359609 (feladilimab) in combination with pembrolizumab, GSK3174998, or chemotherapy), guidance applies to all study drugs; discuss management on a case-by-case basis with the Sponsor/Medical Monitor. Refer to Section 7.18 for guidance on chemotherapy dose modifications.
b. 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.
c. 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.
d. 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

Liver Event Follow-up Assessments

- **Viral hepatitis serology:** 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

- **Blood sample for PK analysis,** obtained within 28 days after last dose of study drug: 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 eCRF. 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
- **Serum creatine phosphokinase and lactate dehydrogenase**
- **Fractionate bilirubin,** if total bilirubin ≥2 x ULN
- **Obtain complete blood count with differential** to assess eosinophilia
- **Record the appearance or worsening of clinical symptoms** of liver injury, or hypersensitivity, on the AE report form
- **Record use of concomitant medications** on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications
- **Record alcohol use** on the liver event alcohol intake case report form
- **For bilirubin or INR criteria:**
    - Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG (or gamma globulins).
    - Serum acetaminophen adduct high-performance liquid chromatography assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]).
- **Liver imaging** (ultrasound, magnetic resonance, or computerized tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eCRF forms.

7.5. Management of Gastrointestinal Events (Diarrhea or Colitis)

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

Differential diagnosis: All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a *Clostridium difficile* titer. Dose modification guidelines for gastrointestinal events are provided in Table 15.

Table 15 Guidelines for Dose Modification and Management of Gastrointestinal Events (Diarrhea or Colitis)

Severity	Management	Follow-up
Grade 1	• Administer anti-diarrheal and symptomatic treatment as appropriate	***Symptoms resolve to baseline within 7 days:*** • Provide close follow-up to evaluate for increased severity. ***Symptoms ongoing > 7 days*:** • Consider following algorithm for Grade 2 events
Grade 2	• Hold study drug(s)[a] • Administer antidiarrheal and symptomatic treatment • Discuss with Sponsor/Medical Monitor	***Symptoms resolve to ≤ Grade 1 or baseline within 3 days***: • Resume study drug(s) ***Symptoms ongoing >3 days, blood or mucus in stool, or ulceration/bleeding on endoscopy*:** • Consider GI consultation and endoscopy to confirm or rule out colitis • Start systemic corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) • Continue steroids until improvement to Grade 1 or resolution; taper steroids as medically appropriate • Resume study drug(s) if toxicity has resolved to ≤Grade 1 and, if applicable, steroid dose is ≤10 mg prednisone or equivalent per day within 12 weeks of last dose. If the last dose was administered >12 weeks, study drug(s) must be permanently discontinued. • If symptoms continue or worsen to Grade 3-4, see below
Grade 3	• Hold study drug(s)[a] • Assess for bowel perforation; do not administer corticosteroids if present • Consult gastrointestinal (GI) service, perform endoscopy with biopsy • Administer 1-2 mg/kg/day IV methylprednisolone, if considered GSK3359609 (feladilimab) pembrolizumab and/or GSK3174998 related • Discuss with Sponsor/Medical Monitor	• Resume study drug(s) if toxicity resolved to ≤Grade 1 **If steroids are indicated:** • When symptoms improve to ≤Grade 1, taper steroids over at least 1 month. • If corticosteroid therapy does not reduce initial symptoms within 48 to 72 hours, treat with additional anti-inflammatory measures. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45-60 days. • If symptoms worsen during steroid taper, re-taper starting at a higher dose followed by a more prolonged taper. • Resume study drug(s) if toxicity resolved to ≤Grade 1 and steroid dose is ≤10 mg prednisone or equivalent per day within 12 weeks of last dose. If the last dose was administered >12 weeks, study drug(s) must be permanently discontinued.

Severity	Management	Follow-up
Recurrent Grade 3/ Grade 4	• Permanently discontinue study drug(s) • Immediately inform Sponsor/Medical Monitor	• Management as per Grade 3

Abbreviations: GI=gastrointestinal; IV=intravenous

a. If >1 study drug is administered per protocol (e.g. GSK3359609 (feladilimab) in combination with pembrolizumab, GSK3174998, or chemotherapy), guidance applies to both study drugs; discuss management on a case-by-case basis with the Sponsor/Medical Monitor. Refer to Section 7.18 for guidance on chemotherapy dose modifications.

7.6. Management of Renal Toxicity

Differential diagnosis: all attempts should be made to rule out other causes such as metastatic disease or infection. Dose modification guidelines for renal toxicity are provided in Table 16.

Table 16 Guidelines for Dose Modification and Management of Renal Events

Severity	Management	Follow-up
Grade 1	• Administer symptomatic treatment as appropriate • Continue study drug(s)[a]	***Symptoms resolve to baseline within 7 days:*** • Provide close follow-up to evaluate for increased severity ***Symptoms ongoing >7 days*:** • Consider following algorithm for Grade 2 events
Grade 2	• Hold study drug(s)[a] • Investigate etiology • Consider consulting nephrologist, biopsy, and/or diagnostic procedure • Discuss with Sponsor/Medical Monitor • Monitor changes of renal function	• Resume study drug(s) if toxicity resolved to ≤Grade 1 • If symptoms continue or worsen to Grade 3 or Grade 4, refer to Grade 3/Grade4 guidance **If steroids are indicated:** • Start systemic steroids (e.g. 0.5 mg/kg/day of prednisone or equivalent) • Continue steroids until toxicity resolves to ≤Grade 1; taper steroids as medically appropriate • Resume study drug(s) if toxicity has resolved to ≤Grade 1 within 12 weeks of last dose and steroid dose is ≤10 mg prednisone or equivalent per day within 12 weeks
Grade 3/Grade 4	• Permanently discontinue study drug(s)[a] • Consult subspecialist • Administer 1-2 mg/kg/day IV methylprednisolone, if considered GSK3359609 (feladilimab) pembrolizumab and/or GSK3174998 related • Discuss with Sponsor/Medical Monitor • Monitor changes of renal function	***Symptoms improve to ≤Grade 2:*** • If applicable, continue steroids until improvement to ≤Grade 1 or baseline; taper steroids over at least 1 month, then if symptoms have improved to ≤Grade 1 and steroid dose is 10 mg prednisone/day or less, consider resumption of study drug(s) at the next lower dose level following consultation with medical monitor ***Symptoms ongoing:*** • Discuss further management with consultant and Sponsor/Medical Monitor • Consider alternative immunosuppressive therapy

Abbreviations: intravenous

a. If >1 study drug is administered per protocol (e.g. GSK3359609 (feladilimab) in combination with pembrolizumab, GSK3174998, or chemotherapy), guidance applies to all study drugs; discuss management on a case-by-case basis with the Sponsor/Medical Monitor. Refer to Section 7.18 for guidance on chemotherapy dose modifications.

7.7. Management of Skin Toxicity

Differential diagnosis: All attempts should be made to rule out other causes such as metastatic disease, infection, or allergic dermatitis. Dose modification guidelines for skin toxicity are provided in Table 17.

Table 17 Guidelines for Dose Modification and Management of Skin Toxicity

Severity	Management	Follow-up
Localized rash	• Symptomatic management	Provide close follow-up
Non-localized rash (diffuse, ≤50% of skin)	• Hold study drug(s)[a] • Discuss with Sponsor/Medical Monitor • Consider dermatology consultation and biopsy	***Symptoms resolve to baseline within 7 days***: • Resume study drug(s) ***Symptoms ongoing > 7 days*:** • Start topical or systemic corticosteroids (e.g. 0.5-1 mg/kg/day of prednisone or equivalent), if considered GSK3359609 (feladilimab), pembrolizumab, and/or GSK3174998 related • Continue steroids until improvement to ≤Grade 1 or resolution; taper steroids as medically appropriate • Resume study drug(s) if symptoms have improved to ≤Grade 1 within 12 weeks of last dose and, if applicable, steroid dose is ≤10 mg prednisone or equivalent per day within 12 weeks • If symptoms continue or worsen, see below
Rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations	• Permanently discontinue study drug(s)[a] • Administer 1-2 mg/kg/day IV methylprednisolone, if considered study treatment related • Discuss with Sponsor/Medical Monitor • Consider dermatology consultation and biopsy	• When dermatitis is controlled, if applicable, taper steroids over at least one month period
Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), or Drug reaction with eosinophilia and systemic symptoms (DRESS)	• Suspected SJS, TEN, or DRESS ○ Hold study drugs[a] • Confirmed SJS, TEN, DRESS ○ Permanently discontinue study drugs[a] Ensure adequate	• • When event is controlled, taper steroids over at least one month period, d, if applicable

Severity	Management	Follow-up
	evaluation to confirm etiology or exclude other causes Based on severity of AE administer corticosteroids	

Abbreviations: IV = Intravenous

a. If >1 study drug is administered per protocol (e.g. GSK3359609 (feladilimab) in combination with pembrolizumab, GSK3174998, or chemotherapy), guidance applies to all study drugs; discuss management on a case-by-case basis with the Sponsor/Medical Monitor. Refer to Section 7.18 for guidance on chemotherapy dose modifications.

7.8. Management of Endocrine Events

Signs/symptoms may include, but are not limited to: fatigue, weakness, headache, mental status and/or behavior changes, fever, vision disturbances, cold intolerance, abdominal pain, unusual bowel habits, loss of appetite, nausea and/or vomiting, and hypotension. Endocrine events may include the following AE terms: adrenal insufficiency, hyperglycemia, hyperthyroidism, hypophysitis, hypopituitarism, hypothyroidism, thyroid disorder, and thyroiditis.

Dose modification guidelines for endocrine events are provided in Table 18.

Table 18 Guidelines for Dose Modification and Management of Endocrine Events

Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and/or electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes an adrenal crisis and must be considered a medical emergency.

Severity/Toxicity	Management	Follow-up[a]
Grade 2 • Signs and/or symptoms of dysfunction • Endocrinopathies requiring hormone replacement or medical intervention	• Consider holding study drug(s)[b] • Grade 2 hypophysitis hold study drug(s) • Assess endocrine function • Consider pituitary imaging • Administer up to 1-2 mg/kg/day IV methylprednisolone if clinically indicated • Initiate appropriate hormone-replacement	***Consider resuming study drug(s) when:*** • Participant is stable (on hormone-replacement therapy if indicated) and symptoms have resolved to ≤Grade 1 within 12 weeks of last dose • If participant is receiving ≤10 mg prednisone or equivalent per day; reduction of corticosteroid must have occurred within 12 weeks.

Severity/Toxicity	Management	Follow-up[a]
	therapy (e.g., hypothyroidism) • Consider consultation with endocrinology • Non-selective beta-blockers are suggested for hyperthyroidism • Discuss with Sponsor/Medical Monitor	

Grade 3/ Grade 4
• Adrenal crisis or other adverse reactions requiring hospitalization, urgent medical intervention.
• Hyper/Hypothyroidism
• Hypophysitis
	• Hold study drug(s)[b]
	  • Hypothyroidism: may continue study treatment[c]
	  • Permanently discontinue study drugs for Grade 4 hyperthyroidism
	• Discuss with Sponsor/Medical Monitor
	• Consider immediate initiation of 1-2 mg/kg/day IV methylprednisolone, if considered GSK3359609 (feladilimab), pembrolizumab, and/or GSK3174998 related
	• Consult endocrinology
	• Other management as above
		Consider resuming study drug(s) when:
		• Participant is stable (on hormone-replacement therapy if indicated) and symptoms have resolved to ≤Grade 1 within 12 weeks of last dose of study treatment
		• If participant is receiving ≤10 mg prednisone or equivalent per day; reduction of corticosteroid must have occurred within 12 weeks.

Severity/Toxicity	Management	Follow-up[a]
• New onset Type I diabetes mellitus including diabetic ketoacidosis • Grade3/Grade 4 hyperglycemia associated with evidence of beta cell failure	• Hold study drugs(s)[a] • Recommend insulin replacement therapy for Type I diabetes mellitus/Grade 3 and Grade 4 hyperglycemia associated with metabolic acidosis or ketonuria • Administer antihyperglycemic in participants with hyperglycemia • Evaluate serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide	***Consider resuming study drug(s) when:*** • Participant is clinically and metabolically stable.

Abbreviations: IV = Intravenous

a. Permanently discontinue study drug(s) if hypophysitis of severity Grade ≥2 or Grade 3 hyperthyroidism does not resolve to ≤Grade 1 or baseline within 12 weeks of last dose or there is an inability to reduce prednisone to ≤10 mg or equivalent per day within 12 weeks.
b. If >1 study drug is administered per protocol (e.g. GSK3359609 (feladilimab) in combination with pembrolizumab, GSK3174998, or chemotherapy), guidance may apply to all study drugs discuss management on a case-by-case basis with the Sponsor/Medical Monitor.
c. Study treatment may continue while thyroid replacement therapy is instituted.

7.9. Management of Pneumonitis

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

Differential diagnosis: All attempts should be made to rule out other causes such as metastatic disease, and bacterial or viral infection.

NOTE: It is important that participants with a suspected diagnosis of pneumonitis be managed as per the guidance below until treatment-related pneumonitis is excluded. Treatment of both a potential infectious etiology and pneumonitis in parallel may be warranted. Management of the treatment of suspected pneumonitis with steroid treatment should not be delayed for a therapeutic trial of antibiotics. If an alternative diagnosis is established, the participant does not require management as below; however, the AE must be reported regardless of etiology. Dose modification guidelines for pneumonitis are provided in Table 19.

Table 19 Guidelines for Dose Modification and Management of Pneumonitis

Severity	Management	Follow-up
Grade 1 (asymptomatic with radiographic findings only)	• Discuss continued treatment with study drug(s) with Sponsor/Medical Monitor • Consider pulmonary consultation and/or bronchoscopy if clinically indicated	• Serial imaging
Grade 2	• Hold study drugs(s)[a] • Consider pulmonary consultation with bronchoscopy and bronchoalveolar lavage (BAL) • Administer 1-2 mg/kg per day IV methylprednisolone, if considered GSK3359609 (feladilimab), pembrolizumab, and/or GSK3174998 related • Discuss with Sponsor/Medical Monitor	**If steroids indicated:** • If toxicity resolves to ≤ Grade 1, taper steroids over at least 1 month. Permanently discontinue study drugs(s) if unable to reduce steroid dose to ≤10 mg prednisone or equivalent per day within 12 weeks. • Rechallenge with study drug(s) at the same dose(s) may be considered if a first event resolves to ≤Grade 1 within 12 weeks of last dose. • Repeat chest imaging monthly as clinically indicated.
Grade 3 and 4 or Recurrent Grade 2	• Permanently discontinue study drug(s)[a] • Bronchoscopy with biopsy and BAL is recommended • Administer 1-2 mg/kg per day IV methylprednisolone, if considered GSK3359609 (feladilimab) pembrolizumab and/or GSK3174998 related • Discuss with Sponsor/Medical Monitor	**If steroids indicated:** • When symptoms resolve to ≤Grade 1, taper steroids over at least 1 month. • If corticosteroid therapy does not reduce initial symptoms within 48 to 72 hours, treat with additional anti-inflammatory measures. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45-60 days. • If symptoms worsen during steroid taper, re-taper starting at a higher dose followed by a more prolonged taper. • Add anti-infective prophylaxis as appropriate.

Abbreviations: IV = Intravenous

a. If >1 study drug is administered per protocol (e.g. GSK3359609 (feladilimab) in combination with pembrolizumab, GSK3174998, or chemotherapy), guidance applies to all study drugs; discuss management on a case-by-case basis with the Sponsor/Medical Monitor.

7.10. Management of Hematologic Events

Dose modification guidelines for hematologic events are provided in Table 20.

Table 20 Guidelines for Dose Modification and Management of Hematologic Events

Severity	Management	Follow-up
Grade 1/ Grade 2	• As clinically indicated	• Provide close follow-up to evaluate for increased severity
Grade 3	• Consider holding study drug(s)[a] • Discuss with Medical Monitor • Obtain flow cytometry study of T and B lymphocytes • Consult hematology • Further management as clinically indicated	• As clinically indicated • Retreatment with study drug(s) may be considered on a case-by-case basis if agreed upon by investigator and Sponsor/Medical Monitor.
Grade 4	• Consider discontinuation of study drug(s) for any severe or life threatening event [a] • Consult hematology • Obtain flow cytometry study of T and B lymphocytes. • Discuss with Sponsor/Medical Monitor	• As clinically indicated • Retreatment with study drug(s) may be considered on a case-by-case basis if agreed upon by investigator and Sponsor/Medical Monitor.

a. If >1 study drug is administered per protocol (e.g. GSK3359609 (feladilimab) in combination with pembrolizumab or GSK3174998) guidance applies to both study drugs; discuss management on a case-by-case basis with the Sponsor/Medical Monitor; refer to Section 7.18 for guidance on chemotherapy dose modifications for hematologic events.

7.11. Management of Uveitis/Iritis

All attempts should be made to rule out other causes such as metastatic disease, infection or other ocular disease (e.g. glaucoma or cataracts). However, the AE must be reported regardless of etiology. Dose modification guidelines for uveitis/iritis are provided in Table 21.

Table 21 Guidelines for Dose Modification and Management of Uveitis/Iritis

Severity	Management	Follow-up
Grade 1	• Symptomatic treatment as appropriate	***Symptoms resolve to baseline within* 7 days*:*** • Provide close follow-up to evaluate for increased severity ***Symptoms ongoing > 7 days*:** • Consider following algorithm for Grade 2 events
Grade 2	• Hold study drug(s)[a] • Consultation with ophthalmologist is strongly recommended • Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics, if considered GSK3359609 (feladilimab) pembrolizumab and/or GSK3174998 related • Discuss with Sponsor/Medical Monitor	***Symptoms resolve to baseline within 7 days*:** • Resume study drug(s) ***Symptoms ongoing > 7 days*:** • Discontinue study drug(s) • If symptoms continue or worsen to Grade 3 or Grade 4, see below
Grade 3	• Permanently discontinue study drug(s) [a] • Administer 1-2 mg/kg per day IV methylprednisolone, if considered GSK3359609 (feladilimab) pembrolizumab and/or GSK3174998 related (local administration of corticosteroids may be considered after consultation with an ophthalmologist) • Consultation with ophthalmologist is strongly recommended • Discuss with Sponsor/Medical Monitor	• If applicable, continue steroids until improvement to ≤ Grade 1; taper steroids over at least one month
Grade 4	• Permanently discontinue study drug(s) • Immediately inform Sponsor/Medical Monitor	• Management as per Grade 3

Abbreviations: IV = Intravenous

a. If >1 study drug is administered per protocol (e.g. GSK3359609 (feladilimab) in combination with pembrolizumab, GSK3174998, or chemotherapy), guidance applies to all study drugs; discuss management on a case-by-case basis with the Sponsor/Medical Monitor.

7.12. Management of Infusion Reactions or Severe Cytokine Release Syndrome (sCRS)

Infusion reactions are a well-documented AE associated with the administration of mAbs, and are known to occur with specific chemotherapies. Infusion reactions typically develop within 30 minutes to two hours after initiation of drug infusion, although symptoms may be delayed for up to 48 hours. The incidence of infusion reactions varies by mAb and chemotherapeutic agent, and there are multiple mechanisms known to lead to infusion-related reactions including both IgE-dependent anaphylactic and non-IgE dependent anaphylactoid hypersensitivities. Cytokine release syndrome, and when severe, cytokine "storm", has been identified as a sequelae of immune system activation associated with infusion reactions. As of March 2021, there have been no reported cases of cytokine release syndrome associated with GSK3359609 (feladilimab) infusions.

7.12.1. Infusion Reaction

Infusion reactions may affect any organ system in the body. Most are mild in severity, although severe and fatal reactions can 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 4.0) [NCI, 2010] for grading adverse reactions during the infusion of a pharmacological or biological substance has a term for grading the severity of infusion reactions and separate terms for grading allergic reactions, anaphylaxis, and cytokine release syndrome. The use of these separate terms in grading severity of the event 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 fever, chills, 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.

7.12.2. Cytokine Release Syndrome

Cytokine-associated toxicity, also known as CRS, is a non–antigen-specific toxicity that occurs as a result of strong immune activation. The magnitude of immune activation typically required to mediate clinical benefit using modern immunotherapies exceeds levels of immune activation that occurs in more natural settings. As immune-based therapies have become more potent, CRS is becoming increasingly recognized.

Symptomatology associated with CRS and the severity of symptoms varies greatly, and management can be complicated by inter-current conditions in these participants. Fever is a hallmark, and many features of CRS mimic infection. It is not uncommon for participants to experience temperatures exceeding 40°C.

Potentially life-threatening complications of CRS include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation. Of concern is cardiac dysfunction, which can be rapid onset and severe, but is typically reversible.

It is difficult to determine the exact etiology of this AE in the clinical setting proximate to its occurrence, which makes it difficult to differentiate between a typical infusion reaction and CRS. Since there is a wide commonality in the clinical presentation of these events, the immediate treatment (refer to Section 7.12.3) does not vary with respect to the etiology.

To better understand the underlying etiology of these events, serum tryptase, C-reactive protein (CRP), ferritin, and a cytokine panel must be drawn during the occurrence of an infusion reaction/CRS of any grade as outlined in Table 22. The serum tryptase, CRP and ferritin panels must be performed. 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 22 Infusion-Related Reaction Laboratory 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]
Serum cytokine panel[b] (IFNγ*^, TNFα*^, IL-2*, IL-4, IL-6*^, IL-8*, IL-10*, IL-12p70, and IL-13)	* Reported to be elevated in CRS [Lee, 2014] ^ Consistently reported as elevated in CRS [Lee, 2014]

Abbreviations: CRP=C-reactive protein; CRS= Cytokine Release Syndrome; IFNγ = Interferon gamma; TNFα = Tumor necrosis factor alfa; IgE: immunoglobulin E; IL = Interleukin

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

7.12.3. Guidelines for Management of Infusion Reactions/CRS

Prophylactic pre-infusion medications/premedications are not permitted prior to the first infusion except in combinations with chemotherapy/chemotherapies where premedication is required/recommended per approved product label or standard practice. In the combinations of GSK3359609 (feladilimab) with pembrolizumab or GSK3174998, prophylactic premedication may be permitted if deemed medically appropriate by the GSK Medical Monitor in consultation with investigators following IRR across cohorts.

If multiple participants experience clinically significant infusion reactions, the infusion rate may be slowed for all future administrations of study drug(s) for all participants; this will be communicated to the sites in writing.

For Grade 1 symptoms (Mild reaction [e.g., localized cutaneous reactions including mild pruritus, flushing, rash] requires infusion rate to be decreased; intervention may be indicated):

- Decrease the rate of the study drug infusion by at least 25% of the original rate
- The participant must be closely monitored until resolution of symptoms.
- Diphenhydramine 50 mg may be administered at the discretion of the treating physician.
- If symptoms resolve, the infusion rate may be increased to the original infusion rate; if no further complications ensue, the rate of subsequent infusions may be increased to the original infusion rate.
- If a participant has a Grade 1 infusion reaction with study drug(s), subsequent infusions can be given without prophylactic medications if the infusion reaction resolves within 3 hours. Prophylactic pre-infusion medications must be given before all subsequent infusions of study drug(s) if symptoms resolve >3 hours.
- The following prophylactic pre-infusion medications are recommended before future infusions of study drug(s): diphenhydramine 50 mg (or equivalent) and/or paracetamol (acetaminophen) 500 mg to 1000 mg should be administered at least 30 minutes before additional study drug administrations.
- Obtain serum for CRP, tryptase, ferritin, and cytokine panel (refer to Table 22, and SRM).

For Grade 2 symptoms (Moderate reaction [i.e., any symptom not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea, or hypotension with systolic blood pressure > 80 mmHg]):

- Discontinue the study drug infusion.
- Consider treatment with IV infusion of normal saline, histamine 1 and/or histamine 2 blockers, acetaminophen, or NSAIDs as appropriate. Corticosteroid therapy may be administered at the discretion of the treating physician.
- Obtain serum for CRP, tryptase, ferritin, and cytokine panel (see Table 22 and SRM).
- Participant must be closely monitored until resolution of symptoms.
- If symptoms resolve to baseline within one hour of stopping drug infusion, restart the infusion at 50% of the original infusion rate; monitor the participant closely.
    - For scheduling purposes, the study drug(s) may be administered the following day if the infusion cannot be continued the same day.
- If no further complications ensue, the rate at subsequent infusions may be increased to 100% of the original infusion rate.
- If symptoms recur, immediately discontinue the infusion; administer diphenhydramine 50 mg IV and continue to monitor the participant closely until

resolution of symptoms to ≤Grade 1. No further study drug will be administered at that visit.

- If symptoms resolve later than one hour, then the infusion should not be restarted. Prophylactic pre-infusion medications must be considered before all subsequent infusions of study drug(s).
- Participant may be premedicated prior to infusion with diphenhydramine 50 mg (or equivalent) and/or paracetamol 500 mg to 1000 mg (acetaminophen) at least 30 minutes before additional study drug administrations. Participants who develop Grade 2 infusion reactions despite adequate premedication should be permanently discontinued from further trial treatment administration.

For Grade 3 or Grade 4 symptoms (Severe reaction [e.g., bronchospasm, generalized urticaria, systolic blood pressure < 80 mmHg, hypoxemia, or angioedema], Grade 3: prolonged [i.e., requiring 6 or more hours to respond to symptomatic medication and/or discontinuation of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]. Grade 4: life-threatening; pressor or ventilatory support indicated):

- Immediately discontinue the study drug infusion. No further study drug will be administered, unless approved by Sponsor/Medical Monitor (criteria for rechallenge include but are not limited to participants who are receiving compelling benefit with study treatment that exceeds risk, no effective alternative therapy is available, participants who did not receive prophylactic treatment for infusion reactions). Participants who have develop severe hypersensitivity reactions related to paclitaxel should not be rechallenged with paclitaxel.
    - Any participant rechallenged with study drug(s) must receive prophylaxis/premedication, as per institutional guidelines, prior to subsequent administration of study drug(s). In these participants, the infusion rate must be reduced by 50% of the original infusion rate and the participant must remain under observation a minimum of three hours, post-administration of study drug(s).
- Begin an IV infusion of normal saline, and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 mg to 1.0 mg of a 1:1,000 solution for subcutaneous administration or 0.1 mg to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed per institutional guidelines.
- Consider administering etanercept or tocilizumab
- Consider additional intervention in consultation with the investigator and the Sponsor/Medical Monitor.
- Obtain serum for CRP, tryptase, ferritin, and cytokine panel (refer to Table 22, and SRM for further details).
- Participant must be closely monitored until resolution of symptoms.

7.13. Management of Myocarditis

Dose modification and management guidelines for myocarditis are provided in Table 23.

Table 23 Guidelines for Dose Modification and Management of Myocarditis

Severity	Management	Follow-up
Grade 1/	• Hold study drug(s)[a] • Based on severity of administer corticosteroids • Consider cardiology consultation • Evaluate to confirm etiology and/or exclude other causes	• Continue steroids until toxicity resolves to ≤Grade 1; taper steroids as medically appropriate • Resume study drug(s) if toxicity has resolved to ≤Grade 1 within 12 weeks of last dose and if applicable steroid dose is 10 mg prednisone or equivalent per day within 12 weeks
Grade 2/Grade 3/Grade 4	• Permanently discontinue study drug(s)[a] • Immediately inform Medical Monitor • Administer corticosteroids • Consider cardiology consultation • Evaluate to confirm etiology and/or exclude other causes	• Continue steroids until toxicity resolves to Grade 1; taper steroids as medically appropriate

a. If >1 study drug is administered per protocol (e.g. GSK3359609 (feladilimab) in combination with pembrolizumab, GSK3174998, or chemotherapy), guidance applies to both all study drugs; discuss management on a case-by-case basis with the Sponsor/Medical Monitor.

7.14. Management of Neurotoxicity

Dose modification and management guidelines for neurological toxicities are provided in Table 24.

Table 24 Guidelines for Dose Modification and Management of Neurological Toxicities

Severity	Management	Follow-up
Grade 2	• Hold study drug(s)[a] • Based on severity administer corticosteroids • Ensure adequate evaluation to confirm etiology and/or exclude other causes	• Continue steroids until toxicity resolves to ≤Grade 1; taper steroids as medically appropriate • Resume study drug(s) if toxicity has resolved to ≤Grade 1 within 12 weeks of last dose and if applicable steroid dose is 10 mg prednisone or equivalent per day within 12 weeks
Grade 3/Grade 4	• Permanently discontinue study drug(s)[a] • Immediately inform Medical Monitor • Administer corticosteroids • Evaluate to confirm etiology and/or exclude other causes	• Continue steroids until toxicity resolves to Grade 1; taper steroids as medically appropriate

a. If >1 study drug is administered per protocol (e.g. GSK3359609 (feladilimab) in combination with pembrolizumab, GSK3174998, or chemotherapy), guidance applies all study drugs; discuss management on a case-by-case basis with the Sponsor/Medical Monitor.

7.15. Management of QTc Events

- The QTcF correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted. The QTcF should be based on single or at time-points where triplicate electrocardiograms (ECGs) obtained over a brief (e.g., 5-10 minute) recording period (refer to Time and Events Table 27) are required, averaged QTc values.

If a participant meets the following criteria, the participant must discontinue study treatment:

- QTcF >500 msec

OR

- Change from baseline of QTcF >60 msec

For participants with underlying **bundle branch block**, follow the discontinuation criteria listed below:

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

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

7.16. Management of Left Ventricular Dysfunction

Echocardiography (ECHO), or Multigated Acquisition Scan (MUGA) in lieu of ECHOs (if not available), must be performed at Screening, and if clinically indicated as outlined in the Time and Events Table 27. The same modality used at Screening must be used in any subsequent assessments; contact GSK if same modality is no longer feasible.

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

Participants with symptoms of LV systolic dysfunction without an accompanying decrease in LVEF by echocardiogram must have a full evaluation performed as appropriate (e.g., cardiology consult, additional workup for swelling/shortness of breath) and symptoms must resolve to <Grade 2 prior to discussion of restarting study treatment at the same or reduced dose with the GSK Medical Monitor.

7.17. Management of Valvular Toxicity

Participants with a Grade 3 or Grade 4 (symptomatic, severe regurgitation/stenosis by imaging with symptoms controlled by medical intervention) valvular toxicity must discontinue study treatment. Valvular toxicity must continue to be monitored every 4 weeks for 16 weeks or until resolution. If recovery occurs (return to baseline via imaging AND symptom resolution) within 4 weeks, the participant may restart study treatment at a reduced dose in consultation with and after approval of the GSK Medical Monitor.

7.18. Management Guidance of Chemotherapy-related Toxicities

Refer to Table 25 and Table 26 for guidance on specific chemotherapy-related AEs; as these tables are guidance only, refer to chemotherapy prescribing information or standard practice guidelines for the management of these AEs, other AEs or potential safety-related issues.

Table 25 Dose Reductions for Chemotherapy-related Hematologic Events

Chemotherapy Regimen	Toxicity	Action[a]
Docetaxel	• ANC <1.5x10^9/L, platelets <75x10^9/L, or hemoglobin <9g/dL (after transfusion if needed) • Febrile neutropenia	• Hold docetaxel until recovery: ANC ≥1.5x10^9/L, platelets ≥100x10^9/L ○ Recovery within 7 days, resume 100% of previous dose; >7 days, resume 80% of previous dose • Hold docetaxel; upon recovery, if ANC < 500/mm^3 for more than 7 days, resume at 55mg/m^2
Pemetrexed/Carboplatin	ANC <1.5x10^9/L, platelets <75x10^9/L, or hemoglobin <9g/dL (after transfusion if needed)	Hold both drugs until recovery: ANC ≥1.5x10^9/L, platelets ≥100x10^9/L. Administer 75% of previous pemetrexed dose if: • ANC were <0.5x10^9/L and platelets were ≥50x10^9/L • Platelets were <50x10^9/L without bleeding Administer 50% of pemetrexed previous dose if: • Platelets were <50x10^9/L with bleeding
Paclitaxel/Carboplatin	ANC <1.5x10^9/L, platelets <75x10^9/L, or hemoglobin <9g/dL (after transfusion if needed)	Hold both drugs until recovery: ANC ≥1.5x10^9/L, platelets ≥100x10^9/L. Administer 80% of previous dose if: • ANC were <0.5x109/L for >7 days

Chemotherapy Regimen	Toxicity	Action[a]
Gemcitabine/Carboplatin	ANC <1.5x10^9/L, platelets <75x10^9/L, or hemoglobin <9g/dL (after transfusion if needed)	Hold both drugs until recovery: ANC ≥1.5x10^9/L, platelets ≥100x10^9/L. Administer 80% of previous dose if: • Refer to approved product label for dose adjustments

a. Resume treatment with chemotherapy after resolution as indicated; treatment with GSK3359609 (feladilimab) and pembrolizumab may continue unless otherwise instructed (refer to Section 7.10)

Table 26 Dose Reductions for Chemotherapy-related Non-Hematologic Events

Chemotherapy Regimen	Toxicity	Action[a]
Docetaxel	• Grade 3/Grade 4 event, except peripheral neuropathy • Grade 3/Grade 4 peripheral neuropathies	• Hold docetaxel upon recovery to ≤Grade 1/baseline, resume treatment at 55mg/m^2 • Consider permanent discontinuation; discuss with medical monitor
Pemetrexed/Carboplatin	• Grade 3/Grade 4 event, or Grade 1/ Grade 2 diarrhea requiring hospitalization, except mucositis or neurological toxicities • Grade 3/Grade 4 mucositis • Grade 3/Grade 4 neurological toxicities or recurrent Grade 3/Grade 4 toxicity resulting in 2 dose reductions	• Hold until recover to ≤Grade 1/baseline, resume treatment at 75% of previous dose • Hold until recover to ≤Grade 1/baseline, resume treatment, except pemetrexed at 50% of previous dose • Consider permanent discontinuation; discuss with medical monitor

a. Resume treatment with chemotherapy after resolution as indicated; treatment with GSK3359609 (feladilimab) and pembrolizumab may continue unless otherwise instructed (refer to Section 7.1-Section 7.19 for further management guidelines)

7.19. Dose Delay

If there is a dose delay between one and 7 days, the procedures at the original scheduled visit (including dosing) should be performed as soon as possible. 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, and subsequent visits will follow Q3W. Participants with infusion delays greater than three weeks due to toxicity should discontinue study drug(s) unless the treating investigator and Sponsor/Medical Monitor agree there is strong evidence supporting continued treatment. For participants requiring elective surgery or radiation therapy, consult the GSK Medical Monitor for study treatment management. (refer to Section 6.9.1 for details on permitted medications and non-drug therapies).

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:
    1. 12-lead ECG
    2. Vital signs
    3. Blood draws (e.g. PK blood draws)

  Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.
- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic/biomarker or other assessments may be altered during the course of the study based on emerging data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- If a change in timing or addition of time points for any planned study assessments occurs, the change will be documented in a Note to File; this will not constitute a protocol amendment.
- The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.
- No more than 500 mL of blood will be collected over the first four doses of study treatment.

8.1. Time and Events Tables

This section presents the Time and Events sections with supplemental footnotes to describe assessments windows and sequencing of assessments and procedures, if applicable.

Informed consent must be signed by a participant before any study required procedures are performed. However, procedures conducted as part of the participant's routine clinical management or as part of another clinical trial within the screening window (e.g., imaging studies) and obtained prior to signing of the study informed consent may be used for screening/baseline assessments provided the procedure fulfils the protocol defined specifications and has been performed within the protocol indicated timeframe.

Table 27 Time and Events: Safety, Laboratory, Efficacy, Study Treatment Procedures

Study Procedure[1]	Screening[2]	Treatment Period[3] Weeks										Treatment Discontinuation[4]	Follow-up	Notes
		0	1	2	3	4	5	6	9	12	>12			
Informed consent[2]	X													
Demography	X													
Inclusion and exclusion criteria	X													
Medical History (past and current)	X													
Disease Characteristics	X													
PD-L1 IHC by 22C3 PharmDx Assay Result (Part 2B HNSCC PD-L1 CPS <1 cohort only)[2]	X													
ICOS IHC assay[2]	X													Required for Biomarker cohort only
Gene Expression assay	X													May be required at Screening for biomarker cohort only
Anticancer Therapy	X												X	Screening=prior anticancer therapy Follow-up= subsequent anticancer therapy
Participant Registration	X													Participant registration will occur after all screening assessments have been performed and the participant has met all eligibility requirements
Safety Assessments														
ECOG PS	X	X	X	X	X	X	X	X	X	X	Q3W	X		
Vital signs, height and weight	X	X	X	X	X	X	X	X	X	X	Q3W	X		Height measured and recorded at screening only

Study Procedure[1]	Screening[2]	Treatment Period[3] Weeks										Treatment Discontinuation[4]	Follow-up	Notes
		0	1	2	3	4	5	6	9	12	>12			
Echocardiogram	X													ECHO required at Screening visit within 28 days prior to first dose of study treatment and during treatment phase, if clinically indicated. MUGA can be used if not available
12-lead ECG[5]	X	X			X			X	X	X	Q12W	X		
AE/SAE review[6]		Continuous: assess at each visit from signing of ICF										X	X	
Concomitant medication review		Continuous: assess at each visit from first dose of study treatment										X	Q12W	
Safety Laboratory Assessments														
Hepatitis B and C	X													
Serum β-hCG	X													Required for females of child bearing potential. Serum pregnancy test must be performed within 7 days prior to first dose of GSK3359609 (feladilimab)
Hematology/Clinical Chemistry (Refer to Table 29)	X	X	X	X	X	X	X	X	X	X	Q3W	X		Must be drawn pre-dose or within 72 h prior to dosing
Thyroid function (Refer to Table 29)	X							X		X	Q6W	X		Must be drawn pre-dose or within 72 h prior to dosing
Troponin		X			X			X	X	X	Q3W	X		Troponin I or Troponin T. Must be drawn pre-dose or within 72 h prior to dosing
Urinalysis	X		X	X	X	X	X	X	X	X	Q3W	X		Must be drawn pre-dose or within 72 h prior to dosing
Part 1 Monotherapy Study Treatment[7]														
Administer GSK3359609 (feladilimab)		X			X			X	X	X	Q3W			

Study Procedure[1]	Screening[2]	Treatment Period[3] Weeks										Treatment Discontinuation[4]	Follow-up	Notes
		0	1	2	3	4	5	6	9	12	>12			
Part 2 Combination Study Treatment[7]														
Administer GSK3359609 (feladilimab) (Q3W)		X			X			X	X	X	Q3W			
Administer GSK3359609 (feladilimab) (Q6W)		X						X		X	Q6W			

Study Procedure[1]	Screening[2]	Treatment Period[3] Weeks										Treatment Discontinuation[4]	Follow-up	Notes
		0	1	2	3	4	5	6	9	12	>12			
Administer Pembrolizumab[8] (Q3W)		X			X			X	X	X	Q3W			
Administer Pembrolizumab[8] (Q6W)		X						X		X	Q6W			
Administer GSK3174998[8]		X			X			X	X	X	Q3W			
Administer Docetaxel[9]		X			X			X	X	X	X^[9]			^Treatment with docetaxel may continue beyond 6 cycles according to standard practice
Administer Pemetrexed[9]/Carboplatin[9]		X			X			X	X	X	X^[9]			^Treatment with pemetrexed may continue beyond 6 cycles according to standard practice
Administer Paclitaxel[9]/Carboplatin[9]		X			X			X	X	X	X[9]			
Administer Gemcitabine^[9]/Carboplatin[9]		X			X			X	X	X	X[9]			^Gemcitabine will be administered on Day 1 and Day 8 of every 3-week/21-day cycle
Administer 5-FU^/Cisplatin[9] or Carboplatin[9]		X			X			X	X	X	X[9]			^Fluorouracil (5-FU) will be administered continuous on Day 1 through Day 4 of every 3-week/21-day cycle
Efficacy Assessments														
Tumor imaging/clinical exam[10]	X								X		Q9W[10]			Up to WK 27 then per institutional guidelines
Tumor imaging/clinical exam for 5-FU Platinum chemotherapy combination cohort[10]	X													Follow institutional guidelines for imaging after screening

Study Procedure[1]	Screening[2]	Treatment Period[3] Weeks										Treatment Discontinuation[4]	Follow-up	Notes
		0	1	2	3	4	5	6	9	12	>12			
Follow-up for Survival													Q12W	Participants will be followed every 12 weeks for survival and subsequent anti-cancer therapy, the window for this visit is ±10 days. The survival follow-up visit will commence after discontinuation of study treatment. Follow-up for survival may not be required when 75% of events have been reached in the last cohort opened; investigators will be notified in writing when survival follow-up is no longer required.

Abbreviations: AE= adverse event; AESI=adverse events of special interest; β-hCG = Beta-human chorionic gonadotropin; ECG=electrocardiogram; ECHO=echocardiography; ECOG PS=Eastern Cooperative Oncology Group Performance Score; EOI=end of infusion; ICF=informed consent form; irRECIST=immune-related RECIST; MUGA=multigated acquisition scan; RECIST=response evaluation criteria in solid tumors; SAE=serious adverse event; W=week

1. Procedures scheduled on study treatment administration days should be done prior to dosing, unless otherwise specified; these assessments can be performed 3 days prior to dosing day. Assessments performed ≤3 weeks can be done ±3 days of scheduled occurrence, those performed >3 weeks can be done ±7 days of scheduled occurrence unless otherwise specified. A participant in Part 1 who upon disease progression is permitted to receive GSK3359609 (feladilimab) in combination with pembrolizumab (crossover) will continue to follow the Part 1 visit assessment schedule to which the participant started.
2. All assessments performed at Screening must be performed within 14 days prior to first dose unless otherwise specified. Informed consent can be signed within 45 days prior to first dose. For participants in the Biomarker cohort (Part 1B), archival tumor tissue OR fresh biopsy obtained at screening is mandatory. NOTE: An evaluable ICOS expression at baseline on either archival or fresh tissue using a validated IHC assay by central laboratory testing is required for eligibility to enroll. In Part 1B biomarker cohort, participants may also require gene expression signature analysis at baseline (NOTE: testing will be retrospective initially but may switch to prospective testing for enrollment depending on prevalence): submitting tumor tissue (archival OR fresh biopsy) at screening for testing can occur after signing of informed consent and within 45 days prior to first dose (Day 1). For participants in Part 2B HNSCC PD-L1 CPS < 1 cohort, a documented CPS score of <1 from FDA approved PD-L1 IHC 22C3 PharmDx assay is required for eligibility; documented test results from local laboratory, if available, may be accepted in lieu of the central test result. For participants requiring central laboratory testing by the PD-L1 IHC 22C3 pharmDx assay: submitting tumor tissue (archival or fresh biopsy) for this testing can occur after signing of informed consent and within 45 days prior to first dose (Day 1).
3. In participants who attain a CR and study treatment is discontinued (early) or in those who complete 35 cycles of study treatment, second course treatment was an option and has been removed.
4. The assessments required at the study treatment discontinuation visit (permanent discontinuation) must be completed within 30 days from the date study treatment was discontinued and must occur prior to the start of subsequent anti-cancer therapy; the window for this visit is +10 days. If tumor imaging/clinical examination assessment occurred within less than the indicated time period, these assessments do not need to be repeated for this visit unless required to confirm disease progression by irRECIST.

5. For Part 1 only: On Day 1 ECG measurements will be performed in triplicate at pre-dose (within 60 minutes prior to start of GSK3359609 (feladilimab) infusion) and at the following times after the infusion: EOI + 30m, EOI + 4h, EOI + 24h, on Day 22 ECG measurements will be performed in triplicate at pre-dose and on Day 85 ECG measurements will be performed in triplicate at pre-dose and at the following times after the infusion: EOI+30m. All other ECG measurements in Part 1 and all ECG measurements in Part 2 are performed as single ECG measurements. For Part 2, ECGs are performed at pre-dose only.
6. AEs and concurrent medications will be collected until at least 30 days after the last dose of study treatment. All AESIs and SAEs, and any concurrent medications relevant to the reported AESIs and SAEs, will be collected until at least 90 days after the last dose of study treatment or until the start of new anticancer therapy, whichever occurs first. Any drug-related or study-related SAEs occurring after 90 days will be reported according to the instructions in Section 8.4.1.1.
7. Study treatment must be administered within $\pm$3 days of scheduled visit unless otherwise indicated. Refer to Section 4.2 for maximum duration of study treatment.
8. GSK3359609 (feladilimab) will be administered first; pembrolizumab or GSK3174998 will be administered at least 30 minutes and no longer than one hour following GSK3359609 (feladilimab) EOI. Refer to Section 4.2 for maximum duration of study treatment.
9. GSK3359609 (feladilimab) will be administered first; chemotherapies will be administered at least 30 minutes and no longer than one hour following GSK3359609 (feladilimab) EOI. Chemotherapy premedication indicated on day of dosing should be administered after GSK3359609 (feladilimab) infusion. Chemotherapies should be administered for a minimum of 4 and maximum of 6 cycles according to standard practice.
10. Disease assessments which include tumor imaging and clinical exams, if indicated, must be performed within 30 days prior to first dose of study treatment and will be performed every 9 weeks until Week 54 then every 12 weeks thereafter until disease progression; participants who discontinue for reasons other than progression will be followed for progression until the start of subsequent anticancer therapy every 9 weeks until Week 54 then every 12 weeks thereafter. Participants who attain a CR and met the requirements defined in Section 5.4 for early discontinuation of study treatment and discontinue study treatment will undergo disease assessments every 12 weeks until progression. Refer to Section 8.3.1 for further details on the use of RECIST 1.1 and irRECIST guidelines in assessing overall tumor burden at Screening and tumor response.

Table 28 Time and Events: Pharmacokinetics, Immunogenicity, Biomarker Assessments (Part 1 and Part 2)

Study Procedure	Screening	Treatment Period Week Day												30 d post-last dose[1,4]	12 w post last dose[1]	Notes
		0		1	2	3	4	5	6	9	12	15	≥18			
		1*#	2	8	15	22*	29	36	43 *#	64 *	85 *#	106*	≥127* #			
Tumor Specimens																
Archival tumor tissue[2]	X															
Fresh tumor biopsy[3^]	X															^Week 6 and 30 d post-last dose biopsy are no longer required/ optional

*Indicates dosing day for Q3W schedule; # indicates dosing day for Q6W schedule

Abbreviations: EOI = end of infusion; d = day; h = hour; min = minute; PBMC = peripheral blood mononuclear cells; PK=pharmacokinetics; w = week

Time-point definitions: X = any time at that visit; pre = collect prior to dosing per institutional guidance, as long as it is collected prior to dosing of the corresponding agent, unless otherwise specified; EOI= within ±1 minute of the end of study treatment infusion; EOI+30 minutes = within ±1 minute; EOI+1 hour= within ±5 minutes; EOI+2 hours= within ±5 minutes; EOI+4 hours = within ±5 minutes; EOI+24 hours = within ±60 minutes of the end of study treatment infusion. Assessments performed ≤3 weeks can be done ±3 days of scheduled occurrence, those performed >3 weeks can be done ±7 days of scheduled occurrence unless otherwise specified. For Part 2: pre = reference is GSK3359609 (feladilimab) infusion time; EOI time-point for biomarker assessments is in reference to EOI of second agent or third agent, if applicable (except for chemotherapy); for chemotherapy combinations, EOI time-points for biomarker assessments is in reference to EOI of GSK3359609 (feladilimab). Refer to the SRM for further details on PK time-points and references.

1. Procedures required at this visit can be performed ±7days, unless otherwise indicated (refer to footnote 4 for biomarker samples taken at 30 days post study treatment visit). If the decision to discontinue study treatment was after 30 days from last dose, then assessments required at this visit should be completed within 10 days from date decision was made to discontinue study treatment.
2. Archival specimen should only be submitted to central laboratory in those participants fulfilling all eligibility criteria. For participants screening for enrollment to Part 2B HNSCC PD-L1 CPS <1 cohort, if PD-L1 IHC testing by 22C3 pharmDx assay by central laboratory is needed, archival tumor tissue can be submitted after signing of consent (within 45 days from Day 1). If archival specimen is not available, a fresh tumor biopsy is required (Note: this procedure can be performed after signing consent and within 45 days from Day 1 for Part 2B HNSCC PD-L1 CPS <1 cohort). In the participants enrolled in the part 1B biomarker cohort, an evaluable result for ICOS expression from central lab testing using archival tissue is acceptable for eligibility although both archival and fresh biopsy at baseline are required; these specimens will be used for assessment of the biomarker status.
3. Screening and on-treatment fresh tumor biopsies are required for monotherapy dose expansion cohorts in Part 1B. Note that both fresh and archival biopsies at screening are required for the biomarker cohort in Part 1B. For Part 2B, fresh screening and on-treatment biopsies are required in HNSCC dose randomized cohort, HNSCC PD-L1 CPS <1 cohort, HNSCC Q6W cohort and melanoma expansion cohort. Also, in Parts 1B and 2B, fresh tumor biopsy should be attempted at screening (any time before first dose) and at

Week 6 (after the 3rd dose of study treatment +7 days). Once evaluable paired tumor biopsies are collected for up to 10 participants per expansion cohort, this requirement may be waived. Fresh screening and on-treatment biopsies are optional in Part 1A. For Part 2A, fresh screening and on-treatment biopsies are required for participants treated at the GSK3359609 (feladilimab)/GSK3174998 combination RP2 doses. Fresh screening and on-treatment biopsies are optional for participants enrolled during the safety/dose escalation phase of these cohorts in Part 2A. Tumor lesions planned for biopsy must not be followed as target lesions for disease assessment unless agreed upon by GSK. Unscheduled tumor biopsies may be performed any time during the treatment period upon participant consent for this optional procedure. Japan Part 1C and Part 2C PK/PD cohort, biopsies are not required.

8.2. Screening and Critical Baseline Assessments

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

- Medical history including cardiovascular medical history/risk factors will be assessed as related to the inclusion/exclusion criteria listed in Section 5.1 and Section 5.2.
- Disease characteristics including medical, surgical, and treatment history including radiotherapy, date of initial diagnosis, stage at initial diagnosis, histology, tumor genetic/genomic features, tumor viral status and current sites of disease will be taken as part of the medical history and disease status; scans from imaging studies performed prior to screening scans required for baseline lesion assessments may be requested (refer to Section 10.7.6.2). Details concerning prior anti-cancer therapy (e.g., systemic and radiation therapy) including best response to prior systemic therapy will be recorded for at least two prior lines of therapy (if available).
- For participants with PD-1/L1 treatment naïve HNSCC screening for enrollment to the Part 2B HNSCC PD-L1 CPS <1 cohort only: An evaluable CPS score of <1 using the PD-L1 IHC 22C3 PharmDx assay for PD-L1 protein expression is required for eligibility. Documented test result of CPS<1 from local laboratory using the PD-L1 IHC 22C3 PharmDx assay and testing conducted as per the guidelines in the assay IFU , if available, may be accepted in lieu of the central laboratory test result; refer to Section 5.1 inclusion criterion 19 for CPS eligibility requirements.
- For participants in the Biomarker cohort (Part 1B), an evaluable result for ICOS expression using a validated IHC assay by central laboratory testing is required; and could be used to enrich for ICOS high expression if prevalence of ICOS expression is low in the initial 15 participants enrolled. Refer to Section 5.1 inclusion criterion 17.
- For participants in the Biomarker Cohort (Part 1B), gene expression using a validated Nanostring gene expression CounterFLEX system assay by central lab; there may be a requirement for gene expression signature result for participant eligibility in the biomarker cohort, and could be used to enrich for signature high if the prevalence of gene expression signature positive participants is low in the initial 15 enrolled participants. Refer to Section 5.1 inclusion criterion 18.

Baseline lesion assessments required within 30 days prior to the first dose of GSK3359609 (feladilimab) include:

- Computed Tomography (CT) scan with contrast of the chest, abdomen, and pelvis
  - For participants with head and neck cancer, a CT/Magnetic Resonance Imaging (MRI) of the head and neck area is required
- Clinical disease assessment for palpable/visible lesions
- Other areas as indicated by the participant's underlying disease present prior to screening

- NOTE: Although CT scan is preferred, MRI may be used as an alternative method of baseline disease assessment, especially for those participants where a CT scan is contraindicated due to allergy to contrast, provided that the method used to document baseline status is used consistently throughout study treatment to facilitate direct comparison. Refer to RECIST version 1.1 guidelines for use of fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT [Eisenhauer, 2009].
- Refer to Section 8.3.1 for baseline documentation of target and non-target lesions.

Safety and laboratory assessments required at baseline include:

- Physical examination
- Performance Status
- Vital Signs
- Concomitant medication
  - Recorded starting from screening through post-study follow-up.
  - At a minimum, the drug name, route of administration, dose and frequency of dosing, along with start and stop dates should be recorded.
- Electrocardiogram
- Echocardiogram or MUGA
- Laboratory assessments (refer to Section 8.4.8)

Refer to Time and Events Table 27, and Table 28 for additional details on assessments required at Screening and prior to start of study treatment.

8.3. Efficacy

8.3.1. Evaluation of Anti-Cancer Activity

- RECIST version 1.1 guidelines will be used to determine the overall tumor burden at screening, select target and non-target lesions, and in the disease assessments through the duration of the study [Eisenhauer, 2009].
- As indicated in RECIST version 1.1 guidelines:
  - Lymph nodes that have a short axis of <10 mm are considered non-pathological and must not be recorded or followed.
  - Pathological lymph nodes with <15 mm, but ≥10 mm short axis are considered non-measurable.
  - Pathological lymph nodes with ≥15 mm short axis are considered measurable and can be selected as target lesions; however, lymph nodes should not be selected as target lesions when other suitable target lesions are available.
  - Measurable lesions up to a maximum of two lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected based on their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

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

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

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

- Disease assessment modalities may include imaging (e.g., CT scan, MRI, bone scan) and physical examination (as indicated for palpable/superficial lesions).
- As indicated in Section 8.2, baseline disease assessment must be completed within 30 days prior to the first dose of GSK3359609 (feladilimab). On-treatment disease assessments occur according to standard practice. At each post-baseline assessment, evaluation of the sites of disease (all target and non-target lesions) identified by the baseline scans is required. CT scans with contrast are required at each post-baseline assessment. To ensure comparability between the baseline and subsequent assessments, the same method of assessment and the same technique will be used when assessing response.
- Refer to the Time and Events Table 27 for the schedule of assessments of anticancer activity. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays.
- For post-baseline assessments, a window of ±7 days is permitted to allow for flexible scheduling. If the last radiographic assessment was more than 9 weeks prior to the participant's discontinuation from study treatment, or >12 weeks if after Week 54, a disease assessment should be obtained.
- Participants with disease progression by RECIST version 1.1 guidelines are required to have a confirmatory disease assessment at least 4 weeks after the date disease progression was declared in order to confirm disease progression by irRECIST guidelines.
- Participants whose disease responds (either CR or PR) must have a confirmatory disease assessment performed at least 4 weeks after the date of assessment during which the response was demonstrated. More frequent disease assessments may be performed at the discretion of the investigator. In the participants who attain a confirmed CR and fulfill the requirement for early discontinuation of study treatment (refer to Section 5.4), disease assessments at a frequency of will be performed per standard of care.
- The visit level responses and treatment-based decisions will incorporate irRECIST guidelines as described in Appendix 6.

8.4. Safety

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

8.4.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 9.

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

8.4.1.1. Time and Frequency for collecting AE and SAE information

- Any AESI and SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant provides consent to participate in the study up to 90 days after the last dose of study treatment. If subsequent anti-cancer treatment is initiated during the 90-day follow-up period yet <30 days after the date study treatment was discontinued, AESI and SAEs must continue to be followed until 30 days after last dose of study treatment.
- AEs will be collected from the start of Study Treatment until the follow-up contact (see Section 8.4.1.2), at the time-points specified in the Time and Events Table (Section 8.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Section 13.9.6.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

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

8.4.1.2. 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 AEs of special interest (as defined in Appendix 8) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-

up (as defined in Section 5.4. Further information on follow-up procedures is given in Appendix 9.

8.4.1.3. Cardiovascular and Death Events

All cardiovascular (CV) events (as defined in Section 8.4.1.3.1) and deaths, whether or not considered SAEs, require specific CV and Death sections of the eCRF to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV death.

The CV eCRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information must be recorded in the specific CV section of the eCRF 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.

8.4.1.3.1. Definition of Cardiovascular Events

A cardiovascular event is defined as:
• Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

8.4.1.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.

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

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

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

8.4.2. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of dosing and until 120 days after date of last dose of study treatment.
- If a pregnancy is reported then the investigator must inform GSK within 24 hours of learning of the pregnancy and must follow the procedures outlined in Section 13.9.7.

8.4.3. Physical Examinations

- A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height (at Screening only) 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).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.4.4. Performance Status

Performance status will be assessed using the ECOG scale as described in Appendix 7.

8.4.5. Vital Signs

- Vital signs will be measured in semi-supine position after 5 minutes of rest and will include temperature, systolic and diastolic blood pressure and pulse rate.
    - In the case of an abnormal first reading, three readings of blood pressure and/or pulse rate must be taken, whereby the first reading should be rejected and the second and third averaged to give the measurement to be recorded in the eCRF.
- Vital signs will be measured more frequently if warranted by clinical condition of the participant.
- On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.
- If a participant develops fever, refer to Section 7.12.3 for fever management guidelines.

8.4.6. Electrocardiogram

12-lead electrocardiograms will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals; manual calculation of QTcF is permitted. Refer to Section 7.14 for QTcF withdrawal criteria and additional QTcF measurements that may be necessary. Refer to Time and Events Table 27 for details on ECG assessment time-points and requirements for triplicate or single ECG measurements.

8.4.7. Echocardiograms

Echocardiograms will be performed at baseline to assess cardiac ejection fraction and cardiac valve morphology for the purpose of study eligibility, as specified in the Time and Events Table 27. Additional ECHO assessments may be performed if clinically warranted. The evaluation of the echocardiography must include an evaluation for LVEF and both right and left-sided valvular lesions. MUGA can be used in lieu of ECHO (if not available) in the assessment of LVEF; the same modality should be used in any subsequent assessments.

Refer to Section 7.15 and Section 7.16 for withdrawal criteria and follow-up assessments in the event of LV dysfunction or valvular toxicity, respectively.

8.4.8. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 29 must be conducted in accordance with the Protocol Time and Events Schedule. Reference ranges for all safety parameters must be provided to the site by the laboratory responsible for the assessments.

Laboratory requisition forms must be completed and samples must be clearly labelled with the subject 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.

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

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

The study-required laboratory assessments indicated in Table 29 will be performed by a local laboratory unless otherwise indicated. The results of each test must be entered into the CRF.

Table 29 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
Cardiac Function	• Troponin I or Troponin T			
Thyroid Function	• Thyroid stimulating hormone • Free T4 • Free T3			
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 (as needed for women of childbearing potential)			

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

a. Required if local laboratory testing is available
b. Creatinine clearance is also required to be calculated using the formula provided in Appendix 10.
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.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment must be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

8.4.9. Patient Reported Outcomes

CCI [redacted]

8.5. Pharmacokinetics

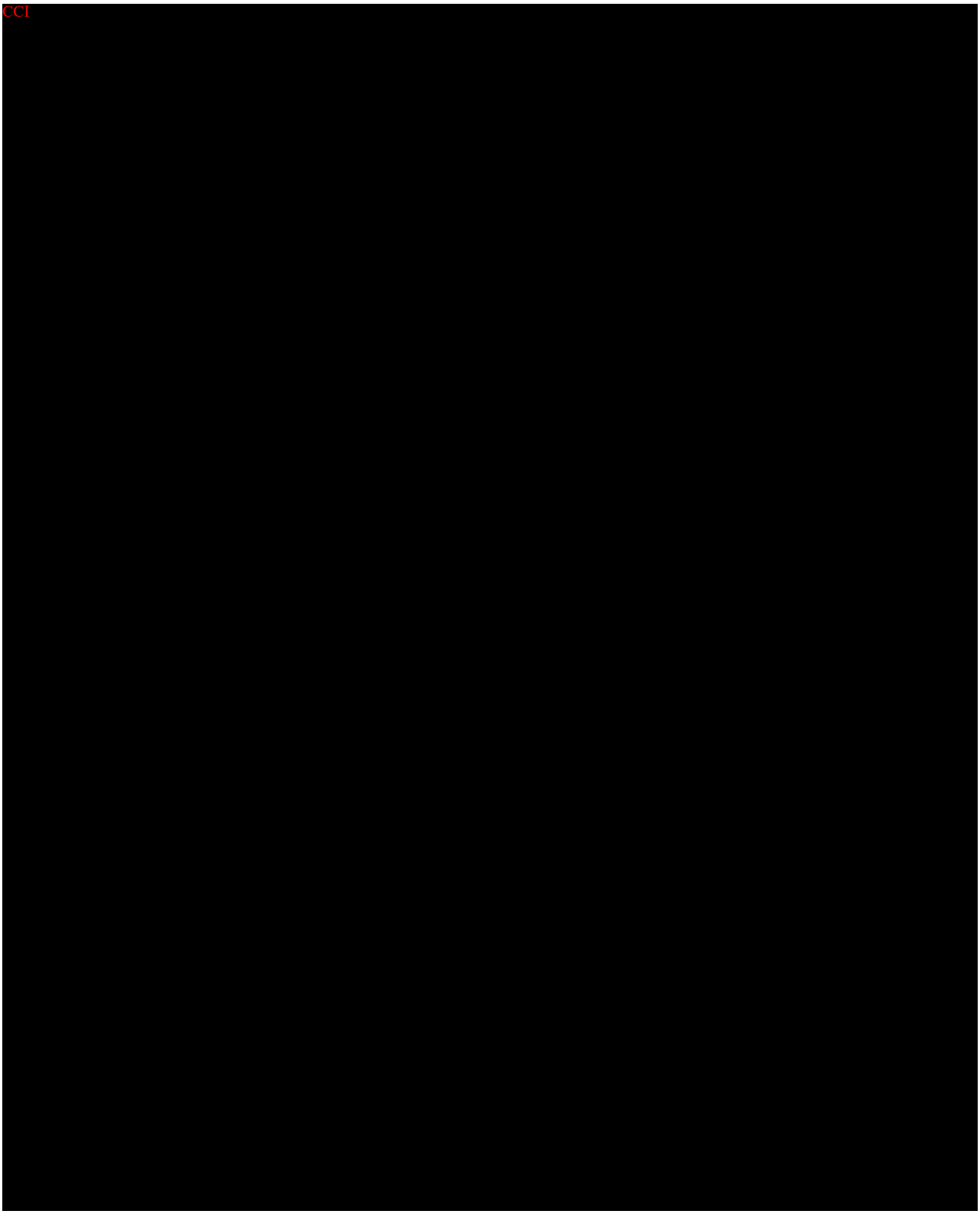
As per this amendment, these samples will no longer be collected.

8.6. Immunogenicity

As per this amendment, these samples will no longer be collected.

8.7. Biomarkers/Pharmacodynamic Markers

CCI



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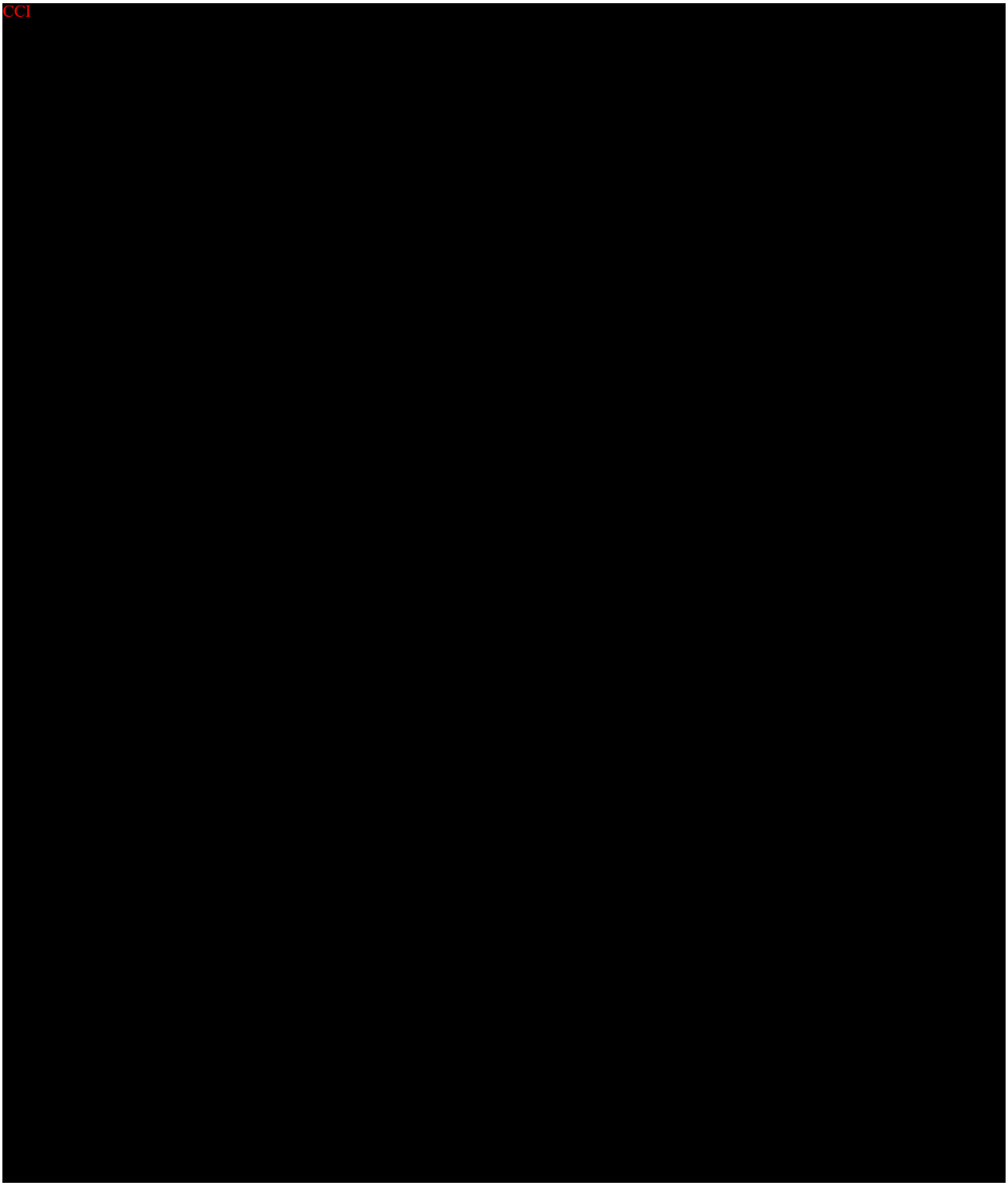

8.8. Genetics

Information regarding genetic research is included in Appendix 11.

9. DATA MANAGEMENT

- For this study, participant data will be entered into GSK defined eCRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- AEs and concomitant medications terms will be coded using MedDRA and an internal validated medication dictionary.
- eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Participant initials will not be collected or transmitted to GSK according to GSK policy.

10. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

10.1. Hypotheses

10.1.1. Part 1A and Part 2A Dose Escalation/Safety Run-in

In Part 1A and Part 2A, the primary aims are determining the recommended dose or doses for further exploration, the safety profile, and the pharmacology of GSK3359609 (feladilimab) monotherapy and in combination with pembrolizumab, chemotherapy (± pembrolizumab), or GSK3174998 in participants with advanced solid malignancies. Descriptive methods will be used in analyses of the data obtained from this study. No formal statistical hypotheses are being tested.

10.1.2. Part 1B GSK3359609 (feladilimab) Monotherapy Expansion/ Part 2B GSK3359609 (feladilimab) Combination with Pembrolizumab Expansion of PD-1/L1 Experienced Participants

The assumptions for the secondary endpoint of overall response rate (ORR) underlying the design are detailed below:

The null hypothesis for the secondary endpoint of ORR is:

H_0: p=10%.

The alternative hypothesis is:

H_A: p=30%.

In the Part 1B Biomarker Cohort, the null hypothesis for the difference in ORR of GSK3359609 (feladilimab) in the biomarker positive population (i.e., ICOS high) and biomarker negative population (i.e., ICOS low) is given below:

The null hypothesis is:

H0: $p_H - p_L \leq 0\%$

The alternative hypothesis is:

HA: $p_H - p_L > 0\%$,

where p_H represents ORR in the ICOS high population and p_L represents ORR in the ICOS low population.

10.1.3. Part 2B GSK3359609 (feladilimab) Combination with Pembrolizumab Expansion of PD-1/L1 Naïve Participants

For each cohort, the aim is to test the null hypothesis that the ORR for the combination is equal to the historical response rate of monotherapy pembrolizumab which is expected to be between 15% to 40% according to tumor types selected for the study. In the KEYNOTE-001 trial, the reported pembrolizumab monotherapy ORR was 19.4% in 495 NSCLC participants across different histologies and PD-L1 status [Garon, 2015].

Overall, the aim of each expansion cohort is to detect an improvement in the ORR of the combination therapy compared with pembrolizumab monotherapy in the range of 20% over the null, with power of at least 80% and no more than a 10% type 1 error rate.

- **PD-1/L1 naïve Expansion Cohorts (HNSCC, NSCLC PD-L1 <50%, Bladder/Urothelial and Viral-positive Cancers)**

The null hypothesis for ORR is:

H_0: p=20%

The alternative hypothesis is:
H_A:p=40%

- **PD-1/L1 Treatment-Naïve HNSCC PD-L1 CPS <1 Cohort**

The null hypothesis for proportion of participants with a change in PD-L1 CPS status from <1 to ≥1 is:

H_0: p=10%

The alternative hypothesis is:

H_A: p=40%

- **PD-1/L1 naïve Expansion Cohort (NSCLC PD-L1 ≥50% and MSI-H/dMMR Cancers)**

The null hypothesis for ORR is:

H_0: p=30%

The alternative hypothesis is:

HA: p=50%

10.2. Dose Escalation

10.2.1. Modified Toxicity Probability Interval (mTPI)

Safety and tolerability of GSK3359609 (feladilimab) administered alone and in combination with a 200-mg fixed dose of pembrolizumab or chemotherapy (± pembrolizumab) will be evaluated using an adaptive mTPI approach. The mTPI design is an extension of the toxicity probability interval method and employs a simple beta-binomial hierarchic model [Ji, 2010]. Decision rules are based on calculating the unit probability mass (UPM) of three intervals corresponding to under dosing, proper dosing, and overdosing in terms of toxicity. Specifically, the under-dosing interval is defined as $(0, p_T - \varepsilon_1)$, the overdosing interval as $(p_T + \varepsilon_2, 1)$, and the proper dosing interval as $(p_T - \varepsilon_1, p_T + \varepsilon_2)$, where ε_1 and ε_2 are small fractions, such as 0.05, to account for the uncertainty around the true target toxicity. A sensitivity analysis showed that the mTPI design is robust to the specification of ε values [Ji, 2010]. In addition, ε_1 and ε_2 could take different values to reflect physician preference and the nature of the disease. For advanced diseases with few treatment options, higher toxicity rates might be considered acceptable, implying a specification of $\varepsilon_2 > \varepsilon_1$. For less-advanced diseases, the two ε values could be identical or $\varepsilon_1 > \varepsilon_2$. The three dosing intervals are associated with three different dose-escalation decisions. The under-dosing interval corresponds to a dose escalation (E), overdosing corresponds to a dose de-escalation (D), and proper dosing corresponds to staying at the current dose (S). Given an interval and a probability distribution, the UPM of that interval is defined as the probability of the interval divided by the length of the interval. The mTPI design calculates the UPMs for the three dosing intervals, and the one with the largest UPM implies the corresponding dose-finding decision. That decision provides the dose level to be used for future participants. For example, if the under-dosing interval has the largest UPM, decision E, to escalate, will be executed, and the next cohort of participants will be treated at the next higher dose level. Analyses showed that the decision based on the UPM is optimal in that it minimized a subsequent expected loss [Ji, 2010]. Under the mTPI design, a trial is terminated when either the lowest dose is above the MTD or a pre-specified maximum sample size is reached.

10.2.2. 2D-CRM

Dose escalation of GSK3359609 (feladilimab) in combination with GSK3174998 will be guided by the 2D-CRM method with a 5-parameter logistic model [Neuenschwander, 2014]. This model will estimate the probability of observing a DLT at each dose combination in the study as DLT information becomes available.

Let p_{1i} and p_{2j} denote the single-agent DLT rate of treatment 1 at dose d_{1i} $(i = 1,\ldots, I)$ and treatment 2 at dose at dose d_{2j} $(j = 1,\ldots, J)$, respectively, where I and J represent the total number of dose levels for treatment 1 and 2. Similarly, let p_{ij} present the DLT rate for treatment 1 at dose d_{1i} in combination with treatment 2 at dose d_{2j}. The 5-parameter logistic model composes of three components, including two independent single-agent logistic model

$$ln\left(\frac{p_{1i}}{1-p_{1i}}\right) = ln(\alpha_1) + \beta_1 ln\left(\frac{d_{1i}}{d_1^*}\right),$$

$$ln\left(\frac{p_{2j}}{1-p_{2j}}\right) = ln(\alpha_2) + \beta_2 ln\left(\frac{d_{2j}}{d_2^*}\right),$$

and a model introducing the interaction coefficient e^{η} in the overall odds of the DLT rate,

$$ln\left(\frac{p_{ij}}{1-p_{ij}}\right) = \eta\left(\frac{d_{1i}}{d_1^*}\right)\left(\frac{d_{2j}}{d_2^*}\right) + ln\left(\frac{1-(1-p_{1i})(1-p_{2j})}{(1-p_{1i})(1-p_{2j})}\right),$$

where $ln(\cdot)$ is the natural logarithm, d_1^* and d_2^* are the reference dose for treatment 1 and treatment 2.

The 2D-CRM model implementation will be performed using the Fixed and Adaptive Clinical Trial Simulator (FACTS) (Version 6.1 or higher) software from Tessella.

10.3. Dose Expansion

The expansion phases of GSK3359609 (feladilimab) alone and in combination with pembrolizumab are designed to evaluate preliminary clinical activity. Futility assessments will be conducted (in select cohorts) to evaluate accumulating data including safety, responses, PK and pharmacodynamics. The methodology is based on the predictive probability of success if enrollment continues until all planned participants are recruited [Lee, 2008].

In the expansion cohorts, after a minimum of 10 participants have been enrolled in one dose/dose level in a cohort, the number of observed responses as well as other available date will be used for futility analysis according to the rules summarized in Section 10.6.

CCI [redacted]

10.4. Sample Size Considerations

10.4.1. Sample Size Assumptions

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

10.4.2. Dose Escalation

Approximately 166 participants are planned to be enrolled in Parts 1A and 2A. The actual total number of participants to be enrolled into Part 1A and Part 2A will depend on the number of dose escalations required to establish the MTD/MAD of GSK3359609

(feladilimab) alone or in combination with pembrolizumab, chemotherapy (± pembrolizumab), and GSK3174998.

To complete dose escalation/safety run-ins in Part 1A and Part 2A GSK3359609 (feladilimab) in combination with pembrolizumab, or chemotherapy (±pembrolizumab) (refer to Figure 1), it is estimated that approximately 131 participants will be enrolled. Doses of GSK3359609 (feladilimab) to be studied in Part 1A and Part 2A GSK3359609 (feladilimab) in combination with pembrolizumab or chemotherapy (±pembrolizumab) will be guided by the mTPI design. Doses of GSK3359609 (feladilimab) in combination with GSK3174998 will be guided by the 2D-CRM design (see Section 4.1.1).

Dose combinations of GSK3359609 (feladilimab) in combination with GSK3174998 will be guided by the 2D-CRM design. It is estimated that approximately 35 participants will be enrolled in Part 2A GSK3359609 (feladilimab) in combination with GSK3174998, including approximately 25 participants completing the DLT evaluation period and an additional ~10 participants enrolled at RP2D of GSK3359609 (feladilimab) in combination with GSK3174998 for further exploration.

Details of the scenarios are provided in Table 30. The dose combinations in the table are the pre-selected dose combinations that are projected to be used in the trial. The actual doses combinations used during the conduct of the trial may be different.

For the 2D-CRM simulations, the selected reference dose was 80 mg for GSK3359609 (feladilimab) and 24 mg for GSK3174998. The prior distributions of each pair of single-agent parameters $(ln(\alpha), ln(\beta))^T$ and the interaction log-odds multiplier η as well as the prior DLT information described in Section 4.1.1.3.3 were used. The simulation results for dose selection under various scenarios are shown in Table 30. Note that GSK3359609 (feladilimab) in combination with GSK3174998 assumes the single run-in participant experiences neither DLT nor drug-related ≥ Grade 2 AE in the DLT observation period (i.e. 0/1 in the (8 mg, 8 mg) dose combination).

Table 30 Results Under Various Scenarios: GSK3359609 (feladilimab) in Combination with GSK3174998 (2DCRM method

GSK3359609 (feladilimab) (mg)	GSK3174998 (mg)	Scenario 1: Low Toxicity		Scenario 2: Moderate Toxicity		Scenario 3: High 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	8	0	0.0	0	0.0	0.05	0.0
8	24	0.01	0.0	0.05	0.0	0.1	0.0
24	24	0.02	0.1	0.1	14.3	0.25	61.1
80	24	0.05	37.9	0.25	82.2	0.45	38.7
80	80	0.1	62.0	0.4	3.5	0.55	0.2

Note: For each scenario, entries are shaded for optimal choice of dose combination; i.e., a dose with a DLT rate in the target toxicity interval [0.16, 0.33) or the highest dose when all dose combinations are under-dosing.

10.4.3. Dose Expansion

Approximately 641 participants will be enrolled in Parts 1B and 2B, including approximately 52 participants in Part 1B PK/PD, an average of 210 participants in the Part 1B non-PK/PD expansion cohorts (to include 60 participants in the ICOS biomarker cohort), and an average of 379 participants in the Part 2B expansion cohorts. In the expansion phases of Part 1 and Part 2, the sample size of a cohort or cohorts may target approximately 30 participants per cohort. The condition by which the sample size will increase depends on the outcome from interim analysis of the null/alternative hypotheses that was determined for a tumor type.

For each tumor indication expansion cohort, an interim analysis will be conducted after efficacy data at any dose level are available on a minimum of participants (refer to Section 10.6); a separate decision will be made for each disease cohort and dose. The trial may continue to enroll the maximum planned sample size to provide a better estimate on the distribution of the response rate in the different doses and target populations.

The trial is not designed to stop early for efficacy but is designed to assess futility if the predictive probability of success is 10% or less. The type I error rate, power, and predictive probability for assessing futility were determined from stating the minimum and maximum sample size, futility stopping rate, and the optimizing criterion as minimizing the sample size under null hypothesis. A very weak informative prior distribution with a mean response rate equal to the target response rate is assumed. Thus,

the predictive probability for the response rate will be primarily driven by the data. The detailed decision criteria for all cohorts are documented in Section 10.6.

For monotherapy therapy expansion cohorts and any PD-1/L1 experienced combination therapy expansion cohorts starting with 10 participants in each cohort and allowing for a maximum sample size of 30 for each cohort, this design will have an overall type I error rate (α) 5%. Under null hypotheses with 10% ORR, the expected sample size of the design is 15 participants per cohort; and probability of early termination (PET) is 35% by 10 participants evaluated and 80% by 20 participants evaluated. Under the alternative hypothesis, if the true response rate is 30%, the probability of success is 83%; the expected sample size of the design is 28 participants in total and PET is 3% by 10 participants and 13% by 20 participants.

For the PD-1/L1 naïve combination expansion cohorts including HNSCC, NSCLC with PD-L1 <50%, bladder/urothelial cancer, cervical, and viral-positive cancers, starting with 10 participants in each cohort and allowing for a maximum sample size of 30 for each cohort, this design will have an overall type I error rate (α) 9.8%. Under null hypotheses with 20% ORR, the expected sample size of the design is 16 participants per cohort; and probability of early termination (PET) is 38% by 10 participants evaluated and 72% by 20 participants evaluated. Under the alternative hypothesis, if the true response rate is 40%, the probability of success is 83%; the expected sample size of the design is 28 participants in total and PET is 5% by 10 participants evaluated and 12% by 20 participants evaluated.

For the HNSCC PD-l/L1 treatment naïve pembrolizumab combination expansion cohort with PD-L1 CPS <1, a sample size of 30 participants will have at least 90% power to detect a difference (P1-P0) of 30% or 40% for the test of hypothesis in the proportion of participants with a change in PD-L1 status from CPS <1 to CPS ≥1 with an overall type I error rate (α) of 2.5% (Refer to Table 31). Assuming a null proportion (P0) of 10% in the number of participants with a change in PD-L1 CPS status, a minimum of 8 participants must be observed to conclude a proportion increase of 30% or 40%.

Table 31 Sample Size and Power Analysis for HNSCC PD-L1 CPS <1 Cohort

Null proportion (P0)	Alternative proportion (P1)	Effect Size (H1-H0)	Power (%)	Minimum # of Converting Participants Needed for Concluding an Effect
0.1	0.4	0.3	95.7	8
0.1	0.5	0.4	99.7	8

In the combined biomarker cohort, a total sample size of 93, which is comprised of 33 participants from the Part 1B melanoma randomized cohort (with known biomarker

groups of 7 ICOS high and 26 ICOS low) and 60 participants from the biomarker cohort (to target approximately 20 ICOS high participants 40 ICOS low participants under a 30% prevalence rate assumption) is sufficient to detect a clinically important difference of 15% between groups in overall response rate (ORR) using a one-tailed z-test of proportions between two groups with 62% power and 10% level of significance. The 15% difference represents a 25% overall response rate in ICOS high participants and a 10% response rate in ICOS low participants.

Sample Size Sensitivity

For the PD-1/L1 naïve combination expansion cohorts including NSCLC with PD-L1≥50% and MSI-H/dMMR cancers, starting with 10 participants in each cohort and allowing for a maximum sample size of 30 for each cohort, this design will have an overall type I error rate (α) 7.9%. Under null hypotheses with 30% ORR, the expected sample size of the design is 19 participants per cohort; and probability of early termination (PET) is 15% by 10 participants evaluated and 55% by 20 participants evaluated. Under the alternative hypothesis, if the true response rate is 50%, the probability of success is 80%; the expected sample size of the design is 29 participants in total and PET is 1.0% by 10 participants evaluated and 6.2% by 20 participants evaluated.

Randomized Expansion Cohorts

In the Part 1B and Part 2B melanoma cohorts, participants will be randomly assigned to a GSK3359609 (feladilimab) dose level of 0.3 mg/kg or 1.0 mg/kg in combination with 200 mg of pembrolizumab in a 1:1 allocation ratio with approximately 10 participants per dose level. In the Part 2B HNSCC randomization cohort, PD-1/L1 Naive participants will be randomly assigned to a GSK3359609 (feladilimab) dose level of 0.1 mg/kg or 1 mg/kg or 3.0 mg/kg in combination with 200 mg of pembrolizumab in a 1:1:1 ratio. The Part 2B HNSCC randomization cohort may target approximately 20 participants per dose level. As in the Part 2B HNSCC randomized cohorts, the Part 2B HNSCC Q6W Cohort (Schedule Optimization Cohort) will enroll participants with PD-1/L1 treatment naive HNSCC. Participants will be assigned to one dose level of GSK3359609 (feladilimab) dosed Q6W in combination with pembrolizumab 400 mg dosed Q6W. Participants will be randomized to a GSK3359609 (feladilimab) fixed dose level of 48 mg Q6W or 160 mg Q6W in combination with pembrolizumab 400 mg in a 1:1 ratio. Similar to the HNSCC dose-randomized cohorts, the Part 2B HNSCC Q6W cohort may target approximately 20 participants per dose level and based on interim analysis, a dose level may be dropped or randomization ratio changed.

The melanoma randomization cohorts and the HNSCC randomization cohort are designed to provide supportive data for the dose selection, primarily on the basis of antitumor activity, tolerability, safety and PK/PD measures. It is not designed to evaluate formal statistical hypotheses. The dose/exposure response relationship may be explored further in the HNSCC population.

Assuming an ORR of 30% at 0.3 mg/kg and 45% at 1 mg/kg in melanoma randomization cohorts, the sample size of ~10 participants per melanoma randomized arm provides a probability of 68.3% that a dosage regimen with truly poorer ORR will not be selected

for further investigation. For the sample size justification purpose, it is assumed that the dose regimen with the larger test statistic compared with a 10% ORR in the historical control will be selected in melanoma cohorts.

Assuming an ORR of 16% at 0.1 mg/kg, 30% at 0.3 mg/kg with 30 participants, 30% at 1 mg/kg and 3 mg/kg in the HNSCC randomization cohort, the sample size of ~20 participants at randomized arm dose levels provides a probability of 98% that a dosage regimen(s) with truly poorer ORR will not be selected for further investigation in HNSCC. For the sample size justification purpose, it is assumed that the dose regimen with the largest test statistic compared with a 16% ORR in the historical control will be selected in the HNSCC cohort.

Interim analyses may be performed with at least ~15 participants evaluable for ORR, PK or PD at HNSCC randomized dose levels to estimate the dose response relationship and to ensure that a dosage regimen with truly poorest ORR will not be selected for further investigation. A sample size of 15 participants across HNSCC randomized dose levels provides a probability of 97% that a dosage regimen with truly poorer ORR will not be selected in the case of true ORR of (16%, 30%, 30%, 30%) at dose levels (0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg); please refer to Section 10.4.4 for details. Based on the interim analysis, a dose level in the HNSCC randomized cohort may be dropped and/or the randomization ratio may be changed.

For the Schedule Optimization Cohort (Part 2B HNSCC Q6W), an equivalence test method was used for comparing the AUC under the Q3W and Q6W dosing schedule, where dose 24 mg (Q3W) is compared to dose 48 mg (Q6W) and dose 80 mg (Q3W) is compared to dose 160 mg (Q6W). Absence of effect of Q6W on the PK of study compound (GSK3359609 (feladilimab) 48 mg/160mg) in combination with pembrolizumab (200 mg Q3W or Q6W) will be concluded if the 90% confidence intervals for the ratios of geometric means, under Q3W and Q6W, are contained within the equivalence interval from 80% to 125% for AUC of the study compound in combination with pembrolizumab. If Q6W has no effect on the PK of study compound in combination with pembrolizumab (vs. Q3W), data from 20 participants will provide at least 90% power with respect to AUC of study compound in combination with pembrolizumab, to conclude that Q6W has no effect on the PK. These calculations use the approach that assumes the log(AUC) of study compound in combination with pembrolizumab are normally distributed with intra-participant coefficients of variation (CV) equal to 50%, as estimated from historical data (CV for AUC under Q3W), and that the no-effect level is defined as 80% to 125% [Hauschke, 1992].

The average sample size in Part 1B is approximately 223 participants in all cohorts under the null hypothesis, including approximately 52 participants in the PK/PD cohort, approximately 20 participants in the randomized cohort, and approximately 151 participants in non-randomized cohorts (to include approximately 60 participants in the biomarker cohort).

The average sample size in Part 2B is 343 in all cohorts under the null hypothesis, including 75 participants in 5 non-randomized PD-1/L1 experienced cohorts, 118

participants in 7 non-randomized PD-1/L1 naïve cohorts, 30 participants in HNSCC CPS<1 cohorts, and 120 participants in randomized cohorts. Similarly, the average sample size in Part 1B is 190 participants if two cohorts (non-biomarker) are under the alternative hypothesis and the biomarker cohort is under the alternative hypothesis. The average sample size in Part 2B is 379 participants if three PD-1/L1 naïve cohorts out of HNSCC, NSCLC with PD-L1<50%, bladder/urothelial cancer, cervical, and viral-positive cancers are under the alternative hypothesis. Note that average sample size under the null and alternative hypothesis is only defined for those cohorts assessing the predictive probability of success (i.e. futility); refer to Section 10.6. All other cohorts use the planned (maximum) sample size.

10.4.4. Sample Size Sensitivity

Table 32 shows the probability of not selecting a dosage regimen(s) with truly worst ORR in the HNSCC cohort based on 10,000 simulations. The calculations are based on the following assumptions:

- An allocation ratio of 1:1:1 among randomized dosage regimens 0.1 mg/kg, 1 mg/kg, 3 mg/kg
- The dosage regimen 0.3 mg/kg has 30 participants.
- The dose regimen with the largest test statistic will be selected in the HNSCC cohort; the test statistics are calculated based on the exact test of the superiority over a 16% historical ORR.

Table 32 Sample Size Sensitivity in the HNSCC Randomized Cohort

ORR at (0.1, 0.3, 1, 3) mg/kg*	Sample Size per randomized arm	Prob(Identify a dose with truly best ORR)
(16%, 30%, 30%, 30%)	5	97.0%
	10	98.8%
	20	98.0%
	30	98.2%
(16%, 30%, 30%, 16%)	5	94.6%
	10	97.9%
	20	96.0%
	30	96.6%
(16%, 30%, 45%, 45%)	5	63.0%
	10	74.2%
	20	98.3%
	30	99.5%

* The dose level of 0.3 mg/kg is not a randomized HNSCC dosage regimen and it is estimated that ~30 participants will be enrolled.

10.4.5. Sample Size Re-estimation or Adjustment

Sample size re-estimation is not planned for this study.

10.5. Data Analysis Considerations

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

In the dose escalation cohorts, the dose will be escalated based on all available data, including pharmacodynamic and PK data and the safety profile of prior cohorts. The DLT information on all participants enrolled in the trial are used to update the estimated dose-toxicity relationship and provide supportive information in addition to the inference stemming from the adaptive dose finding design in the next escalation/de-escalation decision.

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

10.5.1. Analysis Populations

All Treated Population: defined as all participants who receive at least one dose of GSK3359609 (feladilimab). Safety and anti-cancer activity will be evaluated based on this analysis population.

Pharmacokinetic Population: defined as all participants from the All Treated Population for whom a PK sample is obtained and analyzed.

Pharmacodynamic Population: defined as participants in the All Treated Participants Population for whom pre- and on-treatment paired and evaluable tumor biopsies or pre- and on-treatment blood samples were obtained and analyzed for biomarkers.

Additional analysis populations may be defined in the RAP.

10.6. Interim Analysis

No formal interim analyses will be performed using the data generated during the dose escalation phases of the study. Available safety and PK/pharmacodynamic data will be reviewed after completion of each dose level, refer to Section 4.1.1 for further details. This review will support the decision to escalate to the dose level using the rules as described in Section 4.1.1 and Section 10.2. The Steering Committee will guide the transition of the study from dose escalation to cohort expansion for both monotherapy and combination therapy, refer to Section 4.1.1.5 for further details. Analyses may be performed at the end of dose escalation to support choice of the RP2D.

For dose expansion cohorts, continuous assessment of efficacy and safety will be performed after first interim analysis based upon a minimum of 10 participants in at least one of the expansion cohort with available unconfirmed overall response data.

Presented in Table 33, Table 34, and Table 35 are the futility interim analysis decision rules for the 10th to 30th evaluable participants by specifying the number of participants with an unconfirmed ORR for continuing enrollment or stopping for futility when total sample size is up to 30. Additional futility looks may be performed, if necessary. These rules are intended as a guideline only; the basis of the rules for the Part 2B pembrolizumab combination was guided by the response rates reported in pembrolizumab approved product label [KEYTRUDA FDA Pharmacology Toxicology Review, 2014; KEYTRUDA SPC, 2017].

For MSI high or virally mediated cohorts, the assumption and futility assessment may be updated based on emerging information. Participants enrolled in Part 1B and Part 2B will be stratified by prior PD-1/L1 treatment history (i.e., naïve or experienced; best response). The details of these subgroups will be presented in the reporting and analysis plan (RAP).

Actual decisions will depend on the totality of the data and any emerging pembrolizumab clinical trial data. Any additional decision rules will be documented in RAP before the interim analysis. Should the recommendation to stop for futility be disregarded in favor of a decision to continue the trial based on the totality of the data, the overall type I error rate of the expansion phase will be inflated.

Table 33 Futility Boundary for Monotherapy Expansion Cohorts and PD-1/L1 Experienced Pembrolizumab Combination Therapy Expansion Cohorts

Number of Participants[a]	Number of Responders					
	0	1	2	3	4	5
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						

Number of Participants[a]	Number of Responders					
	0	1	2	3	4	5
29						
30						

a. Shaded regions indicate enrollment pause based on meeting futility

Table 34 Futility Boundary for PD-1/L1 Naïve Pembrolizumab Combination Therapy Expansion Cohorts (HNSCC, NSCLC PD-L1 <50%, Bladder/Urothelial Cancer and Viral-positive Cancer)

Number of Participants[a]	Number of Responders							
	1	2	3	4	5	6	7	8
10								
11								
12								
13								
14								
15								
16								
17								
18								
19								
20								
21								
22								
23								
24								
25								
26								
27								
28								
29								
30								

a. Shaded regions indicate enrollment pause based on meeting futility

Table 35 Futility Boundary for PD-1/L1 Naïve Pembrolizumab Combination Therapy Expansion Cohort (NSCLC with PD-L1≥50% and MSI-H/ dMMR Cancers)

Number of Participants[a]	Number of Responders											
	1	2	3	4	5	6	7	8	9	10	11	12
10												
11												
12												
13												

Number of Participants[a]	Number of Responders											
	1	2	3	4	5	6	7	8	9	10	11	12
14												
15												
16												
17												
18												
19												
20												
21												
22												
23												
24												
25												
26												
27												
28												
29												
30												

a. Shaded regions indicate enrollment pause based on meeting futility

The mTPI or 2D-CRM recommended dose-escalation levels, futility assessment rules, and posterior probabilities are only guidelines and the totality of the data across all tumor types will be considered by the team in decision making.

Interim analyses of the HNSCC cohort may be performed with at least ~15 participants evaluable for ORR, PK or PD at HNSCC randomized dose levels to provide supportive data for the dose selection. Dose/Exposure response relationship may be explored.

10.7. Key Elements of the Analysis Plan

10.7.1. Primary Analyses

As the primary endpoints of Part 1A/B and Part 2A/B include safety and tolerability, the primary analyses will be descriptive in nature.

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

10.7.1.1. Safety Analyses

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

10.7.1.2. Extent of Exposure

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

10.7.1.3. Adverse Events

AEs will be coded using the standard MedDRA and grouped by system organ class. AEs will be graded by the investigator according to the NCI-CTCAE v4 [NCI, 2010].

Events will be summarized by frequency and proportion of total participants, by system organ class and preferred term. Separate summaries will be given for all AEs, treatment-related AEs, SAEs, and AEs leading to discontinuation of study treatment. AEs, if listed in the NCI-CTCAE v 4 [NCI, 2010], will be summarized by the maximum severity Grade. Otherwise, the AEs will be summarized by maximum intensity.

DLTs will be listed for each participant and summarized by dose cohort.

AEs of special interest will be outlined in the RAP.

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

10.7.1.4. Clinical Laboratory Evaluations

Clinical laboratory testing data will be summarized using frequencies and proportions according to NCI-CTCAE v4 [NCI, 2010]. Laboratory test results outside the reference ranges that do not have an associated NCI-CTCAE criterion will be summarized using proportions. Further details will be provided in the RAP.

10.7.2. Secondary Analyses

A key aim of Part 1B and Part 2B is to demonstrate clinically meaningful response rates in each of the disease cohorts using Bayesian-based independent tumor type modeling or hierarchical modeling, as described in Section 10.3 [Berry, 2013].

10.7.2.1. Clinical Activity

irRECIST is the primary measure of clinical activity for response endpoints; RECISTv1.1 guidelines are used for disease assessments and PFS. The number and types of responses, as outlined in RECIST 1.1 and irRECIST will be listed and summarized separately, as appropriate.

ORR is defined as the percentage of participants with a best overall confirmed CR or a PR at any time as per disease-specific criteria (refer to Section 8.3.1 and Appendix 6). Disease control rate (DCR) is defined as the percentage of participants with a confirmed CR+ PR at any time, plus SD ≥18 weeks allowing for a one-week window per Table 27, participants with unknown or missing response will be treated as non-responders that is these participants will be included in the denominator when calculating the percentage of ORR and DCR. Exact methods for calculated confidence intervals will be given in the RAP.

Duration of response (DOR) will be summarized for participants with a confirmed CR or PR and is defined as the time from date of initial confirmed response to the date of disease progression or death due to any cause. Censoring rules will follow those of the PFS analysis. Time to overall response (TTR) will be summarized for participants with a confirmed CR or PR and is defined as the time from date of first dose of study treatment to date of first documented confirmed CR or PR. DOR and TTR will be summarized using descriptive statistics if data permit.

PFS is defined as time from the date of first dose of study treatment to the date of disease progression according to clinical or radiographic assessment or death due to any cause, whichever occurs earliest. For the analysis of PFS, if the participant received subsequent anti-cancer therapy prior to the date of documented events, PFS will be censored at the last adequate assessment (e.g. assessment where visit level response is CR, PR, or stable disease [SD]) prior to the initiation of therapy. Progressive disease (PD) will also be defined per standard criteria. Otherwise, if the participant does not have a documented date of events, PFS will be censored at the date of the last adequate assessment. Further details on rules for censoring will be provided in the RAP.

OS is defined as time from the date of first dose of study treatment to the date of death due to any cause. If a participant does not have a documented date of death, time of death will be censored at the date of last contact.

PFS and OS may be summarized using Kaplan-Meier methods if data permit.

In the dose escalation phases, best overall response may be evaluated to explore preliminary antitumor activity.

In addition, participants enrolled in the dose escalation and the PK/PD cohorts with the same tumor histology/characteristic, prior PD-1/L1 treatment history and treated with the same dose regimen may be included in the assessment of futility and final efficacy analysis in the expansion cohorts.

Further details on analysis of clinical activity will be provided in the RAP.

10.7.3. Pharmacokinetic Analyses

CCI

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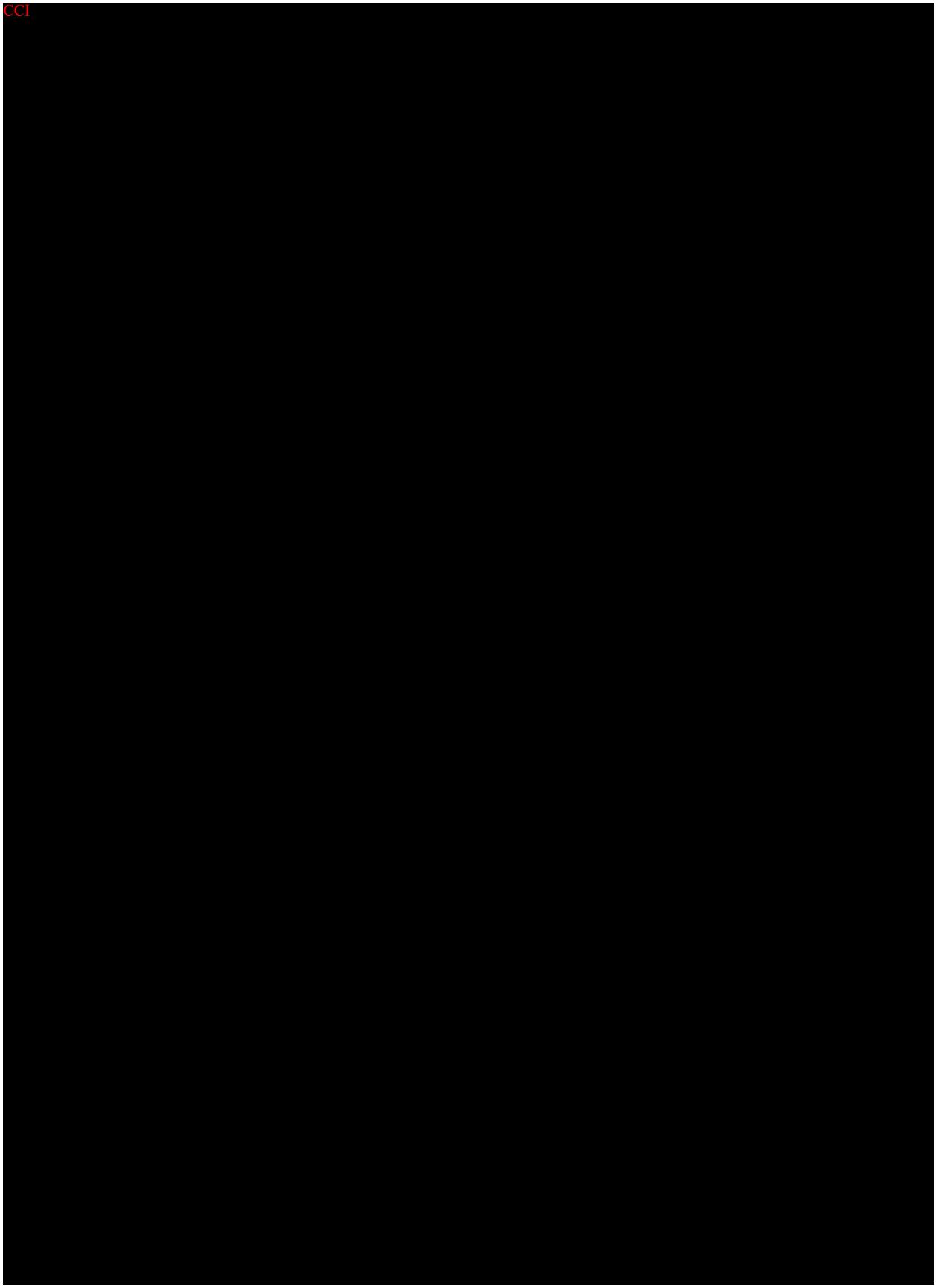

10.7.5. Immunogenicity

Serum samples will be collected and tested for the presence of antibodies that bind to GSK3359609 (feladilimab) (Part 1 and 2), pembrolizumab, (Part 2 only), GSK3174998 (Part 2 only), refer to Table 28. These samples may also be tested for presence of antibodies that bind to Chinese Hamster Ovary (CHO) host cell proteins such as phospholipase B- like 2 (PLBL2). Immunogenicity testing will occur in dosed participants then analyzed, summarized descriptively and/or presented graphically. The cumulative incidence of ADA, i.e. % of participants that develop ADA, magnitude of the response (titers), and duration of the ADA response (transient vs. persistent) may be reported. Data permitting, impact of ADA on safety, efficacy, or PK/PD relationships may be considered.

10.7.6. Other Analyses

10.7.6.1. Translational Research Analysis

CCI [redacted]

The results of translational research investigations may be reported separately from the main clinical study report or as an amendment. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. Further details on the translational research analyses will be addressed in the RAP.

10.7.6.2. Tumor Kinetic Analysis

CCI [redacted]

10.7.6.3. Patient Reported Outcome

CCI [redacted] Refer to the RAP for further details.

11. STUDY GOVERNANCE CONSIDERATIONS

11.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

Prior to initiation of a site, GSK will obtain favorable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

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

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

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

11.3. Quality Assurance

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

11.4. Study and Site Closure

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

11.5. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any

institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.

- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

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

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

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

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

11.7. Steering Committee

A Steering Committee will be established to review safety, PK, and other clinical data during the course of the study to provide an objective interpretation of study results and guidance for key decisions. The remit of the Steering Committee will include but not be limited to guidance for the transition of the study from dose escalation to cohort expansion, the initial starting dose of GSK3359609 (feladilimab) for each combination evaluated in Part 2A, the dose of the combination partner if not standard of care, the dose escalation design to implement in Part 2A, the selection of specific tumor types or features to include in the expansion cohorts, and the selection of the RP2D. In the final determination of the MTD and RP2D, all available safety and tolerability data will be considered. Pending review of emerging data from this study and under the guidance of the Steering Committee, the protocol may be subsequently amended to include investigation of additional immune therapy combinations with GSK3359609 (feladilimab). The remit, membership, roles and responsibilities of the Steering Committee are described in a Steering Committee Charter.

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13. APPENDICES

13.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

2D-CRM	Two-Dimensional Continual Reassessment Method
ADA	Anti-drug antibodies
AE	Adverse Event
AESI	Adverse Events of Special Interest
AKT	v-AKT Murine Thymoma Viral Oncogene
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC(0-t)	Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration)
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
β-hCG	Beta-human chorionic gonadotropin
BAL	Bronchoalveolar Lavage
cfDNA	cell-free DNA
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	Maximum observed concentration
Ctau	Minimum Observed Concentration;
CNS	Central Nervous System
CR	Complete Response
CRC	Colorectal Cancer
CrCl	Creatinine Clearance
CRP	C Reactive Protein
CRS	Cytokine Release Syndrome
CT	Computed Tomography
CTC-AE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein 4
CV	Cardiovascular
DCR	Disease Control Rate
DILI	Drug-induced Liver Injury
DLT	Dose Limiting Toxicity
dMMR	Deficient mismatch repair
DNA	Deoxyribonucleic Acid
DoR	Duration of Response
EC	Effective Concentration
ECHO	Echocardiography
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group

CCI [redacted]

FDA	Food and Drug Administration
eCRF	Electronic Case Report Form
G-CSF	Granulocyte Colony-stimulating Factor
GCP	Good Clinical Practice
GSK3β	Glycogen Synthase Kinase-3 beta
GSK	GlaxoSmithKline
Fc	Fragment Crystallizable
FcγR	FC-gamma Receptor
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FTIH	First-time-in-human
HNSCC	Head and Neck Squamous Cell Carcinoma/Cancer
HPV	Human Papilloma Virus
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICOS	Inducible T Cell Co-Stimulator
IHC	Immunohistochemistry
IL	Interleukin
IFNγ	Interferon, gamma
Ig	Immunoglobulin
IEC	Independent Ethics Committees
INR	International Normalized Ratio
irAE	Immune-related Adverse Event
IRB	Institutional Review Board
IRR	Infusion-related Reactions
irRECIST	Immune-related RECIST
IV	Intravenous
Kg	Kilogram(s)
LVEF	Left Ventricular Ejection Fraction
mAb	Monoclonal Antibody
MABEL	Minimum Anticipated Biological Effect Level
MAD	Maximum Administered Dose
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram(s)
Mg	Milligram(s)
mmHg	Millimeters of Mercury
mL	Milliliter(s)
MPM	Malignant Pleural Mesothelioma
MRI	Magnetic Resonance Imaging
MSDS	Material Safety Data Sheet

MSEC	Millisecond(s)
MSI-H	Microsatellite Instability-High
MTD	Maximum Tolerated Dose
mTPI	Modified Toxicity Probability Interval
MUGA	Multigated Acquisition Scan
NCI-CTCAE	National Cancer Institute - Common Toxicity Criteria for Adverse Events
NK	Natural Killer
nM	Nanomolar(s)
NOAEL	No Observed Adverse Effect Level
NSCLC	Non-small-cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive Disease
PD-1	Programmed Death Receptor Protein 1
PD-L	PD Ligand
PFS	Progression-free Survival
PI	Principal Investigators
PI3K	Phosphatidylinositol 3-kinase
PK	Pharmacokinetics
PR	Partial Response
CCI [redacted]	
PS	Performance Status
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
QTc	Corrected QT interval duration, corrected
RANKL	Receptor Activator of Nuclear Factor-kappa B Ligand
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
CCI [redacted]	
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SD	Stable Disease
SRM	Study Reference Manual
STING	Stimulator of interferon genes
TCR	T Cell Receptor
TDV	Treatment Discontinuation Visit
TIL	Tumor Infiltrating Lymphocytes
TNFα	Tumor Necrosis Factor, alpha
TGFβ	Tumor Growth Factor, beta
Treg	T Regulatory Cells
TSH	Thyroid Stimulating Hormone
TTR	Time to Response

ULN	Upper Limit of Normal
UPM	Unit Probability Mass
WNL	With Normal Limits

Trademark Information

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13.2. Appendix 2: Immune-related Diseases

Table 36 Potential Immune-mediated Diseases

Neuroinflammatory disorders	**Musculoskeletal disorders**	**Skin disorders**
• Cranial nerve disorders, including paralyses/paresis (e.g. Bell's palsy) • Optic neuritis • Multiple sclerosis • Transverse myelitis • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants • Acute disseminated encephalomyelitis, including site specific variants: e.g. non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome • Immune-mediated peripheral neuropathies and plexopathies, (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy). • Narcolepsy	• Systemic lupus erythematosus and *associated conditions* • *Systemic* Scleroderma *(Systemic sclerosis)*, including diffuse systemic form and CREST syndrome • *Idiopathic inflammatory myopathies, including* Dermatomyositis, Polymyositis, • Antisynthetase syndrome • Rheumatoid arthritis *and associated conditions including* Juvenile chronic arthritis and Still's disease) • Polymyalgia *rheumatica* • Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis • Psoriatic arthropathy • Relapsing polychondritis • Mixed connective tissue disorder	• Psoriasis • Vitiligo • Erythema nodosum • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis) • Alopecia areata • Lichen planus • Sweet's syndrome • *Localized Scleroderma* (Morphoea)
Liver disorders	**Gastrointestinal disorders**	***Endocrine disorders***
• Autoimmune hepatitis • Primary biliary cirrhosis • Primary sclerosing cholangitis • Autoimmune cholangitis.	• *Inflammatory Bowel disease, including* Crohn's disease, ulcerative colitis, *microscopic colitis, ulcerative* proctitis • Celiac disease • *Autoimmune pancreatitis*	• Autoimmune thyroiditis (including Hashimoto thyroiditis) • Grave's or Basedow's disease • Diabetes mellitus type I • Addison's disease • *Polyglandular autoimmune syndrome* • *Autoimmune hypophysitis*

Vasculitides	***Blood disorders***	**Others**
• Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis. • Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome (allergic granulomatous angiitis), Buerger's disease (thromboangiitis obliterans), necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis.	• *Autoimmune hemolytic anemia* • *Autoimmune thrombocytopenia* • *Antiphospholipid syndrome* • *Pernicious anemia* • *Autoimmune aplastic anemia* • *Autoimmune neutropenia* • *Autoimmune pancytopenia*	• Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis) • *Ocular autoimmune diseases (including autoimmune uveitis and autoimmune retinopathy)* • Autoimmune myocarditis/cardiomyopathy • Sarcoidosis • Stevens-Johnson syndrome • Sjögren's syndrome • Idiopathic pulmonary fibrosis • Goodpasture syndrome • Raynaud's phenomenon

13.3. Appendix 3: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

Female participants of reproductive potential must use one of the following highly effective contraceptive methods as indicated in Section 5.1 [Hatcher, 2007]:

- Contraceptive subdermal implant with a <1% rate of failure per year as stated in the product label
- Intrauterine device or intrauterine system that meets the <1% failure rate as stated in the product label
- Oral Contraceptive, combined estrogen and progestogen
- Injectable progestogen
- Contraceptive vaginal ring
- Percutaneous contraceptive patches
- Male partner sterilization with documentation of azoospermia prior to the female participant's entry into the study; this male must be the sole partner for that participant.
    - For this definition, “documented” refers to the outcome of the investigator's/designee’s medical examination of the participant or review of the participant's medical history for study eligibility, as obtained via a verbal interview with the participant or from the participant’s medical records.

For male participants with female partners of child-bearing potential the use of one of the following contraceptive methods is required as indicated in Section 5.1:

Vasectomy with documentation of azoospermia

- Male condom plus partner use of one of the contraceptive options below:
    - Contraceptive subdermal implant
    - Intrauterine device or intrauterine system
    - Oral Contraceptive, combined estrogen and progestogen
    - Injectable progestogen
    - Contraceptive vaginal ring
    - Percutaneous contraceptive patches

These lists do not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for participants who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis. This is an all-inclusive list of those methods that meet the GSK definition of highly effective: having a failure rate of less than 1% per year when used consistently and, correctly and, when applicable, in accordance with the product label. For non-product methods (e.g., male sterility), the investigator determines what is consistent and correct use. The investigator is responsible

for ensuring that participants understand how to properly use these methods of contraception.

13.4. Appendix 4: Liver Safety – Study Treatment Restart or Rechallenge Guidelines

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

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

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

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

Following drug-induced liver injury, **drug rechallenge is associated with 13% mortality across all drugs in prospective studies** [Andrade, 2009].

Clinical outcomes vary by drug, with nearly 50% fatality with halothane re-administered within one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include:

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

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

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

- Investigator requests consideration of rechallenge with study treatment for a participant who is receiving compelling benefit with study treatment that exceeds risk, and no effective alternative therapy is available.
- Ethics Committee or IRB approval for rechallenge with study treatment must be obtained, as required.
- If the rechallenge is approved by GSK Medical Governance in writing, the participant must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the rechallenge with study treatment. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Participants approved by GSK Medical Governance for rechallenge with study treatment must return to the clinic twice a week for liver chemistry tests until stable liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If after study treatment rechallenge, participant meets protocol-defined liver chemistry stopping criteria, study treatment must be permanently discontinued.
- GSK Medical Monitor, and the Ethics Committee or IRB as required, must be informed of the participant's outcome following study treatment rechallenge.
- GSK to be notified of any AEs, as per Section 8.4.1.

AND/OR

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

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

Approval by GSK for study treatment restart can be considered where:

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
- Restart risk factors (e.g., fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis, possible study treatment-induced liver injury or study treatment has a

human leukocyte antigen (HLA) genetic marker associated with liver injury (e.g., lapatinib, abacavir, amoxicillin/clavulanate) are reviewed and excluded.

- Ethics Committee or IRB approval of study treatment restart must be obtained, as required.
- If restart of study treatment is approved by GSK Medical Governance in writing, the participant must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Participants approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If after study treatment re-start, participant meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.
- GSK Medical Monitor, and the Ethics Committee or IRB as required, must be informed of the participant's outcome following study treatment restart.
- GSK to be notified of any AEs, as per Section 8.4.1.

13.5. Appendix 5: NYHA Functional Classification System for Heart Failure

The New York Heart Association (NYHA) Functional Classification [NYHA, 1994] provides a simple way of classifying the extent of heart failure. It places participants in one of four categories based on the level of limitation experienced during physical activity:

Class	Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

13.6. Appendix 6: Guidelines for Assessment of Disease, Disease Progression and Response Criteria – adapted from RECIST version 1.1

Assessment Guidelines

Please note the following:

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion. Contrast agents must be used in accordance with the Image Acquisition Guidelines.
- All measurements 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.

Guidelines for Evaluation of Disease

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.

Immune-Related RECIST Response Criteria

Evaluation of target lesions

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

a. Measurable per RECIST v1.1.
b. Treatment decisions will be based upon the immune-related RECIST guidelines.

Antitumor response based on total measurable tumor burden

For Modified RECIST based on RECIST v1.1 and Immune-Related RECIST [Wolchok, 2009; Nishino, 2013], the initial target ('index") and measurable new lesions are taken into account. At the baseline tumor assessment, the sum of the diameters in the plane of measurement of all target lesions (maximum of five lesions in total and a maximum of two lesions per organ representative of all involved organs) is calculated.

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

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

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

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

Evaluation of non-target lesions

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

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

Note:

- In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- Sites of non-target lesions, which are not assessed at a time point based on the assessment schedule, should be excluded from the response determination (e.g. non-target response does not have to be "Not Evaluable").

New lesions

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

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

Evaluation of overall response

Table 37 presents the overall response at an individual disease assessment time-point accounting for all possible combinations of responses in target and non-target lesions with or without the appearance of new lesions for participants with measurable disease at baseline.

Table 37 Evaluation of Overall Response for Participants with Measurable Disease at Baseline

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

Abbreviations: CR = Complete response, PR = Partial response, SD = Stable disease, PD = Progressive disease, NA = Not applicable, and NE = Not Evaluable

Evaluation of best overall response

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

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

Confirmation Criteria:

To be assigned a status of PR or CR, a confirmatory disease assessment must be performed no less than 4 weeks (28 days) after the criteria for response are first met.

13.7. Appendix 7: ECOG Performance Status

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

a. Oken, 1982.

13.8. Appendix 8: Events of Clinical Interest

These are selected events considered of clinical interest; they may be non-serious AEs or SAEs. Events of Clinical Interest are different from Adverse Events of Special Interest (AESI) in that an AESI is defined as an adverse event of potential immunologic etiology. 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.

For the time period beginning with the administration of the first dose of study treatment through 30 days following discontinuation of study treatment, any ECI, or follow up to an ECI, whether or not related to the study drug(s), must be reported to the Sponsor either by electronic media (eCRF [required for AE/SAE] or email) or phone call within the time frame indicated by event. ECI include:

1. Overdose of study drug(s) (GSK3359609 (feladilimab) and pembrolizumab (Part 2 only) that is not associated with clinical symptoms or abnormal laboratory results must be reported within 5 days.
2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.***This ECI must be reported within 24 hours.**

***Note:** These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

Investigators/study coordinators/designated site personnel are required to record these experiences in the eCRF (as described in the eCRF completion guidance document) and to provide supplemental information (such as medical history, concomitant medications, investigations, etc.) about the event.

13.9. Appendix 9: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

13.9.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a participant or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This must 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; progression of the cancer under study is not considered an adverse event unless it is considered to be drug-related by the investigator. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the 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 an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

13.9.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc.).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

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

NOTE:

- 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 out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. If in doubt as to whether "hospitalization" occurred or was necessary, the AE must be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

g. Is associated with liver injury <u>and</u> impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to participants receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

- Refer to Section 7.4 for the required liver chemistry follow-up instructions

13.9.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

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

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension

- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

13.9.4. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- 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 instance, all participant identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

13.9.5. Evaluating AEs and SAEs

Assessment of Severity:

- The investigator will make an assessment of severity for each AE and SAE reported during the study and will assign a grade according to the NCI-CTCAE v4.0 [NCI, 2010].

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey there is evidence, facts or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a 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 the designated reporting time frames.

13.9.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool provided in the SRM. Refer to the SRM for details on submitting the paper SAE forms.

- If paper SAE forms are used to report a SAE, the site will need to enter the serious adverse event data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol and in the SRM on the Sponsor/Medical Monitor Contact Information page.

13.9.7. Collection of Pregnancy Information

Action to be taken if pregnancy occurs in a female participant

- Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Section 13.9.6. 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.
- Discontinue study treatment if applicable; participant may be withdrawn from the study.

Action to be taken if pregnancy occurs in a female partner of a male study participant

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

13.10. Appendix 10: 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] $\times$ 1.159 [if black]

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

13.11. Appendix 11: Genetic Research

Genetics – Background

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including GSK3359609 (feladilimab), pembrolizumab, other immune therapy under investigation in this study, or any concomitant medicines;
- Cancer susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any participant who is enrolled in the study can participate in genetic research. Any participant who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 ml blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A Blood sample is collected at the baseline visit, after the participant has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or "coded") with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the participant by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last participant completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Participants can request their sample to be destroyed at any time.

Informed Consent

Participants who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood being taken.

Participant Withdrawal from Study

If a participant who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the participant will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a participant withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a participant withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the participant does not meet the entry criteria for participation in the study, then the investigator must instruct the participant that their genetic sample will be destroyed. No

forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Participant's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the participant, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the participant's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

13.12. Appendix 12 - Country Specific Requirements

13.12.1. COUNTRY SPECIFIC REQUIREMENTS (JAPAN)

Effective Date: 2020

Version: JPN_01

13.12.1.1. Study Conduct Considerations

13.12.1.1.1. Regulatory and Ethical Considerations

The study will be conducted in accordance with “the Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (MHW Notification No.28 dated 27th March, 1997)” and Pharmaceuticals and Medical Devices Act.

The statement “I acknowledge that I am responsible for overall the study conduct.” on the Investigator Protocol Agreement Page means the investigator’s responsibility defined by Japanese GCP.

GSK will submit the Clinical Trial Notifications (CTN) to the regulatory authorities in accordance with Pharmaceuticals and Medical Devices Act before conclusion of any contract for the conduct of the study with study sites.

13.12.1.1.2. Informed Consent

Prior to participation in the study, the investigator should fully inform the potential participant (and/or the participant's legally acceptable representative) of the study including the written information. The investigator should provide the participant (and/or the participant's legally acceptable representative) ample time and opportunity to inquire about details of the study. The participant (and/or the participant’s legally acceptable representative) should sign and personally date the consent form. The participant may consider the content of the written information at home. The person, who conducted the informed consent discussion and the study collaborator giving supplementary explanation, where applicable, should sign and personally date the consent form. If an impartial witness is required, the witness should sign and personally date the consent form. The investigator should retain this signed and dated form (and other written information) together with the source medical records, such as clinical charts (in accordance with the rules for records retention, if any, at each medical institution) and give a copy to the participant (and/or the participant’s legally acceptable representative).

13.12.1.2. Notes on "Permitted Medications and Non-Drug Therapies"

Of "Permitted Medications and Non-Drug Therapies" accepted in this study (Section 6.9.1), blood products and growth factors (e.g., granulocyte-macrophage colony-stimulating factor, macrophage colony-stimulating factor, erythropoiesis-stimulating factor, platelet-stimulating agent) include drugs that are not approved for the treatment of events associated with cancer chemotherapy in Japan.

13.12.1.3. Considerations for Resuming Lactation After the Last Dose of Study Treatment

If the participant who discontinues lactation and participates in the study strongly wishes to resume lactation after the last dose of study treatment, the investigator will decide to resume lactation after 125 days (5 times the elimination half-life of GSK3359609 (feladilimab)) from the last dose of study treatment, taking into account the condition, circumstances and aftertreatment of the participant.

13.12.1.4. Screening test for Hepatitis B for Japanese Participants Enrolled in Part 2A Chemotherapy Safety Run-in Cohorts

In addition to HBsAg test, HBcAb and HBcAb tests are required at screening for Japanese participants who will be enrolled in the Part 2A chemotherapy safety run-in cohorts (refer to Section 8.4.8).

For HBcAb and/or HBsAb positive Japanese participants, to monitor for hepatitis B reactivation it is required to monitor liver function tests and HBV DNA levels in accordance with guidelines from the Japan Society of Hepatology (Japan Society of Hepatology, 2019).

13.12.1.5. Genetics (Protocol Appendix 11)

In this study, genetics may be evaluated after review by the ethical review committee established by GSK in accordance with Japanese ethical guidelines for human genome/gene analysis research, see Section 8.7 for further details on genetic research.

Where local regulations and IRB/IEC allow, a 6 ml blood sample will be taken for Deoxyribonucleic acid (DNA) extraction.

13.13. Appendix 13 – Substantial Protocol Changes from Previous Amendment

Substantial Amendment Changes with Rationale

Table 28: Elimination of the collection of the following:

-pembrolizumab pharmacokinetics and immunogenicity

-Pharmacodynamic immunogenicity blood samples:

- Pharmacokinetic Blood Specimens

GSK3359609 (feladilimab) (Q3W & Q6W)

GSK3174998

Chemotherapy (excluding 5-FU)

Fluorouracil (5-FU)

-Removed Table 29 and renumbered tables accordingly

-Updated tumor biopsy requirement

Rationale: Assessments no longer required

Section 5.4.1: Clarification of processes for hepatoxicity. The following language was added:

If any of the following criteria are met, all study drugs must be discontinued and hepatotoxicity events must be reported to GSK within 24 hours. Complete liver event eCRF forms and SAE forms if the event also meets the criteria for SAE reporting. The eCRF liver event form does not appear automatically, but must be manually activated.

If treatment is held or discontinued do not restart/rechallenge the participant with study treatment unless all the requirements described in this section have been met, including clearance from the sponsor. Liver chemistry stopping criteria are provided below.Rationale: Reinforce alignment with GSK safety reporting standard operating procedures.

Section 1 update, removal of section 4.3.0, and removal of Table 30 (renumbered accordingly): Elimination of Retreatment Option (Second Course) along with Clarification of End of Study and Off Study procedures

Rationale: Alignment with programmatic changes

Updated Table 27 Efficacy assessment and standarsRationale: Alignment with programmatic changes

Updated Section 8.5 to remove requirements for sample collection, sample analysis, and immunogenicity requirements.

Rationale: Alignment with programmatic changes