TITLE PAGE

Protocol Title: A Phase 2, Randomized, Open-label Platform Trial Utilizing a Master Protocol to Study Novel Regimens Versus Standard of Care Treatment in NSCLC Participants

Protocol Number: 205801/Amendment 10

Short Title: Phase 2 NSCLC Master Protocol

Compound Number:	GSK4428859A

Study Phase: 2

Sponsor Name and Legal Registered Address:

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

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Sponsor Signatory:

Ivan Diaz-Padilla, MD, PhD,
Global Clinical Head, Immuno- oncology
Oncology Clinical Development

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG or TMF Number**
Amendment 10	26 Apr 2023	TMF- 16073217
Amendment 9	30 March 2023	TMF-15772785
Amendment 8	23-May-2022	TMF-14611949
Amendment 7	08-March-2022	TMF- 14511980
Amendment 6	19-Nov-2021	TMF-14000899
Amendment 5	02-Sep-2021	TMF-13833961
Amendment 4	02-Feb-2021	TMF-11698443
Amendment 3	29-Oct-2020	2017N337080_03
Amendment 2	15-Jul-2019	2017N337080_02
Amendment 1	20-Sep-2018	2017N337080_01
Original Protocol	23-Jul-2018	2017N337080_00

Amendment 10 26 Apr 2023

Overall Rationale for the Amendment:

This amendment is considered substantial based on the criteria defined in EU Clinical Trial Regulation No 536/2014 of the European Parliament and the Council of the European Union because it significantly impacts the safety of participants**.**

Overall rationale for the current amendment: Amendment 10 provides updated eligibility requirements with regards to toxicity from previous immunotherapy treatment.

List of main changes in the protocol and their rationale:

Section # and Name	Description of Change	Brief Rationale
6.2 Exclusion Criteria, Criterion 10.	Updated to exclude participants who have experienced any grade of myocarditis with prior immunotherapy.	To further ensure participant safety

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1. SYNOPSIS

Protocol Title: A Phase 2, Randomized, Open-label Platform Trial Utilizing a Master Protocol to Study Novel Regimens Versus Standard of Care Treatment in NSCLC Participants

Short Title: Phase 2 NSCLC Master Protocol

Rationale:

Study 205801 is a randomized, Phase 2 open-label platform trial in two parts utilizing a master protocol to investigate the clinical activity of novel regimens compared with standard of care (SoC) regimens in participants with relapsed/refractory advanced non-small cell lung cancer (NSCLC) who have prior platinum-containing chemotherapy regimen and an immuno-oncology agent treatment failure, such as anti-programmed cell death protein 1 [PD1] / PD-Ligand 1 [PD-L1] – either in combination or as separate lines.

NSCLC is considered intrinsically resistant to immuno-oncology agents owing in part to its broad immune escape and suppressive features that include low antigenicity, despite having one of the highest frequencies of somatic mutations, and a high presence of regulatory T cells (Tregs). However, as shown by the single-agent response rates of anti-PD-1 inhibitors in NSCLC, a subset of tumors are susceptible to T cell-mediated antitumor effects, suggesting those tumors have some degree of prior T-cell immunity. Since effective anticancer immune response involves stepwise multistep processes, lung cancers may possess or acquire features that enable them to evade immune surveillance, suppress immune reactivity, proliferate, and survive within an inflammatory microenvironment, thereby rendering an immune response ineffectual. Therefore, treatment modalities that incorporate combinations with agents targeting different processes within the immune cascade have the potential to reinstate immunosurveillance; these may include regimens containing chemotherapy that possess advantageous immunological effects to potentially improve clinical efficacy.

Objectives and Endpoints (Part 1)

Objectives	Endpoints
Primary	
To determine the safety and tolerability of novel regimen(s)	AEs, SAEs, DLTs, changes in safety/laboratory assessment parameters, dose modifications
Secondary	
To provide a preliminary evaluation of the efficacy of experimental regimen(s)	Objective Response Rate (ORR) Disease Control Rate (DCR)
Characterize the pharmacokinetic properties of experimental regimen(s)	PK parameters that include Cmax and Cmin for experimental regimen(s) (and investigational agent/s included in other arms), as data permit.

Objectives and Endpoints (Part 2):

Objectives	Endpoints
Primary	
Determine whether experimental regimen(s) provide evidence for improved survival over SoC therapy	Overall survival as measured by time from randomization to death
Secondary	
Evaluate milestone survival in participants treated with experimental regimen(s) versus SoC therapy for NSCLC	Milestone survival rate at 12 and 18 months
Evaluate other measures of antitumor activity of the experimental regimen(s) compared with SoC therapy for NSCLC (RECIST 1.1 and iRECIST)	CR, PR, SD, PD, PFS, ORR, DOR, DCR iCR, iPR, iUPD, iCPD, iSD iPFS; iORR; iDOR
Evaluate the safety and tolerability of the experimental regimen(s) compared with SoC therapy for NSCLC	Frequency and severity of AEs, AESI; SAEs and AE/SAEs leading to dose modifications/delays/withdrawals; changes in laboratory, vital signs, and safety assessment parameters, including immunogenicity (ADA)
Characterize the pharmacokinetic properties SoC or experimental regimen(s)	PK parameters that may include C_{max} and C_{min} for experimental regimen(s) and for SoC alone, as data permit.
Determine immunogenicity of experimental regimen(s)	ADA incidence for experimental regimen(s) (where appropriate)

Note: The prefix "i", used for response related abbreviations in the above table indicates immune responses assigned using iRECIST.
ADA= anti-drug antibody; AE = adverse event/s; AESI = adverse event/s of special interest; C_{max} = maximum concentration; C_{min} = minimum concentration; CPD = confirmed progression; CR = complete response; DLT = Dose Limiting Toxicity' DOR = duration of response; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria In Solid Tumors; SAE = serious adverse event; SD = stable disease; SoC = standard of care; UPD = unconfirmed progression.

Overall Design:

This is a randomized Phase 2, open-label, platform trial utilizing a master protocol designed to study novel immunotherapy drug combinations compared with the current SoC, in the treatment of patients with advanced NSCLC who have progressed on prior anti-PD(L)1 and platinum-based combination chemotherapies. The study will initially evaluate 2 treatment regimens/arms, with additional regimens/arms added via protocol amendment(s) (see the Study Design schematic below).

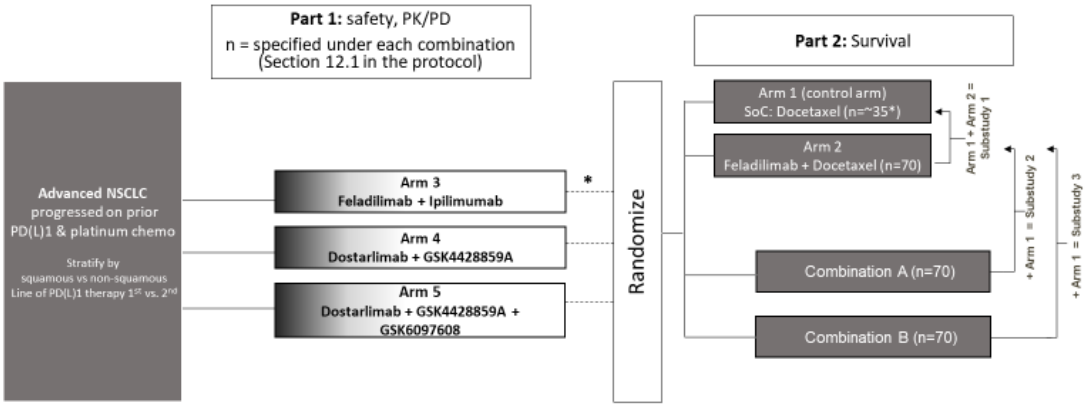
The study will be conducted in two parts; Part 1 is an open-label, optional, non-randomized part based on safety and pharmacokinetics/pharmacodynamics (PK/PD) evaluation. Part 2 is a randomized, Phase 2, open-label part comparing the efficacy and safety of these novel regimens with SoC. Part 2, is structured as a series of substudies that share a common control arm with ongoing updating of the effect size of the control arm through the addition of new participants with each substudy. Each combination will be first evaluated in a separate study/arm for safety. This evaluation may occur prior to adoption into 205801 platform study (dose finding in a separate study) or as a distinct arm within this platform study (Part 1) prior to Part 2. If an experimental regimen meets graduation requirements, i.e., passes criteria for safety and preliminary clinical activity, they may advance to Part 2. Graduation will be the term used throughout the protocol to

refer to the advancement of a combination from Part 1 to Part 2. As a clarification, the combination will be tested in a new population that will be randomized between the combination and the Standard of Care. The study participants enrolled in Part 1 are not pooled with the study participants in Part 2. The two study populations are separate and distinct. Part 1 is open label single arm while Part 2 is randomized.

For the randomized survival evaluation, participants will be stratified by histology (squamous vs. non-squamous) and line of PD(L)1 therapy (1st vs. 2nd line). Patients with NSCLC with undetermined histology (i.e. NSCLC not otherwise specified) will be considered as non-squamous for stratification purposes.

Each additional treatment arm/regimen will be analyzed relative to the SoC treatment and is considered a substudy within the overall master protocol, as depicted below.

Study Design



Between 10-20% of newly enrolled participants in subsequent substudies (depending upon the number of experimental arms in the trial) will be randomized to SoC once the initial 35 participants have been enrolled on control.
*Decision on each combination to proceed will be conditional on criteria from Section 5.1 and 10.5.1.1.
The two study populations (Part 1 and 2) are separate and distinct. Data from Part 1 and 2 will not be combined.

NSCLC: non-small cell lung cancer; PD(L)1: Programmed Cell Death Protein 1 or Programmed Cell Death Ligand 1.
Note: Randomization of participants to experimental treatment regimens/arms may not occur in parallel. It should also be noted that the terms 'regimen' and 'arm' may be used interchangeably throughout the document.

Number of Participants:

As the study uses a master protocol design, the sample size is not fixed.

For Part 1, sample size will be defined for each regimen under the corresponding appendix in Section 12.1; a minimum of 3 participants will be evaluated for safety before further participants will be enrolled.

The initial number of participants for Part 2 in substudy 1 is estimated to be at least 105 (SoC arm: 35; experimental arm: 70 for substudy 1). Additional substudies and their corresponding experimental regimens will be added via protocol amendments. Each

additional experimental arm will enroll a maximum of 70 participants. Randomization to SoC/Arm 1 will be minimized through an alteration of the randomization ratio once 35 participants are randomized to that arm.

Treatment Groups and Duration:

Study participation begins with the signing of the informed consent form (ICF) within 45 days prior to the first dose. After a screening period of up to 28 days, eligible participants will be assigned a treatment arm if participating in Part 1 and receive study treatment (Day 1), or randomly assigned to a treatment arm (SoC or experimental) if participating in Part 2 and receive study treatment (Day 1).

Unless otherwise specified in the treatment-specific appendix, investigational combination study treatment will continue at the indicated schedule for a maximum duration of approximately 2 years or up to 35 treatment visits, whichever comes first, or until disease progression, death, unacceptable toxicity, or withdrawal of consent. Single agent SoC treatment (i.e. docetaxel) may continue until disease progression, death, unacceptable toxicity, withdrawal of consent, or per institutional standard for docetaxel. After the study treatment is permanently discontinued, participants will be followed, via telephone contact, for survival and subsequent anticancer therapy every 12 weeks until death or the participant's withdrawal from further contact. Participants permanently discontinuing study treatment prior to documented disease progression by iRECIST will also be followed every 12 weeks for disease progression or participant's withdrawal from further contact.

The study will be considered 'finished' once the last participant from all open treatment arms has completed their last survival follow-up contact.

2. SCHEDULE OF ACTIVITIES (SoA)

The Schedules of Activities can be found in the corresponding appendix for each arm in Section 12.1.

- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic/biomarker or other assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The Institutional review board/ Independent ethics committees (IRB/IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed consent form (ICF).

3. INTRODUCTION

Study 205801 is an open-label platform trial utilizing a master protocol designed to investigate the clinical activity of novel regimens compared with standard of care (SoC) regimen in participants with relapsed/refractory advanced non-small cell lung cancer (NSCLC) who have prior platinum-containing regimen and anti-programmed cell death protein 1 [PD-1] / PD-Ligand 1 [PD-L1] treatment failure. The study will be conducted in two parts; Part 1 is an optional, non-randomized part based on safety and pharmacokinetics/pharmacodynamics (PK/PD) evaluation. Part 2 is a randomized, Phase 2 part comparing the efficacy and safety of these novel regimens with SoC.

3.1. Study Rationale

While a subset of NSCLC tumors are responsive to immuno-oncology agents, a sizable portion of NSCLC tumors is considered to be intrinsically resistant to immuno-oncology agents, owing in part to its broad immune escape and suppressive features that include low antigenicity, despite having one of the highest frequencies of somatic mutations [Lawrence, 2013], and a high presence of regulatory T cells (Tregs). However, as shown by the single-agent response rates of anti-PD-1 inhibitors in NSCLC, a subset of tumors are susceptible to T cell-mediated antitumor effects, suggesting those tumors have some degree of prior T-cell immunity [Brahmer, 2015; Rittmeyer, 2017; Reck, 2016]. Since effective anticancer immune response involves stepwise multistep processes [Chen, 2013], lung cancers may possess or acquire features that enable them to evade immune surveillance, suppress immune reactivity, proliferate, and survive within an inflammatory microenvironment thereby rendering an immune response ineffectual. Therefore, treatment modalities that incorporate combinations with agents targeting different processes within the immune cascade have the potential to reinstate immunosurveillance; these may include regimens containing chemotherapy that possess advantageous immunological effects to improve clinical efficacy [Galluzzi, 2015].

3.2. Background

Cancer is one of the leading causes of death worldwide, accounting for 8.8 million deaths in 2015. Lung cancer is the most common cause of cancer death, accounting for 1.69 million deaths worldwide [Cancer Fact Sheet, 2017]. Globally, the incidence and mortality rates attributed to cancer vary across regions; nevertheless, lung cancer remains the leading cause of cancer death in men and the second leading cause of cancer death in women [Torre, 2015]. Non-small cell lung cancer accounts for the vast majority of lung cancer cases (up to 85%), with disease stage, histological subtype (e.g., adenocarcinoma, squamous, large cell, etc.), and molecular features playing a principal role in making treatment choices. In advanced-stage metastatic NSCLC positive for a specific molecular alteration (i.e., EGFR/ALK/ROS/BRAF), targeted single-agent approaches are recommended [NCCN, 2021; Planchard, 2018; Postmus, 2017]. In metastatic non-squamous NSCLC, the first-line option for some patients is the approved triplet regimen consisting of pembrolizumab (an anti-PD-1 inhibitor) added to the pemetrexed/carboplatin backbone [Langer, 2016; KEYTRUDA, 2018]. An alternative current standard for NSCLC (squamous or non-squamous) is pembrolizumab as a single-agent for (a) first-line treatment of metastatic NSCLC patients whose tumors have high

PD-L1 expression (Tumor Proportion Score [TPS] ≥50%) or, (b) in subsequent lines (post-platinum) of treatment of patients with metastatic NSCLC (squamous or non-squamous) whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test [Reck, 2016; KEYTRUDA, 2018]. Additional subsequent-line treatment options include other single-agent anti-PD-1/PD-L1 inhibitors (e.g., nivolumab and atezolizumab) if not administered as first-line [Brahmer, 2015; Rittmeyer, 2017]. In patients with advanced or metastatic non-squamous NSCLC without EGFR/ALK alternations and with PD-L1 TPS ≥1%, more durable responses were observed with pembrolizumab monotherapy compared to platinum-based chemotherapy alone, and support pembrolizumab as a standard first-line treatment option for all PD-L1-positive cancers [Lopes, 2016]. Additionally, in patients with previously untreated metastatic squamous NSCLC, the addition of pembrolizumab to platinum-based chemotherapy show significant improved survival regardless of PD-L1 expression level, and may be considered as a standard first-line treatment for metastatic squamous NSCLC regardless of PD-L1 status [Paz-Ares, 2018]. Recently, ESMO clinical practice guidelines have been updated to include the addition of atezolizumab to first-line chemotherapy in the metastatic non-small cell lung cancer setting [Planchard, 2018]. Single-agent chemotherapy such as pemetrexed for non-squamous NSCLC (if not used as part of the platinum-containing chemotherapy regimen earlier) or gemcitabine for squamous NSCLC or docetaxel for all NSCLC sub-types have been relegated to later lines and can be selected based on the patient's treatment history, disease characteristics, and performance status.

Docetaxel is approved by the US FDA and EMA as a single-agent for patients with locally advanced or metastatic NSCLC after platinum-based chemotherapy [TAXOTERE PI, 2020 and TAXOTERE SmPC 2020]. With the recent approvals of nivolumab in the same line of therapy, i.e., after progression on platinum-based doublet [OPDIVO PI, 2018], docetaxel has been relegated to the status of a subsequent therapy, as noted in the ESMO/NCCN guidelines [Herbst, 2016; Horn, 2017; Novello, 2016; NCCN, 2019]. The clinical activity of older single-agent chemotherapies such as docetaxel as second-line treatment in NSCLC is limited with response rates in the range of 9 to 24% [Shepherd, 2000; Hanna, 2004].

Patients with NSCLC that has failed both a platinum-containing chemotherapy regimen and an anti-PD(L)1 inhibitor (used either in combination or as separate lines of therapy) have a high unmet medical need for treatment advances with the potential to improve progression-free survival (PFS) and overall survival (OS).

3.3. Benefit/Risk Assessment

Benefits and risks for each combination partner can be found in the respective subsections under Section 12.1. Detailed information related to the known and expected benefits and risks including expected AEs of each experimental agent may be found in the corresponding Investigator's Brochure (IB). Refer to the latest docetaxel product labels [TAXOTERE PI, 2020; TAXOTERE SmPC, 2020] for information on contraindications, warnings, and precautions related to the use of docetaxel.

3.4. Overall Benefit-Risk Conclusion

There is biologic rationale to study these novel combinations in this setting based on complementary modes of action on the immune system, with the potential for antitumor activity that exceeds either agent's monotherapy activity in preclinical models. Based on the current safety profiles (See Section 12.1 for details) and docetaxel labeling [TAXOTERE PI, 2020; TAXOTERE SmPC, 2020], potential overlapping toxicities with combination therapies are anticipated to be manageable. However, it is unknown whether the combination regimens will have clinical activity in NSCLC that exceeds the SoC treatment. Considering the overall poor outlook for patients who have failed prior therapies and recognizing the risk minimization strategies proposed, any potential risks are justified by the anticipated benefits to participants with advanced NSCLC.

4. OBJECTIVES AND ENDPOINTS

4.1. Objectives and Endpoints: Part 1

Objectives	Endpoints
Primary	
To determine the safety and tolerability of novel regimen(s)	AEs, SAEs, DLTs, changes in safety/laboratory assessment parameters, dose modifications
Secondary	
To provide a preliminary evaluation of the efficacy of experimental regimen(s)	Objective Response Rate (ORR) Disease Control Rate (DCR)
Characterize the pharmacokinetic properties of experimental regimen(s)	PK parameters that include Cmax and Cmin for experimental regimen(s) (and investigational agent/s included in other arms), as data permit.
Exploratory	
CCI [redacted]	

4.2. Objectives and Endpoints: Part 2

Objectives	Endpoints
Primary	
Determine whether experimental regimen(s) provide evidence for improved survival over SoC therapy	Overall survival as measured by time from randomization to death
Secondary	
Evaluate milestone survival in participants treated with experimental regimen(s) versus SoC therapy for NSCLC	Milestone survival rate at 12 and 18 months
Evaluate other measures of antitumor activity of the experimental regimen(s) compared with SoC therapy for NSCLC (RECIST 1.1 and iRECIST)	CR, PR, SD, PD, PFS, ORR, DOR, DCR iCR, iPR, iUPD, iCPD, iSD iPFS; iORR; iDOR

Objectives	Endpoints
Evaluate the safety and tolerability of the experimental regimen(s) compared with SoC therapy for NSCLC	Frequency and severity of AEs, AESI; SAEs and AE/SAEs leading to dose modifications/delays/withdrawals; changes in laboratory, vital signs, and safety assessment parameters, including immunogenicity (ADA)
Characterize the pharmacokinetic properties of SoC or experimental regimen(s)	PK parameters that may include C_{max} and C_{min} for experimental regimen(s) and for SoC alone, as data permit.
Determine immunogenicity of experimental regimen(s)	ADA incidence for experimental regimen(s) (where appropriate)
Exploratory	
CCI [redacted]	

Note: The prefix "i", used for response related abbreviations in the above table indicates immune responses assigned using iRECIST.
AE = adverse event/s; AESI = adverse event/s of special interest; C_{max} = maximum concentration; C_{min} = minimum concentration; CPD = confirmed progression; CR = complete response; DLT = Dose Limiting Toxicity' DOR = duration of response; CCI [redacted]; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; CCI [redacted]; RECIST = Response Evaluation Criteria In Solid Tumors; SAE = serious adverse event; SD = stable disease; SoC = standard of care; TMB = Tumor Mutational Burden; UPD = unconfirmed progression.

5. STUDY DESIGN

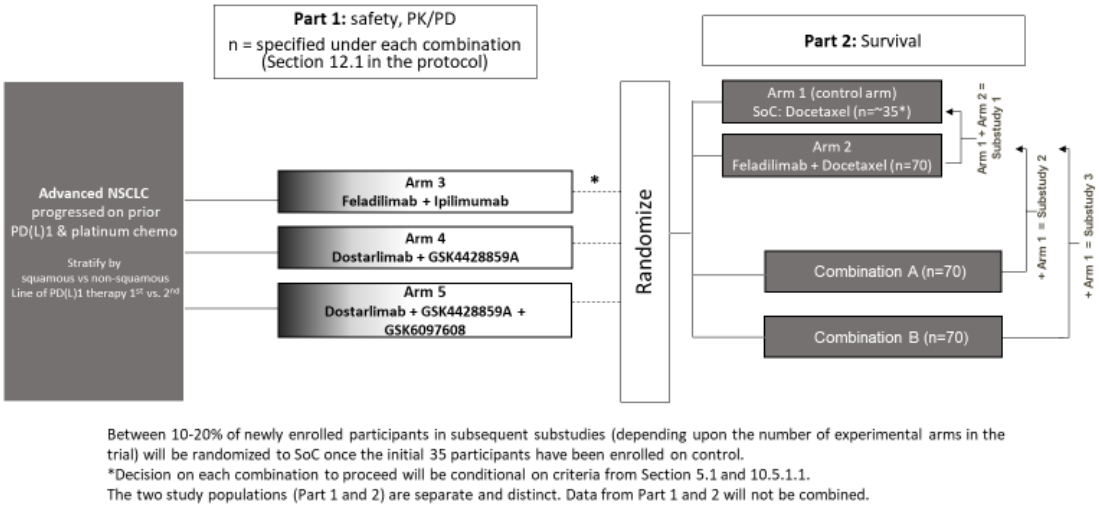
5.1. Overall Design

This is an, open-label, platform trial in two parts utilizing a master protocol to study novel drug combinations compared with the current SoC in the treatment of patients with advanced NSCLC who have progressed on prior anti-PD(L)1 and platinum-based combination chemotherapies. Part 1 is a non-randomized, safety and PK/PD evaluation, Part 2 is a randomized, Phase 2 comparing the efficacy and safety of novel regimens with docetaxel as the SoC control arm (Arm 1). Novel combinations will be evaluated in separate substudies. As shown in Figure 1, the study will initially evaluate the efficacy of feladilimab in combination with SoC (docetaxel) (Arm 2) compared with SoC alone as the standard subsequent-line chemotherapy (substudy 1) in NSCLC. Additional arms will be added via protocol amendment based on emerging nonclinical and clinical data. No treatment crossover is allowed in this study.

Each novel combination will first be evaluated for safety. This evaluation may occur prior to adoption into the 205801 platform study (dose finding in a separate study) or as a distinct arm within this platform study (Part 1) prior to Part 2. Following the initial safety evaluation, additional participants for each regimen and/or dose may be enrolled to further evaluate safety and PK/PD (refer to Section 12.1 for details for each experimental regimen). Once an experimental regimen qualifies for transition evaluation, additional participants will be enrolled to Part 2. Within Part 2, participants will be randomized to receive either SoC or the experimental treatment. Part 2 treatment arms may be dropped based on interim OS results (Section 10.3.3). Part 1 is open label single arm while Part 2 is randomized. Combinations that proceed to Part 2 will be tested in a new group of participants, separate from Part 1 participants, that will be randomized between the combination and the Standard of Care. The study participants enrolled in Part 1 are not pooled with the study participants in Part 2. The two study populations are separate and distinct. Data from Part 1 and 2 will not be combined.

The data generated from each experimental regimen and associated control arm data are considered a substudy within the overall platform study, as depicted in Figure 1.

Figure 1 Study Design



NSCLC: non-small cell lung cancer; PD(L)1: Programmed Cell Death Protein 1 and Programmed Cell Death Ligand 1.
Note: Randomization of participants to experimental regimens may not occur in parallel. It should be noted that the terms 'regimen' and 'arm' may be used interchangeably throughout the document. Between 10-20% of newly enrolled participants in substudies (depending upon the number of experimental arms in the trial) will be randomized to SoC once the initial 35 participants have been enrolled on control arm.

Interim safety and efficacy data for Part 2 will be reviewed by an Independent Data Monitoring Committee (IDMC), independent of the study team. Additional details will be provided in an IDMC Charter. A Steering Committee of lead investigators on study will also be established to provide guidance for key decisions such as introduction of new arms and graduation of existing arms.

At study start, participants will be randomized 1:2 to Arm 1 (SoC) and Arm 2, i.e., 33% and 67%, respectively. As new substudies are initiated, the randomization ratio will be as described below in Table 1. Between 10-20% of newly enrolled participants in subsequent substudies (depending upon the number of experimental arms in the trial) will be randomized to SoC once the initial 35 participants have been enrolled on control.

The 1:4 randomization for a 2-arm trial is for subsequent substudies where a new experimental arm enters the trial and the SoC arm has already enrolled more than 35 participants, and all other experimental arms are no longer enrolling (e.g. completed accrual, or stopped due to toxicity findings, or other reason). Similarly, the 1:4:4 randomization for a 3-arm trial is for subsequent substudies where 2 new arms enter after the SoC arm has already enrolled more than 35 participants, and all other experimental arms are no longer enrolling (e.g. completed accrual, or stopped due to toxicity findings, or other reason).

Table 1 Randomization Ratio and Proportion of Participants Randomized to the SoC Arm When There Are Concurrent Arms

	Randomization Ratio	
	≤35th participants	>35th participants
Two arms (SoC and one treatment)	1:2 SoC:Each Trt	1:4 SoC:Each Trt
Three arms (SoC + two treatments)	1:2 SoC:Each Trt	1:4 SoC:Each Trt
Four arms (SoC + three treatments)	1:1 SoC:Each Trt	1:3 SoC:Each Trt
Five arms or more (SoC + four or more treatments)	1:1 SoC:Each Trt	1:2 SoC:Each Trt

The study will employ a Bayesian decision-making framework based on the predictive probability of observing a significant improvement in OS in a future Phase 3 trial (see Section 10.5.1 for details).

Interim analysis of OS in Part 2 will be performed for each substudy after approximately 45 events (experimental arm and SoC combined) and a minimum of 18 events from experimental arm have been observed. Note, events from the SoC arm will be counted from the initial study start (i.e. SoC events from substudy 1 will be counted with any further events observed in subsequent substudies). Participants will continue to be enrolled during interim analyses. The final analysis for each substudy will be performed once a minimum number of events have been observed. At the final analysis, the experimental regimen within a substudy may be recommended for proceeding to a Phase 3 trial if it meets the predefined criteria for clinical activity. Details of the interim analysis and predefined criteria are provided in Section 10.3.3 and Section 10.3.4.

The requirements for the experimental regimens to advance from earlier Phase 1 studies to the current Phase 2 study (205801) include:

1. Determination of the recommended Phase 2 dose (RP2D) regimen
2. Adequate safety data of the combination at the RP2D
3. For the novel/novel combinations, evidence of potential antitumor activity in the range of the comparator (currently docetaxel) in an unselected solid tumor population.

Additional experimental regimens or populations with the appropriate SoC arm may be introduced to the current design via protocol amendments; these experimental arm(s) may include novel agents other than the aforementioned agents (Figure 1). A biomarker-driven approach may be implemented for any of the experimental arms as an enrichment strategy whereby participants will be stratified based on a biomarker test result prior to treatment allocation. The rationale for the biomarker-driven approach in selecting participants most likely to derive clinical benefit from that particular regimen will be fully delineated in the amendment(s).

5.2. Duration of Treatment

The study consists of 3 periods: screening, treatment, and follow-up. The total duration of study participation begins with the signing of the informed consent form (ICF). Participants will provide informed consent within 45 days prior to the first dose. After a screening period of up to 28 days, eligible participants will be assigned a treatment arm if participating in Part 1 and receive study treatment (Day 1) or randomly assigned to a treatment arm (SoC or experimental) if participating in Part 2 and receive study treatment (Day 1) as specified in the SoA for each arm (Section 12.1).

Combination study treatment will continue to be administered at the indicated schedule for a maximum duration of approximately 2 years or up to 35 treatment visits (unless noted otherwise in sections specific to each arm), whichever comes first, or until disease progression as determined by iRECIST, death, unacceptable toxicity, or other protocol-defined criteria are met. Single agent SoC treatment (i.e., docetaxel) may continue until disease progression, death, unacceptable toxicity, withdrawal of consent, or per institutional standard for docetaxel. After study treatment is permanently discontinued, participants will be followed for adverse events (AEs).

iRECIST is based on RECIST 1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs [Seymour, 2017]. Participants who attain a confirmed complete response (CR) per iRECIST, have received at least 2 additional doses of study treatment beyond the date the initial CR was declared, and have been treated for a minimum of 6 months, may discontinue study treatment; and these participants will continue with the scheduled disease assessments (Section 9.3.1). Participants may be permitted to resume study treatment upon disease progression following consultation between the treating investigator and the Sponsor/Medical Monitor, and upon written consent by the participant. See Section 8.1 for specific conditions under which a participant may continue study treatment beyond disease progression.

Participants who permanently discontinue study treatment will enter the survival follow-up period of the study and undergo the assessments as indicated in Section 9.

5.3. Number of Participants

As the study uses a master protocol design, the sample size for the study overall is not fixed. Participants enrolled to Part 1 will be separate from those enrolled to Part 2.

5.3.1. Sample Size: Part 1

For Part 1, sample size will be defined for each regimen under the corresponding appendix in Section 12.1; a minimum of 3 participants will be evaluated for safety during the 21 day DLT period before further participants will be enrolled.

5.3.2. Sample Size: Part 2

The initial number of participants in Part 2 is estimated to be at least 105 in substudy 1 (SoC arm: 35; experimental arm: 70). Additional experimental regimens may be added via protocol amendments and will be considered as another substudy. Each additional experimental arm will enroll a maximum of 70 participants. The minimum sample size for the SoC arm is 35 with additional participants randomized to SoC concurrently with additional experimental arms/substudies. Further randomization to SoC will be minimized once 35 patients are enrolled in the first substudy. Refer to Table 1 in Section 5.1 and Section 10.3 for additional details on sample size determinations.

Participants who discontinue in Part 2 will not be replaced in this study. See Section 10.4 for definitions of the populations for analyses.

5.4. Participant Completion and End of Study Definitions

5.4.1. Participant Completion Definitions

A participant will be considered to have completed the study if the participant dies during the study treatment period or follow-up period, whichever is sooner, or is still in follow-up at the time of the final analysis. The cause of death will be documented in the CRF/eCRF. A participant will be considered to have withdrawn from the study if the participant has not died and is lost to follow-up, has withdrawn consent, at the investigator's discretion is no longer being followed or if the study is closed/terminated.

5.4.2. Study Completion Definition

Substudy completion: A substudy is considered to have completed once the agreed number of events has been reached, survival follow up for remaining patients may not be needed.

An arm may close during Part 1 for safety or tolerability reasons or if an insufficient number of responders in Part 1 of that arm have been observed.

The end of study is defined as the completion of the last participant's required study visit, telephone contact, or death, as applicable, in the last substudy.

5.5. Scientific Rationale for Study Design

The study will employ a platform design utilizing a master protocol to compare experimental therapies with a common SoC treatment. Novel regimens may enter Part 2 via protocol amendment(s) once adequate safety and preliminary clinical activity data are obtained. If sufficient safety and preliminary clinical activity data are not available for a proposed regimen from other studies, these data may be obtained during a safety and PK/PD evaluation option in this study in Part 1. Once a regimen has passed criteria for safety and preliminary clinical activity, the treatment arm/regimen will be analyzed relative to the SoC treatment (Part 2) and is considered a substudy within the overall master protocol. In addition, different disease settings may be investigated via protocol amendment(s) and would introduce the SoC treatment for that setting. This design

provides efficiencies in the evaluation of experimental therapies by using a common control arm and discontinuing therapies that are deemed ineffective at interim time points while continuing randomization into substudies that may be more efficacious and be subsequently evaluated in confirmatory studies. The SoC arm will remain open to random assignment and the anticancer activity of experimental regimens in substudies that enter the study later will be compared with the overall population treated by the SoC therapy. Thus, the SoC population will always include contemporaneous as well as historical data.

5.5.1. Steering Committee and Data Monitoring Committee (Part 2)

A Steering Committee of lead investigators on study and representatives of the Sponsor study team will be established to provide guidance for key decisions such as introduction of new arms and graduation of existing arms. The remit, membership, and roles and responsibilities of the Steering Committee will be described in a charter.

An IDMC, independent of the study team, will be established to monitor efficacy and safety during the course of the trial. The remit, membership, and roles and responsibilities of the Data Monitoring Committee will be described in a charter.

Key decisions of the Steering Committee as well as the IDMC will be documented and reported to regulatory agencies if requested, all participating principal investigators (PIs) and if required, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) as appropriate with impactful decisions communicated as priority.

5.6. Dose Justification

Dose justification for all study drugs are located in the arm-specific appendices (Section 12.1).

6. STUDY POPULATION

Participants are eligible to be included in the study only if all of the criteria in Section 6.1 and Section 6.2 apply. In addition, participants must fulfill additional inclusion/exclusion criteria for at least one arm. Criteria for each individual arm can be found in the respective appendices for each arm, reported in Section 12.1.

Prospective approval of protocol deviations to recruitment and enrollment criteria (waivers or exemptions) is not permitted.

6.1. Inclusion Criteria

1. Capable of giving signed informed consent/assent as described in Section 12.4 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol
2. Male or female, aged 18 years or older at the time consent is obtained

Note: Participants in Korea must be age 19 years or older at the time consent is obtained.

3. Histologically or cytologically confirmed diagnosis of NSCLC (squamous or non-squamous) and:
    a. Documented disease progression based on radiographic imaging, during or after a maximum of 2 lines of systemic treatment for locally/regionally advanced recurrent, Stage IIIb/Stage IIIc/Stage IV or metastatic disease

    Two components of treatment must have been received in the same line or as separate lines of therapy:

        i. no more than or less than 1 line of platinum-containing chemotherapy regimen, and
        ii. no more than or less than 1 line of PD(L)1 mAb containing regimen.

        Notes:

        - PD(L)1 mAb received during a previous clinical trial may meet this requirement upon consultation with study medical monitor.
        - Participants who received a regimen similar to the PACIFIC regimen [chemoradiotherapy followed by PD(L)1] as part of SoC AND have relapsed within one year from the first dose of chemoradiotherapy would fulfill the protocol requirement for platinum-based chemotherapy treatment and PD-1/L1 treatment. This would be considered a single line of treatment for the purpose of PD(L)1 line of therapy stratification.
        - PD(L)1 mAb can be administered with the platinum-based chemotherapy regimen and this would count as a single line of therapy.
        - PD(L)1 mAb may be counted as a prior treatment if the agent is approved in at least 1 country for the treatment of cancer.

- Participants who have completed 2 years of pembrolizumab or another PD(L)1 mAb, discontinue from that therapy, experience disease progression, and are then retreated with PD(L)1, will be considered as having had one line of PD(L)1 therapy.
- Adjuvant or neo-adjuvant systemic anticancer therapy will not count toward the 2 lines of therapy unless disease recurs during the first year following the start of adjuvant chemotherapy.

b. Participants with known BRAF molecular alterations must have had disease progression after receiving the locally available SoC treatment for the molecular alteration.

c. Participants who received prior anti-PD(L)1 therapy must fulfill the following requirements:
   - Have achieved a CR, PR or SD and subsequently had disease progression (per RECIST 1.1 criteria) either on or after completing PD(L)1 therapy
   - Have not progressed or recurred within the first 12 weeks of PD(L)1 therapy, either clinically or per RECIST 1.1 criteria

4. Measurable disease, presenting with at least 1 measurable lesion per RECIST 1.1 (see Appendix 12 for definition of a measurable lesion)
5. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score of 0 or 1
6. A tumor tissue sample obtained at any time from the initial diagnosis of NSCLC to time of study entry is mandatory. Although a fresh tumor tissue sample obtained during screening is preferred, archival tumor specimen is acceptable. See Study Reference Manual (SRM) and Section 9.9.2 for further details on tumor tissue requirements.
7. Adequate organ function as defined in Table 2.

Table 2 Definitions of Adequate Organ Function

System	Laboratory Values
Hematologic[a]	
ANC (Absolute Neutrophil Count)	≥1.5 x 10^9/L (≥1500/µL)
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Platelets	≥100 x 10^9/L (≥100 000/µL)
Hepatic	
Albumin	≥2.5 g/dL
Total bilirubin Patients with Gilbert's Syndrome (only if direct bilirubin ≤35%)	≤1.5 x ULN (isolated bilirubin >1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) ≤3.0 x ULN
ALT (SGPT)	≤2.5 x ULN, **OR** ≤5 X ULN for participants with documented liver metastases
Renal	
Calculated CrCl[b]	≥30 mL/min

Abbreviations: ALT = alanine aminotransferase; CrCL = creatinine clearance; SGPT = serum glutamate-pyruvate transaminase; ULN = upper limit of normal.

a. Participants may be transfused or receive growth factor treatment to meet minimum hematologic values up to 7 days prior to determining eligibility. Absolute Lymphocyte Count will be included in the baseline assessment, but no range limit requirement for eligibility.

b. Calculated CrCL is required to be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) or Cockcroft-Gault formula. Either formula is acceptable and must be consistently utilized for each participant throughout the study (Appendix 9).

8. A male participant must agree to use a highly effective contraception as detailed in Appendix 6 of this protocol during the treatment period and for at least 120 days after the last dose of study treatment and refrain from donating sperm during this period. Unless otherwise specified under each arm in Section 12.1

   Note: If the participant is randomized to the SoC regimen only, duration of contraception should be as per local label.

9. A female participant is eligible to participate if she is not pregnant (see Appendix 6), not breastfeeding, and at least 1 of the following conditions apply:

   i. Not a woman of childbearing potential (WOCBP) as defined in Appendix 6

      OR

   ii. A WOCBP who agrees to follow the contraceptive guidance in Appendix 6 during the treatment period and for at least 120 days after the last dose of study treatment.

      Note: If the participant is randomized to the SoC regimen only, duration of contraception should be as per local label.

10. Life expectancy of at least 12 weeks

6.2. Exclusion Criteria

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

1. Received prior treatment with the following therapies (calculation is based on date of last therapy to date of first dose of study treatment):

    a. Docetaxel at any time

    b. Any of the investigational agents being tested in the current study, refer to Section 12.1 for additional information

    c. Systemic approved or investigational 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.

    d. Prior radiation therapy: permissible if at least one non-irradiated measurable lesion is available for assessment per RECIST version 1.1 or if a solitary measurable lesion was irradiated, objective progression is documented. A wash out of at least 2 weeks before start of study drug for radiation of any intended use is required.

2. Received >2 prior lines of therapy for NSCLC, including participants with BRAF molecular alterations. (See inclusion criterion #3 for eligible lines of therapy guidance)

Note: Patients with known molecular alterations with therapeutic options available (e.g., EGFR, ALK, ROS1) are excluded from participation in this study, unless no other therapeutic options are available locally.

3. Invasive malignancy or history of invasive malignancy other than disease under study within the last 2 years, except as noted below:

    - Any other invasive malignancy for which the participant was definitively treated, has been disease-free for at least 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 or successfully treated in situ carcinoma of the skin.

4. Carcinomatous meningitis (regardless of clinical status) and uncontrolled or symptomatic central nervous system (CNS) metastases.

    Note: Participants with previously treated brain metastases may participate provided they are asymptomatic (any neurologic symptoms have returned to baseline [participants may be receiving stable doses of anticonvulsants]), radiographically stable (without evidence of progression by imaging for at least 4

weeks prior to the first dose of study treatment), have no evidence of new or enlarging brain metastases, and are clinically stable off steroids for at least 2 weeks prior to study treatment.

5. Major surgery ≤28 days of first dose of study treatment.

6. Autoimmune disease (current or history) or syndrome that required systemic treatment within the past 2 years (Refer to Appendix 14). Replacement therapies which include physiological doses of corticosteroids for treatment of endocrinopathies (for example, adrenal insufficiency) are not considered systemic treatments.

   Note: Participants with controlled Type 1 diabetes mellitus (T1DM) are eligible.

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

Note: Steroids as premedication for hypersensitivity reactions (e.g., computed tomography [CT] scan premedication) are permitted. Use of inhaled corticosteroids, local steroid injection, or steroid eye drops is allowed.

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

9. Receipt of any live vaccine within 30 days prior to first dose of study treatment. Refer to the SRM for clarity on COVID-19 vaccines.

10. Toxicity from previous anticancer treatment that includes:

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

    b. History of myocarditis of any grade during a previous treatment with immunotherapy

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

11. 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 upon by the investigator and Medical Monitor.

12. Recent history (within the past 6 months) of uncontrolled symptomatic ascites, pleural or pericardial effusions

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

14. History or evidence of cardiac abnormalities within the 6 months prior to enrollment which include:

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

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

    c. Symptomatic pericarditis.

    NOTE: Participants with Troponin and/or NT-ProBNP/BNP ≥2 x ULN will require a cardiologist or locally appropriate specialist review to identify underlying conditions that may meet exclusion criteria or that may require increased monitoring on study. In addition, consider cardiologist or locally appropriate specialist review for potentially significant ECG abnormalities such as AV block (except for first degree), new cardiac arrhythmias, or frequent premature ventricular contractions (PVCs). Please inform the Sponsor regarding these participants.

15. Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis.

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

16. Active infection requiring systemic therapy ≤7 days prior to first dose of study treatment.

17. Known human immunodeficiency virus infection

18. History of severe hypersensitivity to monoclonal antibodies or hypersensitivity to any of the study treatment(s) or their excipients.

19. Requires ongoing therapy with a medication that is a strong inhibitor or inducer of the cytochrome 3A4 (CYP3A4) enzyme (Flockhart, 2018). This criterion is applicable to only those participants in treatment arms containing docetaxel.

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

21. Pregnant or lactating female participants

22. Is currently participating in or has participated in a study of an investigational device within 4 weeks prior to the first dose of study treatment.

23. Presence of hepatitis B surface antigen (HBsAg) at screening or within 3 months prior to first dose of study intervention

24. Positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study intervention.

NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained.

25. Positive hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment.

NOTE: Test is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing.

26. Receipt of 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, and recombinant erythropoietin) within 14 days before the first dose of study intervention.

6.3. Lifestyle and Dietary Restrictions

No lifestyle restrictions are planned for this study however male participants with partners of childbearing potential and women of childbearing potential must utilize appropriate contraception as described in Section 12.6.

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting. However, foods that are CYP3A inhibitors must not be consumed during the study for those participants in Part 2 on Docetaxel arm. Grapefruit, star fruit, and pomegranate are known to be CYP3A inhibitors, and should not be consumed for 2 weeks before the first dose of docetaxel and for at least 2 weeks after the last dose of docetaxel. Note that consumption of CYP3A4 inhibitors such as these may significantly increase the levels of docetaxel. St. John's Wort is a CYP3A inducer, and the consumption of St. John's Wort or products containing St. John's Wort may reduce the levels of docetaxel.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized/entered in the study. Laboratory results obtained during screening should be used to determine eligibility criteria. In situations where laboratory results are outside the permitted range, the investigator may opt to retest the participant and the subsequent screening result, if within range, may be used to confirm

eligibility. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants must be assigned a new unique participant number that is different from the initial number.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

6.5. Screening under Molecular Disease Characterization Initiative Study

Participants may be initially screened under GSK protocol 213299 (a molecular disease characterization initiative study) where it is IRB/IEC approved at a site and then referred to this study 205801. Screening assessments performed under protocol 213299 may be accepted for the enrollment into this GSK protocol 205801 to avoid any repeat screening tests.

Baseline Biopsy:

If a biopsy was acquired under GSK protocol 213299, tissue blocks/slides from this biopsy may be used for additional screening or baseline analyses required by this protocol (205801). Another biopsy may be needed for treatment specific screening at baseline in cases where there is not enough remaining material from biopsy acquired under GSK protocol 213299.

Screening/Baseline Imaging and Other Assessments:

If radiographic imaging was performed under GSK protocol 213299, those images may be used for screening/baseline disease assessment. Images must meet the acceptable scanning modalities and anatomical coverage required for this protocol (205801). Additional scans may be needed to meet inclusion/exclusion criteria, safety requirements, or other anatomical areas as required by this protocol (205801). Additional scans are required if imaging falls outside the screening/baseline acceptable visit window.

Please refer to SRM for more information.

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant per the study protocol.

7.1. Treatments Administered

The term study treatment(s) is used throughout the protocol as a general descriptor for any or all treatment arms/regimens or the individual agents.

All investigational agents utilized in this study will be provided to sites by the Sponsor. Docetaxel will be sourced locally from commercial stock, except in countries where local regulations mandate that the Sponsor supply all study treatment(s) required for the trial.

As additional substudies are initiated, treatment details for experimental regimens from those substudies will be provided in Section 12.1.

7.2. Dose Modification

Dose modifications, including interruptions and reductions, may occur for the management of AEs according to the current product label for SoC (e.g., docetaxel) and guidelines provided in the protocol for investigational agents.

Note: If a participant, randomized to an experimental treatment arm, experiences a toxicity attributable to one of the drugs in the combination, the investigator may discontinue the responsible drug but continue treatment with the other drug. In all such scenarios, the SoA applicable to the active treatment(s) must be followed.

Additional dose modification guidelines for specific experimental regimens will be provided in Section 12.1 as needed when new substudies are initiated.

7.2.1. Dose and Safety Management Guidelines

7.2.1.1. General Guidelines for Immune-Related Adverse Events (irAEs)

AEs associated with immunotherapy treatment may be immune-mediated. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of treatment, or during the treatment course, and may affect more than one body system simultaneously. Therefore, early recognition of and initiation of treatment for these events is critical to reduce potential complications.
For suspected irAEs, ensure adequate evaluation to confirm the etiology or exclude other causes. Additional procedures or tests such as, but not limited to, bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue treatment and administer corticosteroids and/or immuno-modulators. Dose modification and toxicity management guidelines for irAEs associated with immunotherapies are provided for each arm in the respective subsections under Section 12.1.

Note: This guidance does not apply to participants randomized to Arm 1 SoC chemotherapy in Part 2.

Before administration of study treatment, investigators are to review a participant's AEs, concomitant medications, and clinical evaluation results, e.g., vital signs, laboratory results, ECOG PS, physical examination findings, responses, etc. as outlined in the Schedule of Activities (Section 12.1) to monitor for new or worsening irAEs and ensure continued dosing is appropriate.

Adverse Events of Special Interest (AESI)

AESI are considered to be Infusion Related Reactions (IRRs) and those of potential immunologic etiology, including irAEs. Such events recently reported after treatment with other immune modulatory therapy include, but are not limited to, the following: pneumonitis, nephritis, hepatitis, colitis, immune related endocrinopathies (such as thyroiditis or hypophysitis) or immune related cutaneous toxicities, to include rashes confirmed via biopsy to be immune-mediated.

AESIs will be reported within 24 hours if the event meets the criteria for a serious event.

Dose modification and toxicity management guidelines for irAEs are provided for each arm in the respective subsections under Section 12.1.

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

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

Infusion reactions may affect any organ system in the body. Most are mild in severity, although severe and even fatal reactions occur. As a group, infusion reactions (including both cytokine-mediated and allergic) usually occur during or within a few hours of drug infusion. Occasionally, a reaction may occur 1 to 2 days after administration. The NCI-CTCAE (version 5.0) for grading adverse reactions during chemotherapy administration has a scale for grading the severity of infusion reactions and separate grading scales for allergic reactions and anaphylaxis. While use of these separate grading scales may be useful for classifying the nature of an infusion reaction for research purposes, they are less useful for clinical care, since it may not be obvious if the participant is having an allergic infusion reaction or a non-allergic infusion reaction.

Clinically, an acute-onset infusion reaction may present with flushing, itching, urticaria, and/or angioedema, repetitive cough, sudden nasal congestion, shortness of breath, chest tightness, wheeze, sensation of throat closure or choking, and/or change in voice quality, faintness, tachycardia (or less often bradycardia), hypotension, hypertension and/or loss of consciousness, nausea, vomiting, abdominal cramping, and/or diarrhea, sense of impending doom, tunnel vision, dizziness, and/or seizure, severe back, chest, and pelvic pain. Dose modification and treatment guidance for immunotherapy infusion reactions are provided for each arm in the respective subsections under Section 12.1.

To better understand the underlying etiology of these events, serum tryptase, C-reactive protein (CRP), ferritin, and a cytokine panel should be drawn during the occurrence of an infusion reaction/CRS of any grade as outlined in Table 3. Only if not possible to collect at the occurrence of the event, samples should be drawn as soon as possible after the event and within 24 hours. The serum tryptase, CRP and ferritin panels must be performed at the investigator's designated local laboratory. The serum cytokine panel will be performed at a GSK designated laboratory. These data will aid in the classifying (albeit retrospectively) the etiology of the infusion reaction AE. Infusion-related reaction management guidelines are provided for each study arm in Section 12.1.

Table 3 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] (IFN-γ*^, TNF-α*^, 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]

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

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

7.2.1.3. Management Guidance of Chemotherapy-related Toxicities

Refer to Table 4 and Table 5 for guidance on specific chemotherapy-related AEs; refer to chemotherapy prescribing information or standard practice guidelines for the management of these AEs, other AEs or potential safety-related issues.

Table 4 Dose Reductions for Docetaxel-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)	• 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
	• Febrile neutropenia	• Hold docetaxel; upon recovery, if ANC <500/mm^3 for more than 7 days, resume at 55 mg/mm^2

a. Resume treatment with chemotherapy after resolution as indicated; treatment with other study treatment may continue unless otherwise instructed.

Table 5 Dose Reductions for Docetaxel-related Non-Hematologic Events

Chemotherapy Regimen	Toxicity	Action[a]
Docetaxel	• Grade 3/Grade 4 event (including severe or cumulative cutaneous reactions), except peripheral neuropathy	• Hold docetaxel upon recovery to ≤Grade 1/baseline, resume treatment at 55 mg/mm^2
	• Grade 3/Grade 4 peripheral neuropathies	• Consider permanent discontinuation; discuss with Medical Monitor

a. Resume treatment with chemotherapy after resolution as indicated; treatment with other study treatment may continue unless otherwise instructed.

Refer to docetaxel prescribing information or standard practice guidelines for the management of these AEs, other AEs or potential safety-related issues [TAXOTERE PI, 2020].

7.2.1.4. Dose Delay for Toxicity or Other Illness

If there is a dose delay between 1 and 7 days, the procedures required at the original scheduled visit (including dosing) should be performed as soon as possible. Refer to the SRM for instructions regarding assessments to be collected and how to record data in the eCRF.

If the delay is ≥8 days, the visit and dose(s) will be considered missed. The procedures at the next regularly scheduled visit should be performed (with dosing), and subsequent visits will follow Q3W.

Participants with infusion delays greater than 3 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.

7.3. Method of Treatment Assignment

Once determined to be eligible for the study, all participants will be centrally randomized using an Interactive Web Response System (IWRS). Before the study is initiated, the directions for the IWRS and log in information will be provided to each site. Once determined to be eligible for the study, participants must be randomized via IWRS. Study drug shipment will be managed via IWRS. Sites must allow up to 7 business days for shipment of study drug.

Study treatment will be dispensed at the study visits summarized in SoA for treatments found within the SoA for each arm (Section 12.1).

7.4. Blinding

This is an open-label study. Sites will record the treatment assignment on the applicable eCRF.

7.5. Preparation/Handling/Storage/Accountability

7.5.1. Preparation

Refer to the SRM for instructions on the preparation of investigational study treatments. Refer to the package insert for docetaxel preparation instructions.

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
1. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments

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

2. 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).
3. Further guidance and information for the final disposition of unused study treatment are provided in the SRM.

7.5.2. 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 generation of aerosols or mists. In case of unintentional occupational exposure notify the monitor, Medical Monitor, and/or GSK study contact.
- A Material Safety Data Sheet (MSDS) or equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.5.3. Storage

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

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

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

7.6. Treatment Compliance

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

7.7. Concomitant Therapy

Participants will be instructed to inform the investigator prior to starting any new medications from the time of the 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 Medical Monitor for clarification.

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

Refer to the drug interaction information in the product package inserts for precautions and prohibited concomitant medications related to docetaxel treatment [TAXOTERE PI, 2020; TAXOTERE SmPC, 2020].

7.7.1. Permitted Medications and Non-Drug Therapies

Participants receiving docetaxel 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. Refer to the SRM for permitted COVID-19 vaccines. 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: Please also refer to Section 12.1 for medications specific to each experimental combination.

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

b. Growth factors: Prophylactic use of growth factors are not permitted during study treatment, unless clinically/therapeutically indicated for toxicity management.

c. Steroids: Refer to Section 7.2.1 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 study treatment; see exclusion criteria in Section 6.2 for further requirements. Steroids used for chemotherapy premedication are permitted.

d. Prescribed medicinal cannabinoids are permitted during the study as palliative therapy.

7.7.2. Prohibited Medications and Non-Drug Therapies

The following medications are prohibited before the first dose of study treatment (see Section 6.2 for specific time requirements) and while on treatment in this study: Please also refer to Section 12.1 for medications specific to each experimental combination.

- 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 7.7.1).
- Any investigational drug(s) other than those referred to as Study Treatment.
- Refer to the SRM for guidance on COVID-19 and other vaccines.
- Strong CYP3A4 inhibitors and inducers for participants receiving docetaxel alone or in combination with another study drug (use as premedication is permitted).
- Herbal preparations or related over the counter (OTC) preparations containing herbal ingredients that are known to affect CYP3A isoenzymes (e.g., St. John's Wort) either during or within 2 weeks prior to the first dose of docetaxel.

7.8. Treatment after the End of the Study

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

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Participants will receive study treatment for the scheduled time period as indicated in Section 12.1 but must discontinue treatment if one of the following events occurs earlier:

- Confirmed disease progression (iCPD as determined by iRECIST)
- death
- unacceptable toxicity, including meeting stopping criteria for liver chemistry abnormalities as defined in Appendix 10

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

- deviation(s) from the protocol or non-compliance with study requirements
- request of the participant or proxy (withdrawal of consent by participant or proxy)
- discretion of the investigator

- participant is lost to follow-up
- closure or termination of the study

Continuation of Treatment Upon Disease Progression

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

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

Termination of a Substudy/Experimental Arm

If a substudy/experimental arm is terminated based on interim results and a participant is currently active in the substudy, receiving study treatment, and in the opinion of the investigator is deriving benefit from that treatment without evidence of disease progression, the participant may continue to receive study treatment upon agreement between the Sponsor and the investigator.

Study Termination

If the study is terminated by the Sponsor for reasons unrelated to safety or efficacy and a participant is currently active in the study, the Sponsor will notify the investigator of the study termination, further enrollment in the study will be terminated, and the Sponsor will communicate to investigative sites the discontinuation procedures and plans for discontinuation of patients from study treatment.

Termination Due to Toxicity

If the participant discontinues from treatment due to toxicity, the relevant AE will be recorded on the eCRF as the primary reason for permanent discontinuation.

Termination from Study Treatment

If a participant discontinues study treatment for reasons other than disease progression, does not have evidence of disease progression and chooses to continue in the study, the participant will continue study assessments according to the visit schedule described in the SoA for the specific arm in Section 12.1. The participant will be followed until disease progression by iRECIST or the start of a new systemic anti-cancer therapy, whichever comes first.

Procedures Following Discontinuation

The primary reason for permanent study treatment discontinuation must be documented in the participant's medical records and eCRF.

Once a participant has permanently discontinued from study treatment, the participant will not be allowed to be retreated but will remain on the observational phase of the study for survival follow-up.

All participants who discontinue from study treatment will have safety assessments at the time of discontinuation and during post-study treatment follow-up as specified in the SoA for the specific substudy in Section 12.1.

All participants who permanently discontinue study treatment without disease progression will be followed for survival according to the protocol schedule until one or more of the following occur:

- death
- withdrawal of consent for the observational phase of survival follow-up

In the observational phase of the study, all participants who permanently discontinue study treatment will be followed via telephone contact every 12 weeks from the date the last dose for survival and new anticancer therapy, including radiotherapy, until death or withdrawal from further contact. New anticancer therapy information should be reported in the eCRF for those participants who die before the first follow-up contact.

Decisions regarding dose interruptions or modifications for reasons other than management of events as already described in this section and elsewhere in this protocol will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.1.1. Liver Chemistry Stopping Criteria

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

Discontinuation of study treatment for abnormal liver tests is required when a participant meets one of the conditions outlined Figure 2 or Figure 3, based on baseline ALT:

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

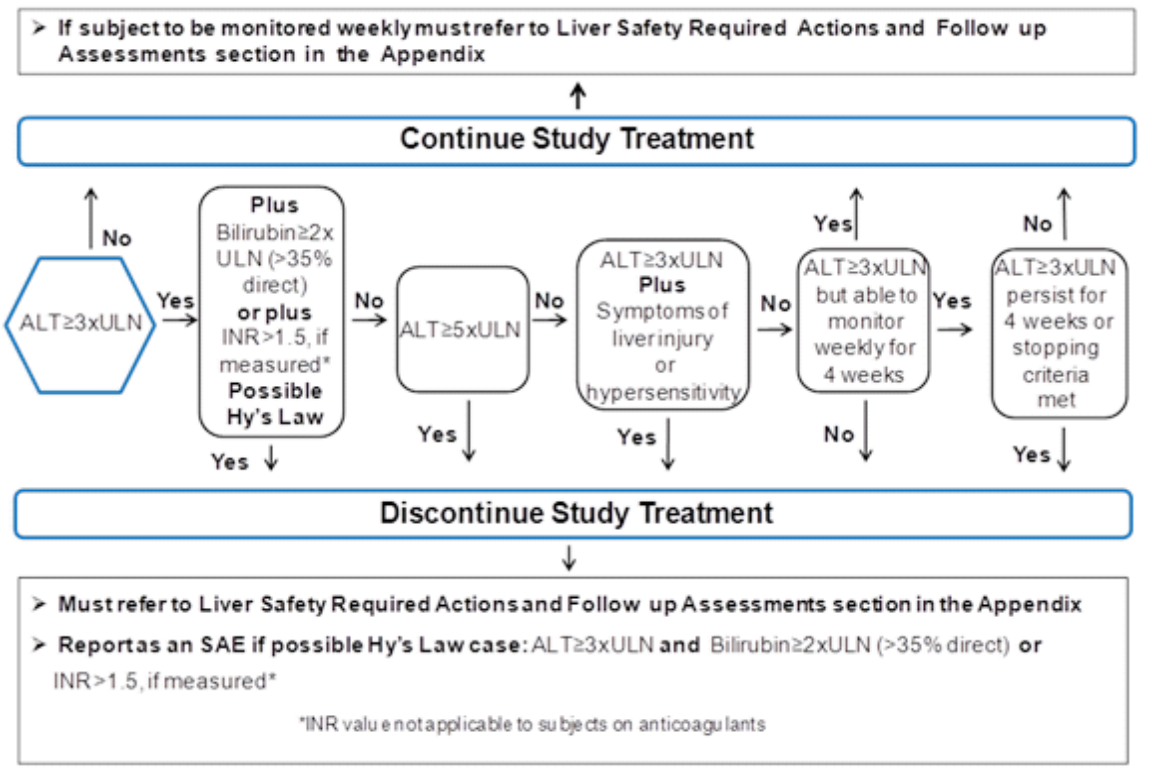
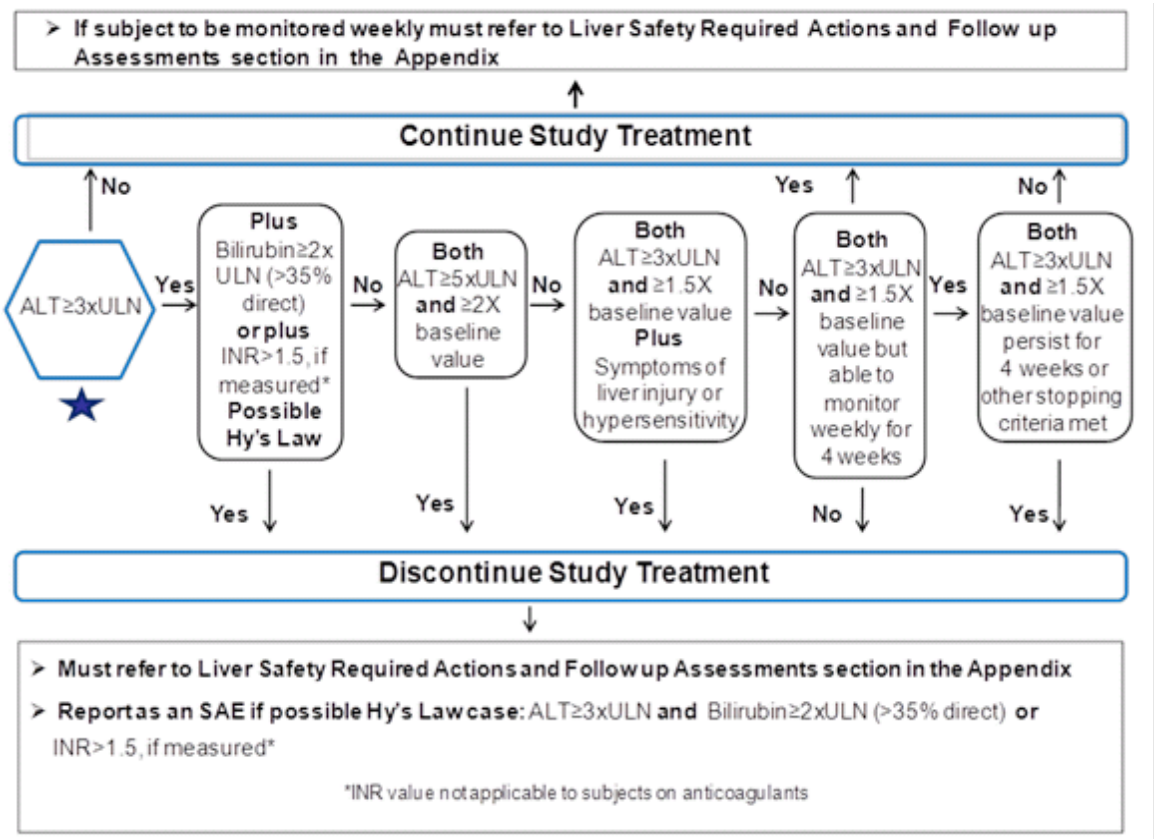


Figure 3 Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm for Participants with documented liver metastases with ALT up to 5 X ULN at Baseline



The details on follow-up procedures are outlined in Appendix 10.

Stopping Rules for Clinical Deterioration

To adequately assess the antitumor effect of immunotherapeutic agents it is reasonable to allow participants experiencing apparent progression as defined by RECIST 1.1 guidelines to continue to receive treatment until progression is confirmed at the next imaging assessment at least 4 weeks later as indicated by iRECIST guidelines. Nevertheless, these considerations should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued study 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 and written consent by the participant must be obtained. Examples of events that may, in the investigator's opinion, indicate a lack of clinical benefit include, but are not limited to, the following:

- Worsening of ECOG PS from baseline by at least 2 points
- Skeletal related events defined by the following:
  - pathologic bone fracture in the region of cancer involvement
  - cancer related surgery to bone, and/or
  - spinal cord or nerve root compression
- Development of new CNS metastases
- Any setting where the initiation of new antineoplastic therapy has been deemed beneficial to the participant even in the absence of any such documented clinical event.
  See Section 8.1 above for specific requirements when considering continuation of treatment.

8.1.2. Study Treatment Restart/Rechallenge

Study treatment restart or rechallenge is not allowed after liver chemistry stopping criteria are met by any participant in this study unless:

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

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.

Refer to Section 12.10 for additional information.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons. No further assessments will be required and the investigator must document this in the site study records.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study after providing study samples, GSK will retain those samples and any results from sample testing prior to participant withdrawal, as described in the informed consent. However, if a participant requests destruction of their samples at the time of withdrawal, the investigator should alert GSK and document this in the site study records. Once notified, GSK will ensure no new testing will be performed on the sample and the sample will be destroyed.
- A participant will be considered to have withdrawn from the study if the participant has not died and is lost to follow-up.
- Refer to the SoA for data to be collected at the time of study discontinuation and for any further evaluations that need to be completed.

8.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

Study procedures are summarized in the SoA tables within each arm Appendix (Section 12.1): Table for Screening assessments, Treatment Period assessments, and Treatment Discontinuation Visit [TDV] and Follow-Up assessments. Visit windows, as allowable, are notated in the SoA tables.

9.1. General Guidance

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

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of 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 procedures fulfill the protocol defined specifications and has been performed within the protocol indicated timeframe.

The following points must be noted:

- Informed consent must be signed by a participant before any study required procedures are performed. However, procedures conducted as part of the routine clinical management (e.g., imaging studies) and conducted prior to signing of the study informed consent may be used for screening/baseline assessments provided the procedure fulfills the protocol defined specifications and has been performed within the protocol indicated timeframe.
- If assessments are scheduled for the same nominal time, then the assessments must occur in the following order:

  1. 12-lead ECG
  2. Vital signs
  3. Blood draws

  Note: The timing of the assessments must allow the blood draw to occur at the exact nominal time.
- The timing and number of planned study assessments, including safety, biomarker or other assessments may be altered during the course of the study based on emerging data to ensure appropriate monitoring.
- The change in timing or addition of time points for any planned study assessments must be approved by the relevant GSK study team member and then archived in the study Sponsor and site study files, but this will not constitute a protocol amendment.
- No more than approximately 1375 mL of blood will be collected from each participant over the full course of study treatment (2 years).

9.1.1. General Guidance for Treatment Continuity when Participants are Unable to Come into the Clinic

Prior to utilization of any of the measures outlined in this section, discussion and approval must be obtained from Sponsor/contract research organization.

It is expected that sites participating in clinical studies will make every effort to ensure proper monitoring and well-being of enrolled participants by adhering to safety monitoring as outlined in the SoA (Section 12.1). The use of local laboratories and local radiology centers to reduce the need for a participant to come into the clinic is supported, if deemed necessary for the well-being of the participant. These local facilities should be added to regulatory documents, as required.

Any restrictions in place at the site that will impact monitoring and/or participant access to the site and care providers should be communicated to the Sponsor/contract research organization.

A global telemedicine platform that allows for continued monitoring of AEs, concomitant medications, protocol deviations, etc., may be engaged. Discussions around utilization of

this technology should be held on a per-site basis, and appropriate documentation of utilization should be captured.

In general, for participants with limited possibility to travel or decreased capacity to come to the clinic, replace non-dosing in-person visits with phone contact or alternative location for assessment (e.g., local laboratories and imaging centers, at-home collection of patient reported outcomes [PROs]).

9.2. Screening and Critical Baseline Assessments

All screening assessments must be performed within 28 days prior to the first dose unless otherwise specified. The ICF may be signed within 45 days prior to first dose.

The term 'baseline' refers to the assessment performed during the screening period prior to first dose of study treatment that serves as a comparison or control. For example, the baseline laboratory assessment is the laboratory assessment performed prior to first dose.

Refer to SoA for each arm (Section 12.1) for additional details on assessments required at Screening and prior to start of study treatment. All assessments performed must be documented in the site source documents.

The following assessments are required during screening:

- Demographic parameters such as year of birth and sex will be captured.

- Medical history including cardiovascular medical history, tobacco use, and other risk factors will be assessed as related to the inclusion/exclusion criteria.
- Disease characteristics including medical, surgical, and treatment history including radiotherapy, date of initial diagnosis, stage at initial diagnosis according to the 8th Edition of TNM for Lung Cancer by the Union for International Cancer Control [UICC], histology, tumor genetic/genomic features sand current sites of disease will be taken as part of the medical history and disease status. Scans from imaging studies performed prior to screening may be requested for assessment of baseline lesions. Details concerning prior anticancer therapy (for example, systemic and radiation therapy), including best response to prior systemic therapy will be recorded.

- If available, any antibiotic use within 90 days prior to the first dose of study should ideally be recorded to help inform the effect of antibiotics on clinical outcome through its manipulation of the immune system.

- PD-L1 protein expression by IHC in patients with NSCLC is commonly utilized to determine PD-L1 status prior to initiation of treatment with a PD-L1 inhibitor. PD-L1 expression by IHC and type of assay utilized (i.e., Ventana SP263, Ventana SP142, Dako 28-8, or Dako 22C3) must be recorded in the eCRF, if known.

Baseline lesion assessments required within 28 days prior to the first dose of study treatment include:

- Computed tomography (CT) scan with contrast of the chest and abdomen

  Note: Although a CT scan is preferred, magnetic resonance imaging (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 the method used to document baseline status is used consistently throughout study treatment to facilitate direct comparison. When MRI is used for disease assessment, a non-contrast CT of the chest should also be performed, to evaluate the lungs. Refer to RECIST 1.1 guidelines for use of fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT [Eisenhauer, 2009; Seymour, 2017].

- MRI of brain with and without IV gadolinium (if clinically indicated)
- Bone scan (if clinically indicated)
- Clinical disease assessment for palpable/visible lesions
- Other areas as indicated by the participant's underlying disease present prior to screening

Refer to Section 9.3.1 for baseline documentation of target and non-target lesions.

Safety and laboratory assessments (Section 9.5) required at baseline include:

- Physical examination
- ECOG Performance Status
- Vital Signs
- Concomitant medication
  - Recorded starting from screening through post-study follow-up.
  - Record all medications the participant is taking including prescription medications, over-the-counter (OTC) drugs or preparations, and herbal preparations including any cannabinoids and/or recreational drugs used.
  - At a minimum, the drug name, route of administration, dose, and frequency of dosing, along with start and stop dates must be recorded.
- Electrocardiogram
- Echocardiogram
- Laboratory assessments

9.3. Efficacy Assessments

Planned time points for all efficacy assessments are listed in in each specific arm SoA Tables within Section 12.1.

9.3.1. Tumor Imaging and Disease Assessments

RECIST 1.1 will be used in the assessment of disease burden (target and non-target lesions determination) at Screening and as the primary measure of tumor response endpoints.

Additionally, iRECIST guidelines will be used in the assessment of response/progression to account for the unique tumor kinetics observed with immunotherapeutic agents which may manifest as an increase in tumor burden then later is followed by regression suggesting the apparent observed neoplastic growth representing transient lymphocyte infiltration. Following approval by the medical monitor and signed informed consent to continue treatment post-progression (Section 8.1), participants with disease progression by RECIST version 1.1 guidelines should have a confirmatory disease assessment no sooner than 4 weeks after the date disease progression was declared in order to confirm disease progression by iRECIST guidelines. The visit level responses and treatment-based decisions will incorporate iRECIST guidelines [Seymour, 2017].

Refer to the SoA for each arm (Section 12.1) for the frequency of disease assessments post screening.

A description of the adaptations and iRECIST process is provided in Appendix 12, with additional details in the iRECIST publication [Seymour, 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression provided in Table 54 and illustrated as a flowchart in Figure 11 in Appendix 12.

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

Notes:

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

All bone scan abnormalities at Screening that could indicate metastases should be evaluated by X-ray, CT, or MRI to determine if they represent malignant lesions. If a bone scan was performed within 6 weeks prior to the first dose, it does not need to be

repeated (in the absence of new or worsening clinical symptoms suggesting bone involvement). Typically bone scanning will be performed using bone scintigraphy. However, positron emission tomography (PET) scan ([^{18}F]-fluorodeoxyglucose or [^{18}F]-fluoride) is acceptable, providing coverage is sufficient to evaluate total spine, clavicle, ribs, pelvis (if performed) and long bones.

In the event a photograph is taken of a particular lesion, the site will submit the photograph to the central imaging vendor. Refer to the site central imaging vendor manual technical requirements for photograph submission.

9.3.1.1. Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to first dose. Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if it is of diagnostic quality and performed within 28 days prior to first dose and can be assessed by the central imaging vendor.

9.3.1.2. Tumor Imaging During the Study

The first on-study imaging assessment must be performed 6 weeks after the first dose of study treatment. Subsequent tumor imaging must be performed every 6 weeks until Week 49 and every 12 weeks thereafter. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the investigator.

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

Per iRECIST (Appendix 12), disease progression should be confirmed by the site at least 4 weeks and up to 8 weeks after site-assessed first radiologic evidence of PD, following approval of treatment continuation by the medical monitor and signed consent by the participant. Participants who have unconfirmed disease progression may continue treatment at the discretion of the investigator until progression is confirmed by the site, provided they have met the conditions detailed in Appendix 12.

9.3.1.3. End of Treatment Imaging

For participants who discontinue study treatment due to disease progression, tumor imaging does not need to be repeated at the TDV. If previous imaging was obtained within 6 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory.

For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring disease status by tumor

imaging using the same imaging schedule used while on treatment until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

9.3.2. Tumor Growth Kinetics

To evaluate the effect of study therapy on the growth rate of individual tumor lesions, pre-baseline images (within approximately 12 months before the baseline scan; images obtained >12 months prior to the baseline scan may also be accepted upon consultation with Medical Monitor) will be requested to support exploratory investigation of tumor growth kinetics. Up to 3 pre-baseline scans may be requested and submitted to the central imaging vendor. Only those participants who consent to this collection will have their pre-baseline images submitted to the central vendor for these analyses.

CT/MRI of the chest and abdomen with IV contrast are preferred, if available, and per local standard of practice. The same modality used at study baseline imaging is encouraged to be submitted, but not required. If performed, imaging of the brain along with any other areas of disease that were imaged in the 6 months prior to baseline scan may also be submitted. PET images are not required but may be submitted; and, the CT portion (with IV contrast if possible) of a PET/CT examination is acceptable if no other CT examinations are available.

9.3.3. Survival Follow-up

After a participant receives the last dose of study treatment, he or she will enter the survival follow-up period. Follow-up for survival and new anticancer therapy (including radiotherapy) will occur every 12 weeks until death, completion or termination of the overall study, or withdrawal of consent. Follow-up will be conducted via telephone contact.

9.4. Adverse Events

The definitions of AEs and SAEs are provided in Appendix 5.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment (see Section 8). Adverse events must be assessed and documented at each patient contact.

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

- All AESIs and SAEs will be collected from the start of treatment until 90 days after the last dose of study treatment at the time points specified in the SoA (Section 2). However, any AESI or SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study. 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 collected until 30 days after last dose of study treatment and documentation of the subsequent anticancer treatment will be recorded in the eCRF.

- All AEs will be collected from the start of study treatment until 30 days after the last dose of study treatment at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded in the Medical History/Current Medical Conditions section of the CRF and not in the AE section.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 5. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 5.

9.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AESIs (Section 7.2.1 and Section 9.4.1), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). 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 collected until 30 days after last dose of study treatment and documentation of the subsequent anticancer treatment will be recorded in the eCRF. Further information on follow-up procedures is given in Appendix 5.

9.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study treatment under clinical investigation are met.

- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAE) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.4.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 5 and all deaths, if they are considered SAEs, specific cardiovascular and death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV (cardiovascular) eCRFs are presented as queries in response to reporting of certain cardiovascular MedDRA terms. The cardiovascular information should be recorded in the specific cardiovascular section of the eCRF within 1 week of receipt of a cardiovascular event data query prompting its completion.

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

9.4.6. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment and until 120 days after the last dose of study treatment. For participants randomized to the SoC only arm, pregnancy details with be collected after the start of study treatment and until at least 3 days after the last dose of study treatment (or per institutional standard).
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 9.4.4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.5. Safety Assessments

Planned time points for safety assessments are provided within each arm SoA Appendix (Section 12.1). Additional time points for safety testing may be added during the study

based on newly available data to ensure appropriate safety monitoring. PK and ADA samples will also be collected for safety. See Section 9.6 and Section 9.7 for additional information.

9.5.1. Physical Examinations

- A complete physical examination performed at Screening will include, at a minimum, assessment of the cardiovascular, respiratory, gastrointestinal, skin and neurological systems.
- A brief physical examination performed at each subsequent visit (refer to SoA tables for each arm in Section 12.1), 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.
- Physical examinations may be performed within one day of dosing (i.e., as opposed to the day of dosing), if necessary.

9.5.2. Performance Status

Performance status will be assessed using the ECOG scale at each visit, on the day of treatment or within 24 hours prior to dosing, if necessary (Appendix 8).

9.5.3. Vital Signs

- Vital signs will be measured after 5 minutes of rest and will include temperature, systolic and diastolic blood pressure, pulse rate, respiratory rate, and oxygen saturation (measured by pulse oximetry). Blood pressure should be taken in the same position throughout the study and captured in the eCRF.
- Vital signs will be measured more frequently if warranted by clinical condition of the participant.
- On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.
- If a participant develops fever and infusion related reaction or cytokine release syndrome is suspected, refer to management guidelines (Section 7.2.1).
- Height will be recorded at Screening only.
- Weight will be measured and recorded (in kilograms) at baseline and every other treatment visit.
- Vital signs must be recorded prior to dosing on treatment days.

9.5.4. Electrocardiograms

A 12-lead ECG will be obtained at screening using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals; manual calculation of QTcF is permitted. ECGs may be repeated during the study as clinically indicated, unless noted otherwise in the SoA for each arm under Section 12.1.

Cardiologist or locally approved specialist review is required if abnormal results are obtained and confirmed as described in Table 34 and Table 46 (Cardiac Investigations).

9.5.5. Echocardiogram

Echocardiograms (ECHO) will be performed locally at baseline to assess cardiac ejection fraction for study eligibility, as specified in the SoA (Section 12.1). Additional ECHO assessments may be performed if clinically warranted. The evaluation of the echocardiography should include an evaluation for LVEF and both right and left-sided valvular lesions. Multigated Acquisition Scan (MUGA) can be used in lieu of ECHO (if not feasible) in the assessment of LVEF; the same modality should be used in any subsequent assessments.

9.5.6. Clinical Safety Laboratory Assessments

Refer to Appendix 3 for the list of clinical laboratory tests to be performed and to the SoA for each arm (Section 12.1) for the timing and frequency.

The investigator must review the laboratory report prior to administration of study treatments, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All protocol required safety laboratory assessments, as defined in Table 51 must be conducted in accordance with the SoA for each arm. Reference ranges for all safety parameters must be provided to the site by the laboratory responsible for the assessments.

All study-required safety laboratory assessments will be performed at the institution’s local laboratory. Laboratory safety assessments required prior to dosing may be performed up to 3 days prior to dosing, if necessary. The results of each test must be recorded in the eCRF. If additional non-protocol specified laboratory assessments are performed at the institution’s local laboratory and result in a change in participant management or are considered clinically significant by the investigator (for example, SAE or AE or dose modification) the results must also be recorded in the eCRF.

For all other protocol required blood and tissue sample collections, laboratory requisition forms must be completed, and samples must be clearly labeled with the participant number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples that are required to be tested by a central laboratory will be provided by the laboratory and are detailed in the laboratory manual.

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

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 must be identified, and the Sponsor notified.

9.6. Pharmacokinetics

Planned time points for all pharmacokinetics assessments are listed in the SoA for each arm (Section 12.1).

9.6.1. Blood Sample Collection

Blood samples for PK analysis are to be collected as indicated in the SoA. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure adequate PK monitoring.

Details on PK blood sample collection, processing, storage, and shipping procedures are provided in the SRM/laboratory manual. If additional study drugs are added to this study for which PK samples are required, details will be provided in the SRM.

9.6.2. Sample Analysis

PK analysis will be performed for participants as indicated in each SoA. Concentrations of the study treatments will be determined using validated bioanalytical methodologies. Once the analysis has been completed, for any remaining samples may be analyzed for other compound-related metabolites. Refer to the SRM for further details.

9.7. Anti-Drug Antibodies

The actual date and time of each blood sample collection will be recorded for each specific analyte. Details of blood sample collection (including volume to be collected), processing, storage, and shipping procedures are provided in the SRM.

The timing and number of planned immunogenicity samples may be altered during the course of the study, based on newly-available data to ensure appropriate safety monitoring. In the event of a hypersensitivity reaction that is either clinically significant in the opinion of the investigator, or leads to the participant withdrawing from the study treatment, blood samples must be taken from the participant for immunogenicity testing at the timepoints indicated in the arm specific SoAs (Section 12.1).

9.8. Genetics

Planned time points for all genetics-related assessments are listed in in the SoA for each arm (Section 12.1).

A whole blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

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

See Appendix 7 for further information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the SRM.

9.9. Biomarkers

Planned time points for all biomarker assessments are listed in the SoA for each arm (Section 12.1).

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9.9.2. Tumor Tissue

9.9.2.1. Screening Biopsies

Part 1: All participants are required to provide fresh tumor tissue AND archival tumor tissue samples at screening prior to start of study treatment, unless specified otherwise in the SoA of each regimen in the respective subsections under Section 12.1.

Part 2: Tumor tissue at screening (either archival or fresh biopsy if archival tissue is unavailable) is required for all participants in Part 2. Fresh tumor tissue AND an archival tissue sample obtained during screening are required for at least 20 participants for each arm.

Participants with inaccessible tumor or those participants that do not consent to the tumor biopsy procedure may be enrolled provided an archival specimen is submitted. However, no participant will be allowed on study without either an archival specimen OR a fresh biopsy. The archival specimen may have been obtained at any time from the time of initial diagnosis to time of study entry. Sufficient and evaluable tumor tissue for protocol specified testing needs to be provided (reference SRM for more details).

9.9.2.2. On-Treatment Biopsies

Part 1: All participants are required to provide paired fresh biopsies at screening and on-treatment at week 7 (± 8 days), unless specified otherwise in the SoA of each regimen in the respective subsections under Section 12.1.

Part 2: Fresh biopsy collected at week 7 (± 8 days) is optional for participants in Part 2, if tumor is amenable to biopsy and upon participant's consent; However, paired fresh tumor biopsies collected at screening and week 7 (± 8 days) is required for at least 20 participants for each arm.

Enrollment may become limited during the study, as required, to ensure collection of fresh tissue samples as noted.

Additional optional fresh tumor tissue sample will be collected at Week 19 (± 8 days) at the time of imaging assessment and/or at the time of confirmed PR or PD, upon participant consent (± 8 days).
When feasible, tumor imaging should be completed prior to tissue collection to avoid potential radiographic alterations due to the biopsy procedure.

These tissues will be evaluated by IHC or other potential methods, including image analysis, for expression of phenotypic and functional immune cell markers on tumor infiltrating lymphocytes (TIL) and other immune cells as well as immune signaling markers on tumor cells to understand the anti-tumor responses. In addition, when possible, similar analyses will be performed on tumor tissue obtained upon progression. Additionally, tumor tissue may be sequenced to assess T-cell diversity (TCR diversity) as well as evaluated for any DNA/RNA/protein changes correlating with response, including tumor mutational load assessments. These samples may also be evaluated for predictive measures of response to include in the biomarker selected population. If a predictive biomarker is identified, these tissues may be used for the development of a diagnostic test.

Other biomarkers may be evaluated as determined by additional data. Details for the samples collection, processing, storage, and shipment will be provided in the SRM.

9.10. Patient-Reported Outcome Assessments

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[redacted]

Table 6 PRO Outcomes Assessed in Study 205801

Instrument	Role	Rationale & Overview
CCI [redacted]		
CCI [redacted]		

CCI

[redacted]

CCI

10. STATISTICAL CONSIDERATIONS

10.1. Primary Endpoint

10.1.1. Primary Endpoint: Part 1

The primary endpoint for Part 1 is the incidence of AEs, SAEs, DLTs, changes in safety/laboratory assessment parameters, and dose modifications.

A key secondary endpoint for Part 1 is Objective Response Rate (ORR) using RECIST 1.1 by investigator assessment. ORR is defined as the percentage of participants with a best overall response of CR or PR at any time.

10.1.2. Primary Endpoint: Part 2

The primary endpoint for Part 2 is OS. OS is defined as the interval from date of randomization to the date of death, irrespective of the cause of death. If a participant does

not have a documented date of death or is lost to follow-up, time of death will be censored at the date of last contact.

10.2. Hypothesis

10.2.1. Hypothesis: Part 1

The primary objective of Part 1 is to establish the safety and tolerability of the experimental combination regimen of each arm.

10.2.2. Hypothesis: Part 2

The primary objective of Part 2 is to determine whether the experimental arms prolong overall survival relative to standard of care. The null hypothesis is that there is no difference in overall survival between each experimental arm and the SoC and alternative hypothesis is that the experimental regimen improves overall survival over the SoC. The predictive probability inference approach will be used as the basis for both interim and final decision making. The predictive probability of success (PoS) in future Phase 3 study (phase 3 success being defined as a statistically significant log-rank test with 1-sided alpha=0.025) will be calculated as a measure of the improvement in OS in the experimental arm compared with the SoC arm. A cutoff of 43% or greater for the PoS of future Phase 3 study, approximately corresponding to an observed HR no greater than 0.8 in a substudy, will be implemented as the criteria for an experimental regimen to be considered for proceeding to Part 2. As this is a signal finding study and not confirmatory, each experimental arm will be compared to control in a pairwise fashion with no adjustment for multiple comparisons.

10.3. Sample Size Determination

10.3.1. Sample Size: Part 1

For Part 1, sample size will be defined for each regimen under the corresponding appendix in Section 12.1.

The FDA approved dose of docetaxel provides the following outcomes, based on the validated data.

	Study			
	TAX 317	**Control for 317**	**TAX320**	**Control for 320**
	Docetaxel 75 mg/m² n=55	**Best Supportive Care n=49**	**Docetaxel 75 mg/m² n=125**	**Vinorelbine or Ifosfamide n=123**
95% CI (Risk Ratio)	(0.35, 0.88)		(0.63, 1.06)	
Median Survival (95% CI)	7.5 months (5.5, 12.8)	4.6 months (3.7, 6.1)	5.7 months (5.1, 7.1)	5.6 months (4.4, 7.9)

	Study			
	TAX 317	**Control for 317**	**TAX320**	**Control for 320**
	Docetaxel 75 mg/m² n=55	**Best Supportive Care n=49**	**Docetaxel 75 mg/m² n=125**	**Vinorelbine or Ifosfamide n=123**
% 1-year Survival (95% CI)	37% (24, 50)	12% (2, 23)	30% (22, 39)	20% (13, 27)
Time to Progression (95% CI)	12.3 weeks (9.0, 18.3)	7.0 weeks (6.0, 9.3)	8.3 weeks (7.0, 11.7)	7.6 weeks (6.7, 10.1)
Response Rate (95% CI)	5.5% (1.1, 15.1)	N/A	5.7% (2.3, 11.3)	0.8% (0.0, 4.5)

Additional information is available from the control arm of the FDA approved label for pembrolizumab where docetaxel was used as a control. The following table summarize those data.

Endpoint	**Docetaxel 75 mg/m2 every 3 weeks n=152**
OS Deaths (%)	86 (57%)
OS Median in months	8.2 (6.4, 10.7)
PFS Events	118 (78%)
PFS Median in months	4.1 (3.6, 4.3)
ORR	8% (4, 13)
Median duration of response in months (range)	8.1 (2.1+, 8.8+)

Examining the confidence intervals for docetaxel response rates across not only the FDA approved package inserts, but other published studies show that while the point estimates for response rate may vary, the 95% Confidence Intervals around the point estimates remain in the 5%-15% range. Consequently, using a 10% Response Rate as a benchmark is reasonable based on available data. Data from 205801 platform study Substudy 1, if available, may be used to calibrate this assumption of the docetaxel monotherapy response rate for the futility analysis.

10.3.2. Sample Size: Part 2

In Part 2, 70 participants in each experimental arm and a minimum of 35 participants in the SoC arm will be randomized. Sample size and associated operating characteristics were evaluated via simulation.

The 8-month milestone survival in the SoC arm is estimated to be ~40% in squamous cell lung cancer (Brahmer, 2015), ~60% in non-squamous lung cancer (Borghaei, 2015), and ~50% in PD-L1 positive population (Herbst, 2016). The participant population in the current study is expected to be a mixed population with both squamous and non-squamous lung cancer participants; therefore, mean target rate is assumed to be ~50% (Figure 4).

For the target effect of experimental regimens, there is a potential delayed effect at treatment start and sustained effect after prolonged follow-up (Brahmer, 2015; Borghaei, 2015). The survival probability in these arms is expected to overlap in the SoC arm for up to 4 months from start of treatment followed by a separation. It is hypothesized that percentage of surviving participants is maintained at 20% after 24 months (Figure 4).

Under the alternative hypothesis three-piece piecewise Weibull distributions are used to describe the survival distribution of each experimental arm and two-piece piecewise Weibull distributions are used to describe the survival curve of docetaxel (Refer to Appendix 13 for simulation parameters). Details of the piecewise Weibull model are provided in the statistical appendix (Section 12.13). Using this modeling approach for the primary endpoint of OS, the assumed survival curve for the SoC arm is presented using blue dashes and the target survival curve for the experimental arm is presented as the solid red curve in Figure 4. Based on these two curves, the hazard ratio is approximately 0.58.

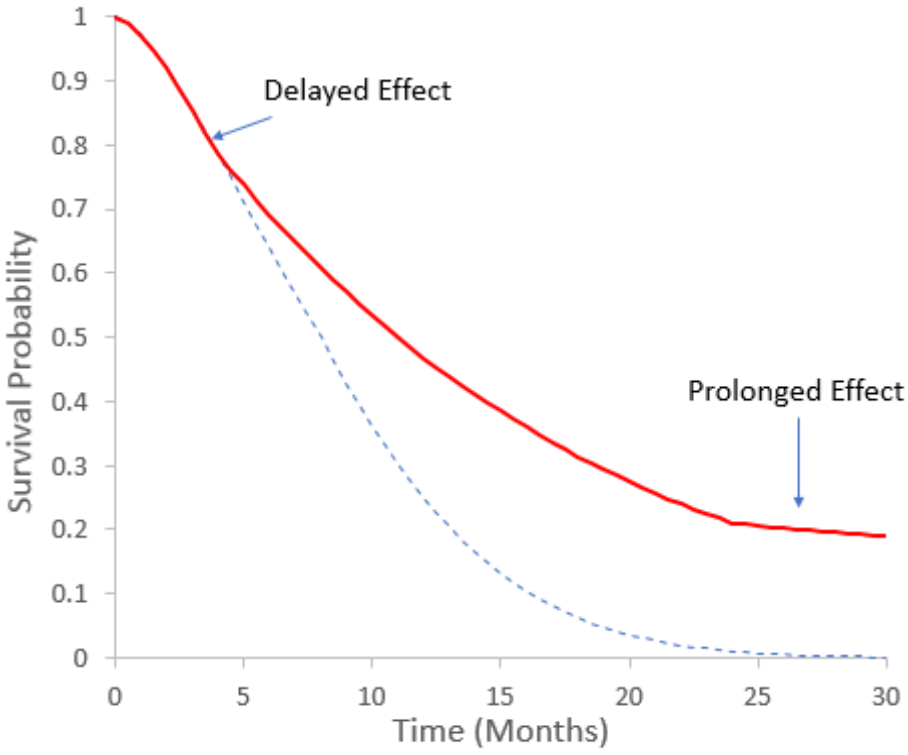
Sample size was chosen by simulating the entire platform in which 4 experimental arms enter the master protocol at different points in time. Enrollment of 9 participants per month is assumed. Interim and final analyses are performed based on predetermined decision rules as specified in Section 10.3.3 and Section 10.5.1, respectively. The planned Phase 3 sample size is 300 (150 participants per arm and a total of 210 events). The future phase 3 trial will use the log-rank (frequentist) test and the decision rule at interim and end of phase 2 will use the (Bayesian) predictive probability, given the results in phase 2, that the future log-rank test in phase 3 study will be significant, thus, resulting in a methodology that is a mixture of Bayesian and frequentist. Simulations assess the Operating Characteristics of the predictive probability decision criteria under the null and alternative hypotheses, as described in Section 10.3.4. A cutoff of 43% or greater for the PoS of future phase 3 study, approximately corresponding to an observed HR $\leq$ 0.8 for each substudy, is used as a guide for future development of each experimental arm. Sample size was calculated under the simulated survival curves shown in Figure 4.

The final analysis of OS for a substudy will be performed when approximately 85 death events have occurred in the experimental arm and SoC arm combined, and the last participant in that substudy has been randomized for at least 6 months. In the case death events occur at a rate lower than expected due to potentially prolonged survival benefit,

to avoid substantial delay of final analysis for a substudy, the primary analysis for a substudy may be conducted once approximately 75 events have occurred and the last participant in that substudy has been randomized for at least 6 months, at the discretion of the Sponsor. A minimum of 35 events are needed from the experimental arm for both primary and final analysis.

Assuming the true HR≈0.58, 85 death events will provide 94.2% probability (power) of achieving the guidance criteria with future phase 3 study success ≥ 43%. In the case of primary analysis being performed with 75 death events, it will provide 88.3% probability of achieving the guidance criteria. If the true HR is 1, 85 and 75 death events will have 16.6% and 18.2% Type I error, respectively.

Figure 4 Assumed Survival Probability Under Alternative Hypothesis in Experimental Regimens (Red) and Docetaxel (Blue)



10.3.3. Interim Analyses

10.3.3.1. Interim Analyses: Part 1

An interim evaluation of futility in terms of ORR may be conducted for an arm if data permits. Details for futility analyses are provided in the respective subsection for each arm in Appendix Section 12.1.

10.3.3.2. Interim Analyses: Part 2

This is a platform study utilizing a master protocol designed so that additional experimental arms may enter and leave the trial at different time points as determined by pre-specified decision criteria.

Part 2 of the study will be conducted under the auspices of an IDMC and steering committee. The membership and activities are outlined in the IDMC and steering committee charters. This committee will review all available interim safety and efficacy data as the study progresses. Interim analyses will be performed approximately every 6 months depending on the amount of additional data accrued.

Interim Analyses for OS

An interim analysis of OS will be conducted for each substudy after approximately 45 events (experimental arm and SoC combined) and a minimum of 18 events from experimental arm have been observed. Note, events from the SoC arm will be counted from the initial study start (i.e. SoC events from substudy 1 will be counted with any further events observed in subsequent substudies). Stopping guidelines will be provided as part of the IDMC charter. Final decisions on termination of an arm will be based on the totality of the data.

Final analysis for Graduation

The final analysis for each substudy will occur after observing 85 events (experimental regimen and SoC combined) and the last participant in a substudy has been randomized for at least 6 months. A minimum of 35 events are needed from the experimental arm for the final analysis of that substudy. In the case of death events occur at a rate slower than expected due to potentially prolonged survival benefit, to avoid substantial delay of final analysis for a substudy, primary analysis for a substudy may be conducted once approximately 75 events have occurred and at least 35 events observed in the experimental arm, and the last participant in that substudy has been randomized for at least 6 months, at the discretion of the Sponsor. A cutoff of 43% or greater for the PoS of future phase 3 study is used as graduation criteria for an experimental regimen to be considered for proceeding to Part 2. The final decision of proceeding to Part 2 will be based on the totality of data. An experimental regimen may be discontinued at any time due to safety concerns.

Additional details of the interim analysis will be provided in the RAP and IDMC charter.

10.3.4. Statistical Operating Characteristics

For Part 1, please see details under the corresponding appendix for each arm in Section 12.1.

For Part 2, simulations were carried out to determine the operating characteristics for the primary comparisons for Part 2. The simulation results are presented in Table 7 and Table 8. Since the randomization ratios for subsequent studies range from 1:4 to 1:2 (as shown in Table 1), the simulations for subsequent studies were performed for both 1:4 and 1:2 scenarios. Table 7 shows simulation results for 85 events at final analysis as planned and Table 8 shows simulation results for the primary analysis with 75 events in the case primary analysis is decided to be conducted.

The simulations on OS are based on the following assumptions:

1. The sample size for the experimental arm is 70 for all substudies. The sample size for the control arm is 35 for substudy 1, and for subsequent studies it follows dynamic randomization ratios as described in Table 1.

2. The required minimum number of death events in the experimental arm are 18 for the interim analysis and 35 for the final (or primary) analysis.

3. The survival curve for the SoC arm and the experimental arm are assumed to be same as presented in Figure 4, with target HR≈0.58. The Weibull parameters of each curve used for the simulations are detailed in Section 12.13.1.

4. The recruitment rate is approximately 9 participants per month.

5. The start date of Part 2 of subsequent studies is ~34 months after the start date of substudy 1.

6. The futility threshold for interim analysis is 5% or less for the PoS of future phase 3 study , as described in Appendix C of the IDMC charter.

7. A cutoff of 43% or greater for the PoS of future phase 3 study is used as graduation criteria for each experimental arm.

It is noted that the simulations were performed for single substudy scenario instead of multiple experimental arms randomized concurrently. Although concurrent randomization may potentially affect the enrolment speed, since substudies are event driven, it is not expected to lead to substantial change of the operating characteristics except for timing of interim and final analysis.

Table 7 Statistical Operating Characteristics for Target Effect (HR ≈ 0.58) and Null Effect (HR=1) for 85 Events at Interim and Final Analysis

Treatment Effect Scenarios	Substudies	Number of Participants in SoC Arm		Interim Analysis of OS			Final Analysis (85 events)		
		Participants from Substudy 1	Participants from Subsequent Substudy	Average Events		Prob. of Futility	Average Events		Power or Type I error (Pred. prob.≥43%)
				SoC	Trt		SoC	Trt	
HR ~ 0.58	Substudy 1	35	NA	17.4	27.6	3.4%	33.1	51.9	94.2%
	Subsequent substudy (ratio 1:4)	35	18	40.8	18	9.3%	47.8	37.3	81.9%
	Subsequent substudy (ratio 1:2)	35	35	46.1	18	9.2%	58.4	35	76.3%
HR =1	Substudy 1	35	NA	15	30	19.0%	28.3	56.7	16.6%
	Subsequent substudy (ratio 1:4)	35	18	39.9	18	22.6%	45.3	39.7	14.9%
	Subsequent substudy (ratio 1:2)	35	35	44.5	18	22.0%	53	35.4	15.6%

Note: The simulation did not incorporate the minimum requirement of 6 months from randomization date of the last participant to analysis date.

Table 8 Statistical Operating Characteristics for Target Effect (HR ≈ 0.58) and Null Effect (HR=1) for 75 Events at Primary Analysis

Treatment Effect Scenarios	Substudies	Number of Participants in SoC Arm		Primary Analysis (75 events)		
		Participants from Substudy 1	Participants from Subsequent Substudy	Average Events		Power or Type I error (Pred. prob.≥43%)
				SoC	Trt	
HR ~ 0.58	Substudy 1	35	NA	29.8	45.2	88.3%
	Subsequent substudy (ratio 1:4)	35	18	47	35	76.7%
	Subsequent substudy (ratio 1:2)	35	35	58.4	35	76.3%
HR =1	Substudy 1	35	NA	25	50	18.2%
	Subsequent substudy (ratio 1:4)	35	18	44.2	35	16.2%
	Subsequent substudy (ratio 1:2)	35	35	52.8	35	15.6%

Note: The simulation did not incorporate the minimum requirement of 6 months from randomization date of the last participant to analysis date.

10.3.5. Sample Size Sensitivity

It is expected that the statistical operating characteristics will be dependent on assumptions around target treatment effects and survival curve of SoC. Evaluations of sensitivity analysis were performed varying one assumption at a time (See Table 9, Table 10, Figure 5, and Figure 6). Sensitivity analysis with respect to HR was conducted using simulations under two scenarios: HR=0.48 and HR=0.70. For the case where HR=0.48, the target survival curve for the experimental arm is presented in Figure 6A using the thick solid orange curve and the assumed survival curve for SOC is presented using blue dashes. For the case where the HR=0.70, the target survival curve for the experimental arm in Figure 6B is presented using the thick solid green curve and the assumed survival curve for SOC is presented using blue dashes. The experimental target survival curve (with HR=0.58 relative to SOC) is also presented (with notation) in both figures. Sensitivity analysis simulation results showing the operating characteristics of the predictive probability decision criteria under these 2 scenarios (HR=0.48 and HR=0.70) are presented in Table 9.

Table 9 Sensitivity Analysis to Evaluate the Assumption of Treatment Effects

Treatment Effect Scenarios	Substudies	Number of Participants in SoC		Interim Analysis of OS			Final Analysis (85 events)		
		Participants from Substudy 1	Participants from Subsequent Substudy	Average Events		Prob. of Futility	Average Events		Overall Power (Pred. prob.≥43%)
				SoC	Trt		SoC	Trt	
Greater than Target Effect (HR ≈ 0.48)[1]	Substudy 1	35	NA	18.3	26.7	1.8%	34.3	50.7	99.2%
	Subsequent substudy (ratio 1:4)	35	18	41.1	18	6.6%	48.9	36.4	93.9%
	Subsequent substudy (ratio 1:2)	35	35	46.9	18	6.5%	61.1	35	90.0%
Lower than Target Effect (HR ≈ 0.7)[2]	Substudy 1	35	NA	16.6	28.4	6.3%	31.6	53.4	76.8%
	Subsequent substudy (ratio 1:4)	35	18	40.4	18	12.6%	46.9	38.2	61.7%
	Subsequent substudy (ratio 1:2)	35	35	45.5	18	13.0%	56.2	35.1	56.3%

[1] Greater than target effect as shown in Figure 6A (Solid Orange Curve).
[2] Lower than Target effect as shown in Figure 6B (Solid Green Curve).
Note: The simulation did not incorporate the minimum requirement of 6 months from randomization date of the last participant to analysis date.

Sample size sensitivity analysis is also performed assuming higher survival probability of SoC, while the survival probability of experimental arm does not change. The simulation results are presented in Table 10.

Table 10 Sensitivity Analysis with Higher Survival Probability in SoC (median survival = 9 months as described in solid blue line in Figure 5)

Substudies	Number of Participants in SoC Arm		Interim Analysis of OS			Final Analysis (85 events)		
	Participants from Substudy 1	Participants from Subsequent Substudy	Average Events		Prob. of Futility	Average Events		Power or Type I error (Pred. prob.≥43%)
			SoC	Trt		SoC	Trt	
Substudy 1	35	NA	16.7	28.3	5.9%	32.3	52.7	83.8%
Subsequent substudy (ratio 1:4)	35	18	40.4	18	12.8%	47.1	37.9	66.1%
Subsequent substudy (ratio 1:2)	35	35	45.5	18	12.2%	56.8	35.1	61.0%

Note: The simulation did not incorporate the minimum requirement of 6 months from randomization date of the last participant to analysis date.

Figure 5 Survival of SoC (solid blue line) is Higher than Target Survival of SoC (dotted blue line)

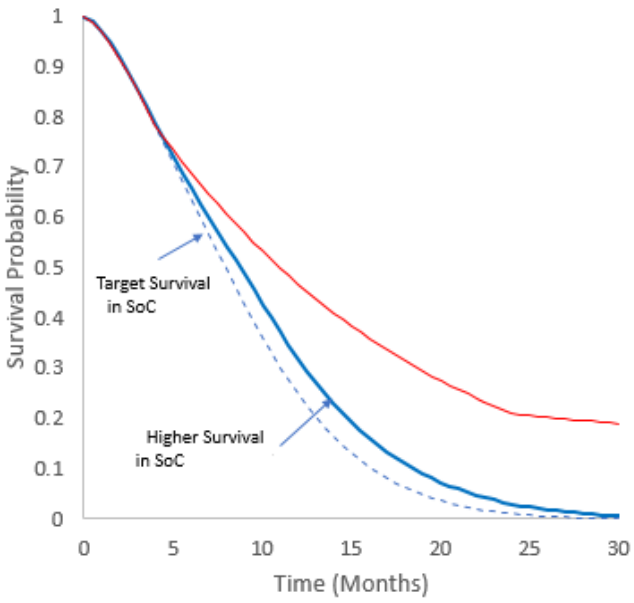
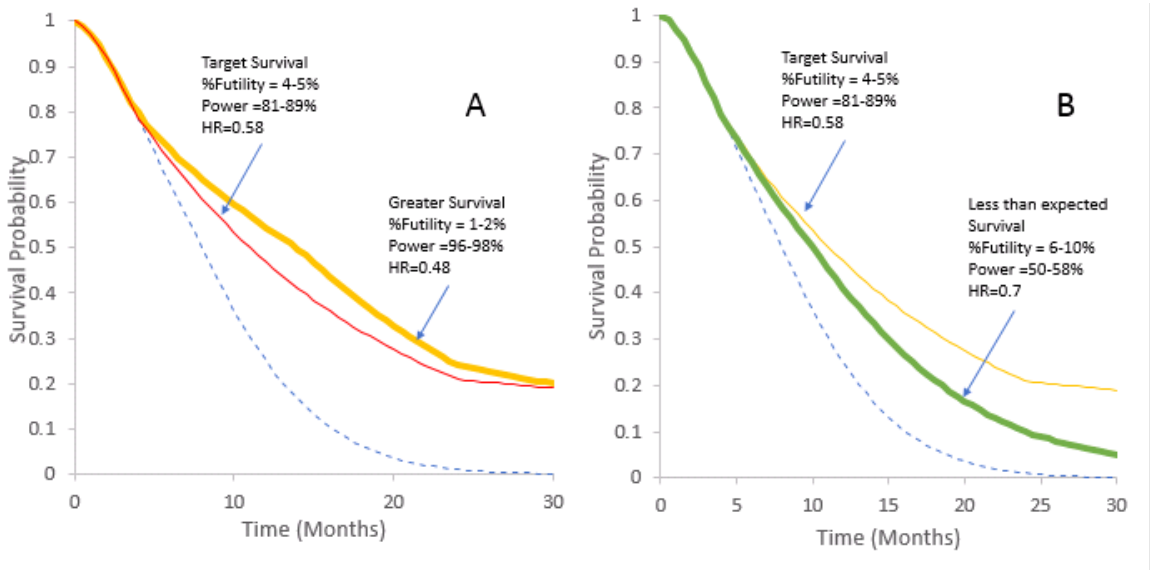


Figure 6 Survival Curves of Experimental Arms in Greater Than Expected Survival (A: Orange Solid Line) and Less Than Expected Survival (B: Green Solid Line)



10.3.6. Sample Size Re-estimation

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

10.4. Populations for Analyses

For analysis purposes, the following populations are defined:

The **Intent to Treat Population (ITT)** is defined as all participants who were randomized to treatment regardless of whether the participants actually received study treatment. All efficacy endpoints will be evaluated based on this population.

The **Safety Population** is defined as all participants who receive at least 1 dose of SoC or experimental regimen based on actual treatment received. All safety endpoints will be evaluated based on this population.

The **PK Population** will consist of all participants from the ITT Population from whom a blood sample is obtained and analyzed for PK concentration.

DLT-evaluable participants are defined as all participants who take at least 1 dose of study intervention and are followed for the DLT observation period or are withdrawn within the DLT observation period due to meeting the DLT criteria and no resolution/recovery per dose modifications and toxicity management guidelines. (Note: participants enrolled in a PK/PD cohort at a previously cleared dose will not be included in the DLT evaluable population).

10.5. Statistical Analyses

This is a platform study utilizing a master protocol with different arms for each experimental regimen(s), the statistical analyses will be conducted separately for each arm. Data will be listed and summarized according to the GSK reporting standards, where applicable. Complete details of the analysis will be documented in the Reporting and Analysis Plan (RAP). Any changes to the analysis plan described in this protocol will be documented in the RAP and final clinical study report (CSR).

10.5.1. Analysis

10.5.1.1. Part 1 Analysis

The primary objective of Part 1 is to establish the safety and tolerability of experimental regimens prior to transition to Part 2 of the study.

Safety and tolerability will be guided using the methodology and associated dose decision rule as described in the respective subsection for each substudy in Appendix Section 12.1. However, to ensure safety of participants, dose recommendations based on the statistical methodology can be overridden at the discretion of the Medical Monitor, especially in the event of DLT.

10.5.1.2. Part 2 Primary Efficacy Analysis

The primary endpoint for Part 2 is OS. The primary analysis is HR and its 95% confidence interval from the Cox model with a single treatment covariate. The PoS of future phase 3 study will also be reported. A cutoff of 43% or greater for the PoS of future phase 3 study is used as a guide for future development of each experimental arm.

The theorem and details for the calculation of PoS are provided in Appendix Section 12.13.2.

10.5.1.2.1. Sensitivity Analysis

To evaluate the exchangeability assumption between non-concurrent and concurrent SoC data, sensitivity analyses will be conducted to evaluate time-dependency in the SoC arm. The exchangeability assumption will be examined by comparing overall survival between non-concurrent and concurrent SoC data, by using Cox's proportional hazard model with indicator in control data (0: nonconcurrent, 1: concurrent data) as a covariate. If there is a difference in OS between non-concurrent and concurrent SoC, this difference will be further investigated or examined. Sensitivity analysis will be conducted if there is evidence of a violation of the exchangeability assumption. An example of a sensitivity analysis is one where only the concurrent data will be included (i.e., no non-concurrent data are used) in evaluating the treatment effect of the experimental regimen at data analysis.

10.5.1.3. Key Secondary Endpoint

The key secondary endpoints are the milestone survival rates at 12 and 18 months, which will be estimated using the Kaplan-Meier method. The milestone survival and the differences between the experimental arm and SoC will be presented. The details of the analysis will be further discussed in RAP.

10.5.2. Other Secondary Analyses

10.5.2.1. Anticancer Activity Analyses

The ITT Population will be used for anticancer activity analyses. Anticancer activity will be evaluated based on clinical evidence and response criteria. The response data will be summarized by each treatment (iRECIST will be used for response endpoints and disease measurements for iORR, iDCR, iDOR and iPFS; RECIST 1.1 guidelines will be used for response endpoints and disease measurements for ORR, DCR, DOR and PFS).

ORR, DCR, DOR, PFS, and OS as well as iORR, iDCR, iDOR and iPFS will be calculated and summarized.

- ORR or iORR is defined as the percentage of participants with a best overall confirmed CR or PR at any time as per disease-specific criteria.
- DCR or iDCR is defined as the percentage of participants with a confirmed CR + PR at any time, plus SD ≥12 weeks.
- DOR or iDOR is defined as the first documented evidence of CR or PR until disease progression or death due to any cause among participants who achieve an overall response (i.e., unconfirmed or confirmed CR or PR). Censoring rules will follow those of the PFS analysis. TTR is defined as the interval from the first dose of study treatment to the date of the first documented CR or PR.
- PFS or iPFS defined as time from the date of randomization to the date of disease progression per clinical or radiological assessment or death due to any cause, whichever occurs earlier. For the analysis of PFS, if the participant received subsequent anticancer 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 SD) prior to the initiation of therapy. Otherwise, if the participant does not have a documented date of event, PFS will be censored at the date of the last adequate assessment.

At each interim analysis, if a participant does not have an event or is lost to follow-up, the participant will be censored at the last contact date (OS) or last imaging date (PFS). Further details on rules of censoring will be provided in the RAP. PFS and OS will be summarized using the Kaplan-Meier method.

10.5.3. Safety Analyses

The Safety Population will be used for the analysis of safety data. All safety endpoints (e.g., adverse event data, clinical laboratory assessments, vital signs, etc.) will be summarized according to the scheduled, nominal visit at which they were collected and across all on-treatment time points. Complete details of the safety analyses will be provided in the RAP.

10.5.3.1. Extent of Exposure

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

10.5.3.2. Adverse Events

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

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, AESIs and AEs leading to dose modifications for toxicity management if irAEs of study treatment. AEs, if listed in the NCI-CTCAE (version 5.0) will be summarized by the maximum grade, otherwise, the AEs will be summarized by maximum intensity.

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

10.5.3.3. Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be summarized using frequencies and proportions according to NCI-CTCAE (version 5.0). Laboratory test results outside the reference ranges that do not have an associated NCI-CTCAE criteria will be summarized using proportions. Further details will be provided in the RAP.

10.5.3.4. Other Safety Measures

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

10.5.4. Pharmacokinetic Analyses

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

PK analysis of drug concentration-time data will be conducted by non-compartmental methods under the direction of CPMS. The following PK parameters may be determined as data permit:

- maximum observed concentrations (C_{max})

- trough concentrations (C_{trough} or C_{min})
- Any additional PK parameters that may be calculated as data permit, e.g., area under the plasma or serum concentration-time curve ($AUC_{(0-t)}$) will be presented in the study report

Statistical analyses of the PK parameters data will be the responsibility of Clinical Statistics, GSK.

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

The data from this study may be combined with the data from other studies for a population PK analysis. The details of such analysis will be outlined in a separate RAP; results of this analysis may be reported separately.

10.5.5. Pharmacokinetic/Pharmacodynamic Analyses

If deemed appropriate and if data permit, exploratory Pharmacokinetic / Pharmacodynamic analyses such as exposure-response relationships between exposure (e.g., dose, C_{max} or C_{min}) and safety/efficacy/PD parameters (e.g.: anti-tumor response, biomarkers) may be conducted. The details of such PK/PD analyses will be outlined in a separate RAP; results of these analyses may be included in a report separate from the clinical study report. The data from this study may be combined with the data from other studies, which may be reported separately.

10.5.6. Tumor Kinetic Analyses

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

If deemed necessary, additional statistical analyses will be discussed in a separate RAP. The data from this study may be combined with the data from other studies, which may be reported separately.

10.5.7. Other Analyses

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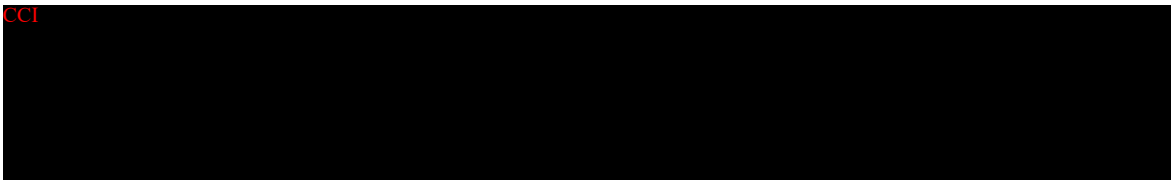

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12. APPENDICES

12.1. Appendix 1: Arms

12.1.1. Standard of Care Arm 1: Docetaxel Alone (Part 2 ONLY)

12.1.1.1. Protocol Amendment 4 Summary of Changes Specific to Docetaxel Arm

Section # and Name	Description of Change	Brief Rationale
Schedule of Activities Section 12.1.1.2	Added physical exam for dosing visits.	To align with the changes made to the other substudies Schedule of Activities.
Schedule of Activities Section 12.1.1.2	Removed details on number of slides for tissue sample to be sent by site.	Decided this detail should be included in the SRM instead and was removed from protocol.
Schedule of Activities Section 12.1.1.2	Clarified that Docetaxel PK samples do not need to be collected after cycles have been completed.	To provide clarity and address site questions.
Schedule of Activities Section 12.1.1.2	At the follow up visit, footnote added: If the participant dies before the first follow up, any subsequent anticancer therapy or radiotherapy should be recorded in the eCRF.	To record any subsequent therapy the participant may have received after study discontinuation, if they die before first follow up is completed.
Schedule of Activities Section 12.1.1.2	Added footnote: **Pre:** predose sample to be collected prior to dosing per institutional guidance, as long as it is collected prior to dosing of the corresponding agent**; EOI**: End of infusion sample is in reference to EOI of the corresponding agent.	To clarify the sample collection reference for predose and EOI.

Protocol Amendment 3 Summary of Changes Specific to Docetaxel Arm

Section # and Name	Description of Change	Brief Rationale
Schedule of Activities Section 12.1.1.2	Added Schedule of Activities specific to docetaxel only treatment.	To provide individual specific Schedule of Activities Table specific to standard of care arm in Part 2.
Study Treatment Section 12.1.1.3	Added required cycles for docetaxel.	Provide additional guidance to align with standard practices for docetaxel administration.

12.1.1.2. Schedule of Activities Specific to Arm 1 Docetaxel (Part 2)

The timing and number of planned study assessments, including [safety, pharmacokinetic, ADA, biomarker or others] assessments may be altered during the course of the study based on newly available data.

Table 11 Schedule of Activities – Screening: Standard of Care Arm 1: Docetaxel Alone

Screening Study Assessments	Screening[1]	Notes
Visit Window	≤4 Weeks	
Informed Consent[1]	X	1. All screening assessments must be performed within 4 weeks (28 days) prior to first dose of study treatment unless otherwise specified. The informed consent may be signed within 45 days prior to first dose.
Participant Registration[2]	X	2. Participants will be registered in RAMOS NG at screening.
Inclusion/Exclusion Criteria	X	Review eligibility prior to randomization.
Demographics, Medical History (including alcohol and tobacco use), Prior Medications, Disease History[12]	X	12. All known mutations should be entered in the eCRF as disease history.
Prior Anticancer Treatment, Radiotherapy	X	
Screening Safety		
AE/SAE/AESI Assessment[3]	X	3. After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. Refer to Section 9.4 for further details.
ECOG PS	X	
Physical Examination	X	
Vital Signs, Height and Weight[4]	X	4. Vital signs include blood pressure, temperature, pulse, respiratory rate, and oxygen saturation. Height is recorded at Screening only. Record weight in kilograms.
12-lead ECG	X	
Echocardiogram or MUGA scan[5]	X	5. ECHO required at Screening within 28 days prior to first dose of study treatment, and during treatment phase if clinically indicated. MUGA scan may be used if ECHO not feasible.
Screening Local Laboratory Assessments (Safety)		
Hepatitis B and C[6]	X	

Screening Study Assessments	Screening[1]	Notes
Visit Window	≤4 Weeks	
Serum β-hCG (for women of childbearing potential)	≤3d	
Clinical Chemistry[6], Coagulation[6], Hematology[6], Thyroid function[6]	X	6. Refer to Appendix 3 for a complete list of required assessments. Required within 7 days of randomization day. If Hepatitis B and C was performed within 3 months prior to first dose of SoC, repeat testing at screening is not required; otherwise, this testing is mandatory.
Calculated CrCl[7]	X	7. CrCl is calculated by the CKD-EPI or Cockcroft-Gault formula. See Appendix 9.
Troponin I or Troponin T	X	
Urinalysis[6]	X	
Screening Other Laboratory Assessments		
PD-L1 expression by IHC[8]	X	8. PD-L1 expression by IHC and type of assay utilized (i.e., Ventana SP263, Ventana SP142, Dako 28-8, or Dako 22C3) must be recorded in the eCRF, if known. Note: Test is not required to be performed by the site if not previously performed.
Screening Disease Assessments		
Tumor Imaging[9]	X	9. Diagnostic quality CT scan of chest and abdomen with contrast must be obtained within 28 days of first dose. Baseline brain scan (MRI with and without IV gadolinium) should be obtained within 6 weeks of first dose if history of CNS disease or if clinically indicated. Bone scan should be obtained within 6 weeks of first dose if clinically indicated. See additional information regarding bone scans in Section 9.3.1.
Pre-Baseline scans for Tumor Growth Kinetics[10]	X	10. Upon participant consent, up to 3 pre-baseline scans (within 12 months before the baseline scan) will be collected to assess tumor growth rate to support exploratory investigation of tumor growth kinetics (See Section 9.3.2 for details on images for submission).
Screening Tumor Biopsies		
Fresh tumor tissue sample and Archival tumor[11]	X	11. Part 2: Tumor tissue at screening (either archival or fresh biopsy if archival tissue is unavailable), is required for all participants in Part 2: Fresh tumor tissue at screening is required in addition to an archival tissue for at least 20 participants in the SoC arm. Participants with inaccessible tumor or those participants that do not consent to the tumor biopsy procedure may be enrolled provided archival specimen is submitted. The archival specimen may have been obtained at any time from the time of initial diagnosis to time of study entry. Note: Enrollment may become limited during the study, as required, to ensure collection of fresh tissue samples as noted.

Abbreviations: AE = adverse event; AESI = adverse events of special interest; β-hCG = β -human chorionic gonadotropin; CKD-EPI = chronic kidney disease epidemiology collaboration; CrCl = creatinine clearance; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiography; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; IHC = Immunohistochemistry; IWRS = interactive web response system; MRI = magnetic resonance imaging; MUGA = multi-gated acquisition; SAE = serious adverse event.

Table 12 Schedule of Activities – Treatment Period: Standard of Care Arm 1: Docetaxel Alone

On Treatment Study Assessments												Notes
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28 - 49**	**52 - 106**	
Day	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190 - 337**	**358 - 736**	
Visit Window	**±3-day window on treatment days unless otherwise noted (Visits occur once every 3 weeks during treatment period)**											
Inclusion/Exclusion Criteria	X											
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	
Participant Randomization[1]	X											1. Once determined to be eligible, participants must be randomized via IWRS. Drug shipments will be managed via IWRS. Sites must allow up to 7 business days for shipment of study drug. Randomization can be done prior to Day 1, but no more than 3 days prior to Day 1. (Refer to SRM).
Study treatments[1]												
Part 2 ONLY Docetaxel/SOC arm[2]	X	X	X	X	X	X						2. For those participants randomized to the SOC arm – docetaxel can be discontinued after 6 cycles as according to local prescribing information. Participants should receive premedication prior to receiving docetaxel as per local standards.
On Treatment Safety												
AE/SAE/AESI Assessment[3]	X	X	X	X	X	X	X	X	X	X	X	3. After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AESIs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.
ECOG PS**	X	X	X	X	X	X	X	X	X	Q6W*	Q6W*	*Q6W procedures are counted starting from Week 25 (i.e. the first Q6W visit is Week 31, then Week 37, etc.).
Physical Examination**	X	X	X	X	X	X	X	X	X	Q6W*	Q6W*	** Physical examinations and ECOG may be performed within one day of dosing (i.e., as opposed to the day of dosing), if necessary.
Vital Signs and Weight[4]	X	X	X	X	X	X	X	X	X	X	X	4. Vital signs include blood pressure, temperature, pulse, respiratory rate, and oxygen saturation. Weight is to be recorded

On Treatment Study Assessments												Notes
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28 - 49**	**52 - 106**	
Day	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190 - 337**	**358 - 736**	
Visit Window	**±3-day window on treatment days unless otherwise noted (Visits occur once every 3 weeks during treatment period)**											
												at every other treatment visit in kilograms. Vital signs are to be performed predose on treatment days.
On Treatment Local Laboratory Assessments (Safety) – assessments may be performed up to 3 days prior to treatment												
Serum β-hCG (for women of childbearing potential)[5]	X	X	X	X	X	X	X	X	X	X	X	5. Monthly urine pregnancy testing may also be performed as consistent with local standards however if a urine test is positive or borderline, or in the event of a missed menstrual period or suspicion of pregnancy, a serum β-hCG test will be required.
Clinical Chemistry, Hematology, Coagulation[6]	X	X	X	X	X	X	X	X	X	X	X	6. Refer to Appendix 3 for a complete list of required assessments. Laboratory testing may be performed one day prior to dosing if necessary. Not required to be tested on Day 1 if screening labs are within 72 hours from time of scheduled first dose.
Thyroid function tests			X		X		X		X	Q6W*	Q6W*	*Q6W procedures are counted starting from Week 25 (i.e. the first Q6W visit is Week 31, then Week 37, etc.).
Calculated CrCl[7]	X	X	X	X	X	X	X	X	X	X	X	7. CrCl is calculated by the CKD-EPI or Cockcroft-Gault formula. Either formula is acceptable and must be consistently utilized for each participant throughout the study. See Appendix 9.
Urinalysis		X	X	X	X	X	X	X	X	X	X	

On Treatment Study Assessments												Notes
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28 - 49**	**52 - 106**	
Day	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190 - 337**	**358 - 736**	
Visit Window	**±3-day window on treatment days unless otherwise noted (Visits occur once every 3 weeks during treatment period)**											
On Treatment Disease Assessments												
Tumor Imaging/Response Assessment[8]			X		X		X		X	X[8]		8. Diagnostic quality CT scan of chest and abdomen with contrast is required every 6 weeks (±1 week) until Week 49 and every 12 weeks thereafter. Imaging/clinical assessments should be performed as indicated in Section 9.2. The same method of assessment is required throughout the study. Brain scan (MRI with and without IV gadolinium) and bone scan to be performed as clinically indicated during the treatment period. If a participant has achieved a PD, CR, or PR in the previous radiologic assessment, a repeat scan should be performed after at least 4 weeks to confirm the response.
On Treatment Patient-Reported Outcomes/Health-Related Quality of Life: completed in Part 2 ONLY												
CCI [redacted]												

On Treatment Study Assessments												Notes
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28 - 49**	**52 - 106**	
Day	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190 - 337**	**358 - 736**	
Visit Window	**±3-day window on treatment days unless otherwise noted (Visits occur once every 3 weeks during treatment period)**											
CCI [redacted]												
On Treatment Biomarkers												
CCI [redacted]												
On Treatment Tumor biopsies												
Fresh tumor tissue sample[13]			X				X[13]					13. At least 20 participants in the SoC arm will have paired fresh tumor biopsies collected at Screening (prior to randomization) and Week 7 (±8 days). If tumor is amenable to biopsy and upon patient consent. Additional optional fresh tumor tissue sample will be collected at Week 19 at the time of imaging assessment and at the time of confirmed PR or PD (± 8 days), upon participant consent. Note: Enrollment may become limited during the study, as required, to ensure collection of fresh tissue samples as noted.
On Treatment Pharmacokinetics												
Plasma SoC PK[14]	X	X	X	X	X	X	X	X				14. Draw sample at: predose on Day 1 only; at end of SoC infusion (within 5 minutes) for all marked visits; and draw an additional sample between 2 and 5 hours after end of SoC

On Treatment Study Assessments												Notes
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28 - 49**	**52 - 106**	
Day	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190 - 337**	**358 - 736**	
Visit Window	**±3-day window on treatment days unless otherwise noted (Visits occur once every 3 weeks during treatment period)**											
												infusion for all marked visits. There is a +5 minute window allowance for the EOI time points. PK samples do not need to be collected after docetaxel cycles have been completed.
On Treatment Pharmacogenetics												
Genetic research [15]	X											15. Informed consent for optional genetic research must be obtained before collecting this sample. It is recommended that the optional research sample be taken at the first opportunity after a participant has met all eligibility requirements before Day 1 or on Day 1.

Abbreviations: ; AE = Adverse event; AESI = Adverse events of special interest; β-hCG = Beta-human chorionic gonadotropin; CKD-EPI = Chronic kidney disease epidemiology collaboration; CR = complete response; CrCl = Creatinine clearance; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECOG PS = Eastern Cooperative Oncology Group performance status; EOI = End of infusion; CCI [redacted] r; IRR = infusion related reaction; CCI [redacted] PD = Progressive Disease; CCI [redacted]; PR = Partial response; Pre = Predose; CCI [redacted] SAE = Serious adverse event.

Pre: predose sample to be collected prior to dosing per institutional guidance, as long as it is collected prior to dosing of the corresponding agent**; EOI**: End of infusion sample is in reference to EOI of the corresponding agent.

Table 13 Schedule of Activities – Treatment Discontinuation Visit (TDV) and Follow-Up: Standard of Care Arm 1: Docetaxel Alone

TDV and Follow Up Assessments	Treatment Discontinuation Visit[1]	Survival Follow-Up[1a]	Notes
Visit Window	**+ 10 days**		
Anticancer Treatment		X*	*If the participant dies before the first follow up, any subsequent anticancer therapy or radiotherapy should be recorded in the eCRF. *Follow up for survival will no longer be required once 85 events are reached for this arm.
Concomitant Medications	X		
TDV and Follow Up Safety			
AE/SAE/AESI Assessment[2]	X		2. After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. Refer to Section 9.4.1 and Section 9.4.3 for further details.
ECOG PS	X		
Physical Examination	X		
Vital Signs and Weight[3]	X		3. Vital signs include blood pressure, temperature, pulse, respiratory rate, and oxygen saturation.
TDV and Follow Up Local Laboratory Assessments			
Clinical Chemistry	X		
Serum β-hCG (for women of childbearing potential)	X		
Hematology	X		
Thyroid function tests	X		
Calculated CrCl	X		
Urinalysis	X		
TDV and Follow Up Disease Assessments			
Tumor Imaging/Response Assessment[4]	X		4. At the TDV, CT scan is required only if the last disease assessment did not show PD and was performed ≥6 weeks before TDV. For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment until the start of a new anticancer treatment, disease

TDV and Follow Up Assessments	Treatment Discontinuation Visit[1]	Survival Follow-Up[1a]	Notes
Visit Window	**+ 10 days**		
			progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first. See additional information in Section 9.3.1
Telephone call for survival status[1a]		X	
TDV and Follow Up Tumor Biopsies			
Fresh tumor tissue sample	X[5]		5. If possible and upon participant consent, obtain an optional tumor tissue sample at time of confirmed PD or PR.
TDV and Follow Up Patient-Reported Outcomes/Health-Related Quality of Life			
CCI [redacted]			
TDV and Follow Up Biomarkers			
CCI [redacted]			

Abbreviations: AE = Adverse event; AESI = Adverse events of special interest; β-hCG = Beta-human chorionic gonadotropin; CR = complete response; CrCl = Creatinine clearance; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = Electronic case report form; CCI [redacted]; PD = Progressive Disease; CCI [redacted] PR = Partial response; CCI [redacted]; SAE = Serious adverse event; TDV = Treatment Discontinuation Visit

1. The assessments required at the study treatment discontinuation visit must be completed within 30 days from the date study treatment was discontinued and must occur prior to the start of subsequent anticancer therapy. If participant attends clinic for scheduled visit and decision is made to discontinue treatment, site can use this visit as the TDV and complete all assessments.

1a. Survival Follow-Up is the Observational Phase of the study. Participants will be followed for survival and subsequent anticancer therapy every 12 weeks after the last dose of study treatment, via telephone contact. Participants will be contacted every 12 weeks (±7 days) until death or participant's withdrawal from further contact. Subsequent anticancer treatment and death date will be documented in the eCRF

12.1.1.3. Study Treatment

Table 14 Description and Administration of Docetaxel

Name	Docetaxel
Description	Microtubule stabilizer small molecule
Dosage form/strength	Refer to package insert[b,c]
Dosage	75 mg/m^2
Route of administration	IV infusion
Dosing instructions[a]/frequency	Administer diluted product/once Q3W

a. Refer to the Study Reference Manual for detailed instructions on dosage and administration requirements.
b. TAXOTERE PI, 2020; TAXOTERE SmPC, 2020.
c. Docetaxel 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.

All participants randomly assigned to docetaxel-containing arms should be premedicated with oral corticosteroids (such as dexamethasone 16 mg per day or its equivalent) per local standards (e.g., 8 mg twice daily) **for 3 days** starting 1 day prior to docetaxel administration to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions [TAXOTERE PI, 2020; TAXOTERE SmPC, 2020]. Intravenous corticosteroid premedication may also be utilized per local standard and at the discretion of the investigator.

Docetaxel should be given for 6 cycles and may be discontinued after 6 cycles at the discretion of the investigator.

The SRM will contain details on product handling, storage, preparation, and administration. Docetaxel will be administered according to the package insert and/or local standard.

12.1.1.4. Dose Justification

The dosage of docetaxel for this study, as a single agent and in combination, will be 75mg/m^2 Q3W, as described in the labels [TAXOTERE PI, 2020; TAXOTERE SmPC, 2020] which is approved (a) as a single-agent for patients with locally advanced or metastatic NSCLC after platinum-based chemotherapy, and (b) in combination with cisplatin for unresectable, locally advanced or metastatic NSCLC for patients who have not received prior chemotherapy.

12.1.1.5. Treatment of Overdose

In the event of docetaxel overdose, refer to the instructions in the approved product label. Contact the Medical Monitor immediately and closely monitor the participant for AEs.

12.1.2. Substudy 1 (Arm 2): Feladilimab and Docetaxel Combination

12.1.2.1. Protocol Amendment 5 Summary of Changes Specific to Feladilimab and Docetaxel Combination

Section # and Name	Description of Change	Brief Rationale
Schedule of Activities Section 12.1.2.2	Added footnote to TDV SoA for survival follow up requirements	To remove the survival follow up requirement for Substudy 1 when 85 events are reached as this will trigger final analysis

Protocol Amendment 3 Summary of Changes Specific to Feladilimab and Docetaxel Combination

Section # and Name	Description of Change	Brief Rationale
Schedule of Activities Section 12.1.1.2	Added Schedule of Activities specific to docetaxel only treatment.	To provide individual specific Schedule of Activities Table specific to standard of care arm in Part 2.
Clinical Safety Summary Section 12.1.2.4.1, GSK3359609 PK/PD Summary Section 12.1.2.5.1, GSK3359609 Dose Rationale Section 12.1.2.5.2	Updated safety and PK/PD for GSK3359609.	To align with GSK3359609 IB update version 5 and recent clinical data.

12.1.2.2. Schedule of Activities Specific to Feladilimab and Docetaxel Combination (Substudy 1)

Table 15 Schedule of Activities – Screening: Substudy 1 (Arm 2): Feladilimab and Docetaxel Combination

Screening Study Assessment	Screening[1]	Notes
Visit Window	≤4 Weeks	
Informed Consent[1]	X	1. All screening assessments must be performed within 4 weeks (28 days) prior to first dose of study treatment unless otherwise specified. The informed consent may be signed within 45 days prior to first dose.
Participant Registration[2]	X	2. Participants will be registered in RAMOS NG at screening.
Inclusion/Exclusion Criteria[12]	X	12. All known mutations should be entered in the eCRF as disease history.
Demographics, Medical History (including tobacco use), Prior Medications, Disease History	X	
Anticancer Treatment	X	
Screening Safety		
AE/SAE/AESI Assessment[3]	X	3. After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AESIs will be followed until the event is resolved, stabilized, otherwise explained, or until the participant is lost to follow-up.
ECOG PS	X	
Physical Examination	X	
Vital Signs, Height and Weight[4]	X	4. Vital signs include blood pressure, temperature, pulse, respiratory rate, and oxygen saturation. Height is recorded at Screening only. Record weight in kilograms.
12-lead ECG	X	
Echocardiogram or MUGA scan[5]	X	5. ECHO required at Screening within 28 days prior to first dose of study treatment, and during treatment phase if clinically indicated. MUGA scan may be used if ECHO not feasible.
Screening Local Laboratory Assessments (Safety)		
Hepatitis B and C[6]	X	
Serum β-hCG (for women of childbearing potential)	≤3d	
Clinical Chemistry[6], Coagulation[6], Hematology[6], Thyroid function[6]	X	6. Refer to Appendix 3 for a complete list of required assessments. Laboratory testing performed within 14 days of first dose of study intervention does not need to be repeated unless clinically indicated. If Hepatitis B and C testing was performed within 3 months prior to first dose of study intervention or SoC, repeat testing at screening is not required; otherwise, this testing is mandatory.
Calculated CrCl[7]	X	7. CrCl is calculated by the CKD-EPI or Cockcroft-Gault formula. See Appendix 9.

Screening Study Assessment	Screening[1]	Notes
Visit Window	≤4 Weeks	
Troponin I or Troponin T	X	
Urinalysis[6]	X	
Screening Other Laboratory Assessments		
PD-L1 expression by IHC[8]	X	8. PD-L1 expression by IHC and type of assay utilized (i.e., Ventana SP263, Ventana SP142, Dako 28-8, or Dako 22C3) must be recorded in the eCRF, if known. Note: Test is not required to be performed by the site if not previously performed.
Screening Disease Assessments		
Tumor Imaging[9]	X	9. Diagnostic quality CT scan of chest and abdomen with contrast must be obtained within 28 days of first dose. Baseline brain scan (MRI with or without IV gadolinium) should be obtained within 6 weeks of first dose if history of CNS disease or if clinically indicated. Bone scan should be obtained within 6 weeks of first dose if clinically indicated. See additional information regarding bone scans in Section 9.3.1.
Pre-Baseline scans for Tumor Growth Kinetics[10]	X	10. Upon participant consent, up to 3 pre-baseline scans (within 6 months before the baseline scan) will be collected to assess tumor growth rate to support exploratory investigation of tumor growth kinetics (See Section 9.3.2 for details on images for submission).
Screening Tumor Biopsies		
Fresh tumor tissue sample and Archival tumor[11]	X	11. Fresh tumor tissue sample AND an archival tissue sample obtained during screening is mandatory for at least 15 participants per study arm. Participants with inaccessible tumor or those participants that do not consent to the tumor biopsy procedure may be enrolled provided archival specimen is submitted. However, no participant will be allowed on study without either an archival specimen OR a fresh biopsy. The archival specimen may have been obtained at any time from the time of initial diagnosis to time of study entry. If only 10 unstained archival slides are available, participant may be considered eligible upon consultation/approval of the GSK Medical Monitor. Note: Enrollment may become limited during the study, as required, to ensure collection of fresh tissue samples as noted.

Abbreviations: AE = adverse event; AESI = adverse events of special interest; β-hCG = β -human chorionic gonadotropin; CKD-EPI = chronic kidney disease epidemiology collaboration; CrCl = creatinine clearance; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiography; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; IHC = Immunohistochemistry; IWRS = interactive web response system; MRI = magnetic resonance imaging; MUGA = multi-gated acquisition; SAE = serious adverse event.

Table 16 Schedule of Activities – Treatment Period: Substudy 1 (Arm 2): Feladilimab and Docetaxel Combination

On Treatment Study Assessment												Notes
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28 - 49**	**52 - 106**	
Day	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190 - 337**	**358 - 736**	
Visit Window	**±3-day window on treatment days (Visits occur once every 3 weeks during treatment period)**											
Inclusion/Exclusion Criteria	X											
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	
Participant Randomization[1]	X											1. Once determined to be eligible, participants must be randomized via IWRS. Drug shipments will be managed via IWRS. Sites must allow up to 7 business days for shipment of study drug.
Study treatments[1]												
Administer Feladilimab (GSK3359609)*	X	X	X	X	X	X	X	X	X	Q3W	Q3W	*Feladilimab (GSK3359609) must be administered first. Administration of Docetaxel must be started 1 hour and no more than 2 hours after the end of feladilimab (GSK3359609) infusion.
Docetaxel[2]	X	X	X	X	X	X	X	X	X	Q3W[2]	Q3W[2]	2. Docetaxel will be administered according to the package insert and/or local standard. Chemotherapy premedication indicated on the day of dosing should be administered after feladilimab (GSK3359609) EOI.
On Treatment Safety												
AE/SAE/AESI Assessment[3]	X	X	X	X	X	X	X	X	X	X	X	3. After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AESIs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.
ECOG PS	X	X	X	X	X	X	X	X	X	Q6W*	Q6W*	*Q6W procedures are counted starting from Week 25 (i.e. the first Q6W visit is Week 31, then Week 37, etc.).
Physical Examination**	X			X			X	X	X	Q6W*	Q6W*	** Physical examinations may be performed within one day of dosing (i.e., as opposed to the day of dosing), if necessary.
Vital Signs and Weight[4]	X	X	X	X	X	X	X	X	X	X	X	4. Vital signs include blood pressure, temperature, pulse, respiratory rate, and oxygen saturation. Weight is to be recorded

On Treatment Study Assessment												Notes
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28 - 49**	**52 - 106**	
Day	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190 - 337**	**358 - 736**	
Visit Window	**±3-day window on treatment days (Visits occur once every 3 weeks during treatment period)**											
												at every other treatment visit in kilograms. Vital signs are to be performed predose on treatment days.
On Treatment Local Laboratory Assessments (Safety) – assessments may be performed up to 3 days prior to treatment												
Serum β-hCG (for women of childbearing potential)[5]	X	X	X	X	X	X	X	X	X	X	X	5. Monthly urine pregnancy testing may also be performed as consistent with local standards however if a urine test is positive or borderline, or in the event of a missed menstrual period or suspicion of pregnancy, a serum β-hCG test will be required.
Clinical Chemistry, Hematology[6]	X	X	X	X	X	X	X	X	X	X	X	6. Refer to Appendix 3 for a complete list of required assessments. Laboratory testing performed within 14 days of first dose does not need to be repeated unless clinically indicated. Laboratory testing may be performed one day prior to dosing if necessary.
Thyroid function tests			X		X		X		X	Q6W*	Q6W*	*Q6W procedures are counted starting from Week 25 (i.e. the first Q6W visit is Week 31, then Week 37, etc.).
Calculated CrCl[7]				X			X	X	X	X	X	7. CrCl is calculated by the CKD-EPI or Cockcroft-Gault formula. Either formula is acceptable and must be consistently utilized for each participant throughout the study. See Appendix 9.
Urinalysis		X	X	X	X	X	X	X	X	X	X	
On Treatment Disease Assessments												
Tumor Imaging/Response Assessment[8]			X		X		X		X	X[8]		8. Diagnostic quality CT scan of chest and abdomen with contrast is required every 6 weeks (±1 week) until Week 49 and every 12 weeks thereafter, until disease progression is confirmed by iRECIST. The same method of assessment is required throughout the study. Brain scan (MRI with or without IV gadolinium) and bone scan to be performed as clinically indicated during the treatment period. If a participant has achieved a PD, CR, or PR in the previous radiologic assessment, a repeat scan should be performed after at least 4 weeks to confirm the response. See additional information in Section 9.3.1.

On Treatment Study Assessment												Notes
Week	1	4	7	10	13	16	19	22	25	28 - 49	52 - 106	
Day	1	22	43	64	85	106	127	148	169	190 - 337	358 - 736	
Visit Window	±3-day window on treatment days (Visits occur once every 3 weeks during treatment period)											
On Treatment Patient-Reported Outcomes/Health-Related Quality of Life												
CCI [redacted]												
On Treatment Biomarkers												
CCI [redacted]												
On Treatment Tumor biopsies												
Fresh tumor tissue sample			X				X[13]					13. At least 15 participants per treatment arm will have paired fresh tumor biopsies collected at Screening (prior to randomization) and Week 7 (± 8 days), if tumor is amenable to biopsy and upon participant consent.

On Treatment Study Assessment												Notes
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28 - 49**	**52 - 106**	
Day	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190 - 337**	**358 - 736**	
Visit Window	**±3-day window on treatment days (Visits occur once every 3 weeks during treatment period)**											
												Additional optional fresh tumor tissue sample will be collected at Week 19 at the time of imaging assessment and at the time of confirmed PR or PD (± 8 days), upon participant consent. Note: Enrollment may become limited during the study, as required, to ensure collection of fresh tissue samples as noted.
On Treatment Pharmacokinetics and Anti-Drug Antibodies (ADA)												
Plasma SoC PK[14]	X	X	X	X	X	X	X	X				14. For Arm 1 and Arm 2: Draw sample (2 mL) at: predose on Day 1 only; at end of SoC infusion (within 5 minutes) for all marked visits; and draw an additional sample between 2 and 5 hours after end of SoC infusion for all marked visits. There is a +5 minute window allowance for the EOI time points.
Plasma Feladilimab (GSK3359609; ICOS Agonist) PK[15]	X	X	X	X	X	X	X	X	X	X	X[15]	15. For Arm 2 only: Draw sample (2 mL) at predose for all marked visits. Additional samples also drawn at the following time points: Week 1 (Day 1) at end of infusion (EOI) (within 5 minutes) and EOI+4h. EOI samples also drawn at Week 13 and Week 25. After Week 25, draw samples every 12 weeks at predose only. There is a +5 minute window allowance for the EOI time points.
Serum Feladilimab (GSK3359609; ICOS Agonist) ADA[16]	X	X	X	X	X	X	X	X	X	X	X[16]	16. For Arm 2 only: Draw sample (4 mL) at predose on ALL treatment visits; then starting with Week 25 predose samples to be collected every 12 weeks. Draw a sample at any time during visit for non-treatment visits. For participants with a positive ADA result at last regular visit an additional sample will be drawn at 6 months after the last dose. Serum samples will be collected and tested for the presence of antibodies that bind to investigational agents as deemed appropriate. Feladilimab serum samples may also be tested for presence of antibodies that bind to Chinese Hamster Ovary (CHO) host cell proteins such as phospholipase B- like (PLBL2).

On Treatment Study Assessment												Notes
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28 - 49**	**52 - 106**	
Day	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190 - 337**	**358 - 736**	
Visit Window	**±3-day window on treatment days (Visits occur once every 3 weeks during treatment period)**											
Serum: IRR lab panel[17]												17. Assessment ONLY required in participant experiencing anaphylaxis, serious hypersensitivity, or AEs related to study treatment administration that led to withdrawal from the study. Refer to Table 3 for list of analytes. Predose analysis will be performed on the serum sample collected for feladilimab (GSK3359609) immunogenicity assessments.
On Treatment Pharmacogenetics												
Genetic research[18]	X											18. Informed consent for optional genetic research must be obtained before collecting this sample. It is recommended that the optional research sample) be taken at the first opportunity after a participant has met all eligibility requirements before Day 1 or on Day 1.

Abbreviations: ADA = Anti-drug antibody; AE = Adverse event; AESI = Adverse events of special interest; β-hCG = Beta-human chorionic gonadotropin; CKD-EPI = Chronic kidney disease epidemiology collaboration; CR = complete response; CrCl = Creatinine clearance; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECOG PS = Eastern Cooperative Oncology Group performance status; EOI = End of infusion; CCI [redacted] IRR = infusion related reaction; CCI [redacted]; PD = Progressive Disease; CCI [redacted]; PR = Partial response; CCI [redacted] SAE = Serious adverse event.

Table 17 Schedule of Activities – Treatment Discontinuation Visit (TDV) and Follow-Up: Substudy 1 (Arm 2): Feladilimab and Docetaxel Combination

TDV and Follow Up Assessments	Treatment Discontinuation Visit[1]	Survival Follow-Up[1a]	Notes
Visit Window	**+ 10 days**		
Anticancer Treatment		X*	*Follow up for survival will no longer be required once 85 events are reached for this arm.
Concomitant Medications	X		
TDV and Follow Up Safety			
AE/SAE/AESI Assessment[2]	X		2. After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AESI will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.
ECOG PS	X		
Physical Examination	X		
Vital Signs and Weight[3]	X		3. Vital signs include blood pressure, temperature, pulse, respiratory rate, and oxygen saturation.
TDV and Follow Up Local Laboratory Assessments			
Clinical Chemistry	X		
Serum β-hCG (for women of childbearing potential)	X		
Hematology	X		
Thyroid function tests	X		
Calculated CrCl	X		
Urinalysis	X		
TDV and Follow Up Disease Assessments			
Tumor Imaging/Response Assessment[4]	X		4. At the TDV, CT scan is required only if the last disease assessment did not show PD and was performed ≥6 weeks before TDV.
Telephone call for survival status[1a]		X*	*Follow up for survival will no longer be required once 85 events are reached for this arm.
TDV and Follow Up Tumor Biopsies			
Fresh tumor tissue sample	X[5]		5. If possible, obtain an optional tumor tissue sample at time of confirmed PD or PR.

TDV and Follow Up Assessments	Treatment Discontinuation Visit[1]	Survival Follow-Up[1a]	Notes
Visit Window	+ 10 days		
TDV and Follow Up Patient-Reported Outcomes/Health-Related Quality of Life			
CCI			
TDV and Follow Up Biomarkers			
CCI			

Abbreviations: AE = Adverse event; AESI = Adverse events of special interest; β-hCG = Beta-human chorionic gonadotropin; CR = complete response; CrCl = Creatinine clearance; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = Electronic case report form; CCI ; PD = Progressive Disease; CCI PR = Partial response; CCI ; SAE = Serious adverse event; TDV = Treatment Discontinuation Visit

1. The assessments required at the study treatment discontinuation visit must be completed within 30 days from the date study treatment was discontinued and must occur prior to the start of subsequent anticancer therapy.
1a. Survival Follow-Up is the Observational Phase of the study. Participants will be followed for survival and subsequent anticancer therapy every 12 weeks after the last dose of study treatment, via telephone contact. Participants will be contacted every 12 weeks (±7 days) until death or participant's withdrawal from further contact. Subsequent anticancer treatment will be documented in the eCRF.

12.1.2.3. Study Treatments

Table 18 Description and Administration of Arm 2 Study Treatments

Name	Docetaxel	Feladilimab (GSK3359609; ICOS Agonist)
Description	Microtubule stabilizer small molecule	Humanized anti-ICOS IgG4 mAb
Dosage form/strength	Refer to package insert[a]	Solution for injection/ 10 mg/mL
Dosage	75 mg/m^2	80 mg
Route of administration	IV infusion	IV infusion[b]
Dosing instructions[a]/frequency	Administer diluted product/once Q3W	Administer diluted product/once Q3W

a. TAXOTERE PI, 2020; TAXOTERE SmPC, 2020
d. The study reference manual contains the details on product handling, storage, preparation, and administration.

In feladilimab (ICOS Agonist)-containing arms, feladilimab will be administered first as a 30-minute IV infusion (infusion time may be adjusted based on infusion related reactions). The administration of the second agent in these arms must be started 1 hour and no more than 2 hours after the end of feladilimab infusion. Chemotherapy premedication indicated on the day of dosing should be administered after feladilimab EOI. Docetaxel will be administered according to the package insert and/or local standard. Participants should remain under observation at the study site post-study treatment infusion per the judgement of the investigator or as per institutional guidelines to monitor for potential infusion reactions or other adverse events.

12.1.2.4. Rationale for ICOS Agonist/Docetaxel Combination

Cancer immunity is described as a multistep process that elicits 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 are 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. Robust antitumor responses including complete cure have been achieved in some cancers by modulating the 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 as anticancer immunotherapies in a broad range of tumors including some solid tumors otherwise considered poorly immunogenic.

However, a majority of tumors are non-responsive to this class of agents. One reason for the lack of response could be the existence of multiple mechanisms of immune suppression in the tumor microenvironment which prohibits effective antitumor immune responses. In these instances, combination therapies will likely be required. The clinical data generated by the combination of ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) in patients with metastatic melanoma is an example of the practice changing clinical benefit of such combinations [Wolchok, 2013].

In some patients, inhibition of negative immune checkpoint pathways alone may not elicit an effective antitumor response, and additional co-stimulatory signals may be

necessary to mount an effective response. 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. The ultimate aim is to improve the survival outcome in all disease settings including the advanced setting.

Feladilimab is a humanized IgG4 anti-ICOS monoclonal antibody [Mayes, 2018] selected for its nanomolar (nM) binding to and agonist activity in ICOS-expressing CD4+ and CD8+ effector T cells. 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 feladilimab that would result in depletion of ICOS-positive T cells through antibody-dependent or complement-dependent cell mediated mechanisms, respectively. Moreover, the IgG4PE isotype retains functional binding to the Fcγ inhibitor receptor, FcγRIIb, a feature described as critical for modulating antibody agonist activity [Li, 2011], which also may be essential for optimal ICOS agonist activity and its associated antitumor effects in humans.

ICOS is a co-stimulatory receptor of the CD28/CTLA immunoglobulin super family with expression restricted to T cells [Horn, 2018]. ICOS is weakly expressed on resting TH17, follicular helper T and regulatory T (Treg) cells and yet is highly induced on CD4+ and CD8+ T cells upon T cell receptor (TCR) engagement and activation [Parmar, 1998, Paulos, 2010; Wakamatsu, 2013]. Upregulation of ICOS leads to both Th1 and Th2 cytokine secretion and sustained effector T cell proliferation and function [Sharpe, 2002]. A growing body of evidence supports the concept that activating ICOS on CD4+ and CD8+ effector T cells has antitumor potential.

The rationale for targeting ICOS in cancer has been established by multiple lines of nonclinical and clinical evidence. Engagement of the ICOS pathway with an ICOS-L-Fc fusion protein is shown to have potent antitumor activity in multiple syngeneic mouse tumor models [Ara, 2003]. Emerging data from patients treated with anti-CTLA-4 antibodies suggest a positive role of ICOS+ effector T cells in mediating an antitumor immune response. Patients with metastatic melanoma [Di Giacomo, 2013], urothelial [Carthon, 2010], breast [Vonderheide, 2010] and prostate cancer [Chen, 2009] who have increased absolute counts of circulating and tumor infiltrating CD4+ICOS+ and CD8+ICOS+ T cells after ipilimumab treatment have significantly better treatment related outcomes than patients where little or no increases are observed. Importantly, it was shown that ipilimumab changes the ICOS+ T effector to Treg ratio, reversing an abundance of Tregs pre-treatment to a significant abundance of T effectors vs. Tregs following treatment [Liakou, 2008; Vonderheide, 2010]. As evidenced by the clinical data, ICOS+ T effector cells may be a positive predictive biomarker of ipilimumab response, and activation of this population of cells with an ICOS agonist antibody may confer an advantage by mounting a more robust immune antitumor response.

Similar to the combination of platinum-containing chemotherapy with immuno-oncology agents (anti-PD-1) in metastatic non-squamous disease, i.e., the incorporation of the anti-PD-1 inhibitor, pembrolizumab, to the pemetrexed/carboplatin backbone in the first-line

metastatic non-squamous disease is an example for the IO agents to provide a higher degree of benefit including a prolonged benefit combined with the immediate cytotoxic effects of the chemotherapy. The ICOS agonist/docetaxel combination has the potential to deliver a similar promise to later line NSCLC participants building on the existing docetaxel standard of care.

Chemotherapy can promote tumor immunity by inducing immunogenic cell death as part of its intended therapeutic effect, as well as modulating distinct features of tumor immunobiology [Emens, 2015]. In preclinical models, combinations with various chemotherapy agents including docetaxel and platinum-based treatments with anti-PD-L1 treatment showed increased efficacy associated with increased frequency of intratumoral subsets without antagonizing functional changes mediated by anti-PD-L1 [Cubas, 2016]. Combination of anti-ICOS surrogate antibody with carboplatin and paclitaxel showed some increase efficacy in the CT26 tumor model [Kilian, 2017a; Kilian, 2017b; Kilian, 2017c; Kilian, 2017d].

12.1.2.4.1. Clinical Safety Summary

As of the feladilimab Investigator Brochure data cutoff date of 16 March 2020, 249 participants received at least 1 dose of monotherapy feladilimab in study 204691 at the following dose levels: 0.001 mg/kg (n=1), 0.003 mg/kg (n=1), 0.01 mg/kg (n=2), 0.03 mg/kg (n=7), 0.10 mg/kg (n=25), 0.30 mg/kg (n=56), 1.0 mg/kg (n=126), 3.0 mg/kg (n=24), and 10 0 mg/kg (n=7). In these 249 participants, the most common AEs (occurring in ≥15% of participants overall regardless of dose level or relationship) were anemia (22%), asthenia (21%), nausea (19%), fatigue (18%), diarrhea (16%), and vomiting (15%).

In study 204691, 10 participants received at least 1 dose of feladilimab 80 mg in combination with docetaxel 75 mg/m^2 once every 3 weeks (safety cohort), 9 participants (90%) experienced at least 1 ≥Grade 3 AE, 2 of whom experienced Grade 5 events: 1 participants had Grade 5 aspiration pneumonia and the other participant had Grade 5 methicillin-resistant staphylococcus aureus (MRSA) chest infection and Grade 5 lower respiratory infection. Seven participants (70%) experienced at least 1 serious adverse event (SAE) of ≥Grade 3; Grade 3: fatigue, dyspnea (1 event), hyponatremia, aspiration pneumonia, respiratory failure, hypotension, and diarrhea Grade 5: aspiration pneumonia, lower respiratory tract infection and staphylococcal infection. The Grade 5 events were reported in 2 participants (1 participant with aspiration pneumonia; 1 participant with lower respiratory tract infection and staphylococcal infection); the 3 events were not considered related to study treatment and the primary cause of death in both cases was sepsis.

Refer to GSK3359609 IB [GSK Document Number 2017N319717_03] for further details.

12.1.2.5. Dose Justification (Substudy 1)

12.1.2.5.1. Feladilimab Pharmacokinetics and Pharmacodynamics Summary

The PK of feladilimab was evaluated after 30 minutes of IV infusion at doses from 0.001 mg/kg to 10.0 mg/kg every 3 weeks (Q3W) in participants with solid tumors in Study 204691. The plasma PK samples (received prior to the 2020 IB update cutoff date of 16 March 2020) were analyzed with a validated bioanalytical method with a lower limit of quantitation (LLOQ) of 0.1 µg/mL.

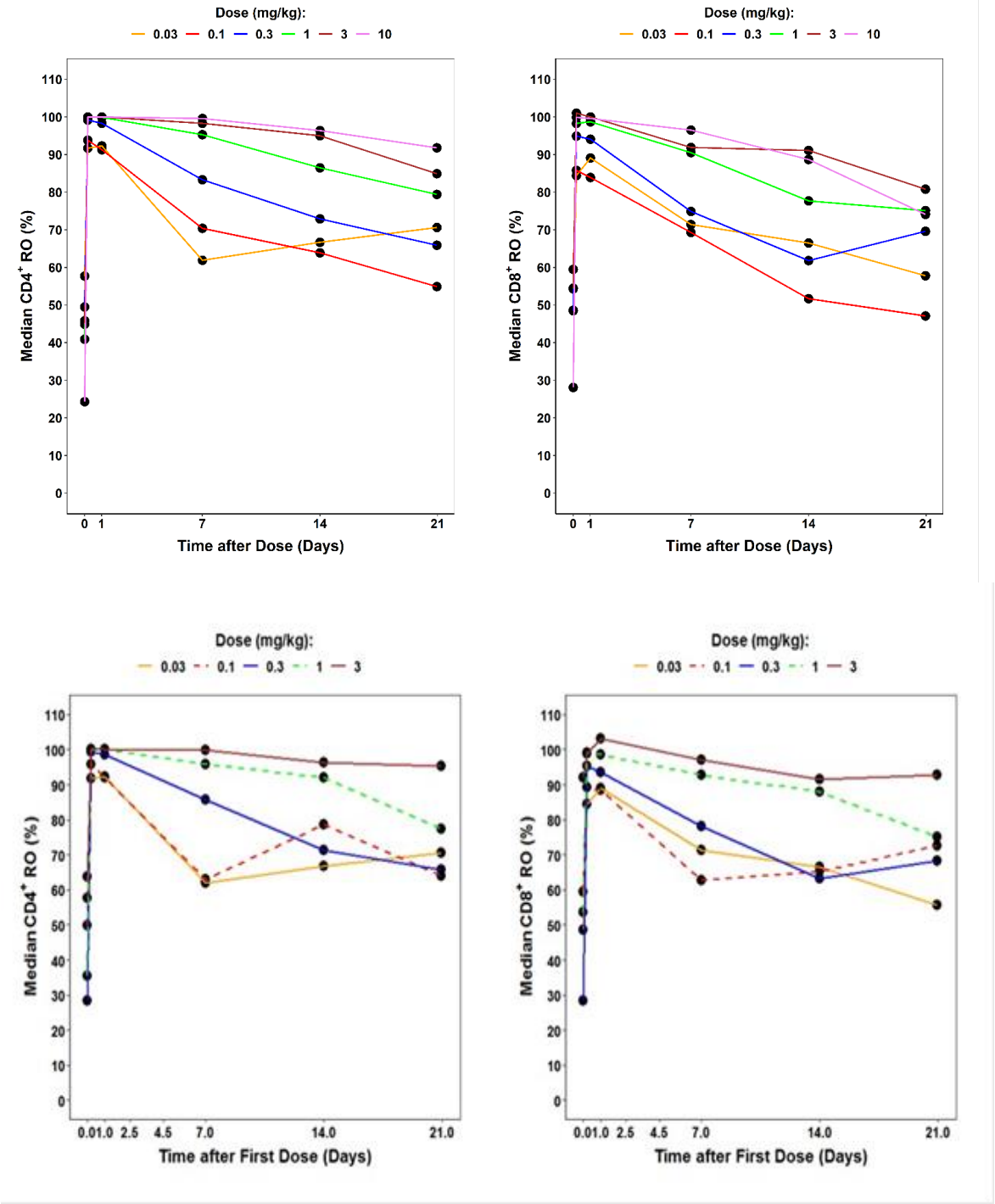
As of 16 March 2020, preliminary PK data in monotherapy cohorts were available in 1 participant at 0.003 mg/kg, 2 participants at 0.01 mg/kg, 7 participants at 0.03 mg/kg, 25 participants at 0.1 mg/kg, 52 participants at 0.3 mg/kg, 123 participants at 1.0 mg/kg, 23 participants at 3.0 mg/kg, and 7 participants at 10.0 mg/kg dose. Preliminary PK data in pembrolizumab combination cohorts were available in 5 participants at 0.01 mg/kg, 5 participants at 0.03 mg/kg, 13 participants at 0.1 mg/kg, 244 participants at 0.3 mg/kg, 38 participants at 1.0 mg/kg, and 18 participants at 3.0 mg/kg dose. Preliminary PK data in GSK3174998 combination cohorts were available in 5 participants each at 8 and 24 mg and 1 participant at 80 mg fixed dose. Preliminary PK data in chemotherapy combination cohorts of the safety run-in were available in 55 participants at 80 mg fixed dose of feladilimab.

Based on these preliminary data, the median plasma concentration-time profiles of feladilimab exhibit a bi-exponential decline. There are no changes in GSK3359609 PK when co-administered at doses from 0.01 to 3.0 mg/kg with biologic or chemotherapy partners. Furthermore, median feladilimab plasma PK profiles after dosing at 8, 24, and 80 mg fixed doses were superimposable to the median PK profiles observed with 0.1, 0.3, and 1.0 mg/kg doses. Preliminary plasma PK parameters of feladilimab computed using noncompartmental analysis methods (AUC, $C\tau$, and C_{max}) calculated over the first dosing interval (up to 503 hours) exhibit approximate dose proportional increases in feladilimab exposure over the range of 0.01 to 10.0 mg/kg doses. Observed exposures (AUC and $C\tau$) from body-weight based dose of 1.0 mg/kg (combined monotherapy and combination cohorts) and corresponding fixed dose equivalent of 80 mg (chemotherapy safety run-in) overlap with each other, indicating similar exposures can be achieved with a fixed dosing regimen. Preliminary population PK estimated geometric mean systemic half-life ($t_{1/2}$) of feladilimab is approximately 19 days.

Based on the preliminary data, median CD4 and CD8 receptor occupancy (RO) was maintained at or above 70% during the dosing interval of first cycle for doses ≥0.3 mg/kg as shown in Figure 7.

Refer to GSK3359609 IB [GSK Document Number 2017N319717_03] for further details.

Figure 7 Median CD4+ and CD8+ Receptor Occupancy (%RO) During the First Cycle of Feladilimab Administration as Monotherapy



Feladilimab Dosing Frequency

The systemic half-life of feladilimab is approximately 19 days based on the preliminary population PK analysis of data from ongoing study 204691. The existing feladilimab

Q3W regimen in the ongoing clinical study is also consistent with the Q3W dosing regimen typical with other IgG4 based monoclonal antibody therapies. The docetaxel label prescribes a Q3W regimen. Thus, feladilimab will be dosed Q3W in combination with docetaxel. Combination of feladilimab with any other treatment in other arms of this study may have a different dosing regimen as deemed appropriate.

Rationale for Fixed Dose

Therapeutic monoclonal antibodies are often dosed based on body-size due to the concept that this reduces inter-participant variability in drug exposure. However, body-weight dependency of PK parameters does not always explain all or even a majority of observed variability in the exposure of monoclonal antibodies [Zhao, 2017]. Hence, the selection of body-weight based versus fixed dosing in this study was evaluated through population PK modelling and simulation efforts.

A preliminary population PK model (N = 637 participants; March 2020), which characterized the influence of body weight, age, and other participant covariates on exposure was developed. Results of this analysis indicate a feladilimab fixed dose is appropriate for trial participants across the bodyweight spectrum. Simulations show a feladilimab body weight-based dose results in slightly higher exposure in heavier weight participants and a feladilimab fixed dose results in slightly higher exposures in lighter participants. However, the range of exposures are similar between body-weight based and fixed dosing across the entire body weight spectrum and the exposures are maintained well within established clinical boundaries of safety at doses in the range of 24 to 80 mg Q3W (the highest studied dose in monotherapy deemed tolerable was 10 mg/kg or ~800 mg). This suggests that there is no advantage of body-weight based dosing over fixed dosing and that lighter patients will not be more susceptible to treatment-related adverse events arising from marginal increases in exposure.

Overall, these preliminary population PK simulations indicate that using fixed dosing would result in a similar range of exposures as that of body weight-based dosing. Also, fixed dosing offers the advantage of reduced dosing errors, reduced drug wastage, shortened preparation time, and improved ease of administration. Thus, a feladilimab fixed dose for Substudy 1 based on a reference body weight of 80 kg is reasonable and appropriate.

Refer to GSK3359609 IB [GSK Document Number 2017N319717_03] for further details.

12.1.2.5.2. Feladilimab Dose Rationale (Substudy 1)

Based on the preliminary PK data described above in Section 12.1.2.5.1 and target engagement shown in Figure 7, median CD4 and CD8 receptor occupancy was maintained at or above 70% during the dosing interval of first cycle for doses ≥0.3 mg/kg. Sufficiently high CD4+ RO is expected at peak exposures (89% to >99% RO) as well as at trough exposures (69% to >99% RO) at steady-state with the proposed 80 mg dose in substudy 1.

Collectively, based on the safety and exposure data from the Phase 1 study and the predicted target engagement, the 80-mg dose will be evaluated in combination with docetaxel in this study. No drug-drug interaction related changes are expected in feladilimab PK with docetaxel co-administration. The currently planned 80 mg feladilimab dose may be adjusted lower to 24 mg or increased to 240 mg based on any emerging safety, exposure and/or pharmacodynamic data.

12.1.2.5.3. Docetaxel 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 75 mg/m^2, every three weeks; thus, this dose and schedule was selected in combination with feladilimab. There are no drug-drug interaction related changes expected in docetaxel PK on co-administration with feladilimab.

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

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

There is no specific antidote for overdose with the experimental treatments being evaluated in this study. 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.

12.1.3. Arm 3: Feladilimab and Ipilimumab Combination

12.1.3.1. Protocol Amendment 5 Summary of Changes Specific to Feladilimab and Ipilimumab Arm

Section # and Name	Description of Change	Brief Rationale
Schedule of Activities Section 12.1.3.2	Added footnote to SoAs (on-treatment and TDV) for biomarker, PK, and ADA samples SoA	To align with decision to no longer collect samples from participants in this arm
Schedule of Activities Section 12.1.3.2	Added footnote to TDV SoA for survival follow up requirements	To remove the survival follow up requirement for this arm
Dose Modification and Management Guidelines Section 12.1.3.10	Moved dose modification guidelines to this section from the master protocol	To include the dose modification guidelines specific to the regimen in this arm
Safety Evaluation Section 12.1.3.11	Moved Part 1 Analysis text from master protocol	To avoid duplication and better clarify the analysis for this arm
Risk-benefit Section 12.1.3.14	Moved risk management and mitigation strategy to this section from the master protocol	To include risk management and mitigation strategy specific to the regimen in this arm

Protocol Amendment 4 Summary of Changes Specific to Feladilimab and Ipilimumab Arm

Section # and Name	Description of Change	Brief Rationale
Schedule of Activities Section 12.1.3.2	Added physical exam for dosing visits.	As this is a new combination being tested, decision was made to require a physical exam at every dosing visit.
Schedule of Activities Section 12.1.3.2	Time window for plasma feladilimab end of infusion PK was extended from 5 min to 15 min	To allow the site a longer time window to collect the end of infusion PK sample

Schedule of Activities Section 12.1.3.2	Removed details on number of slides for tissue sample to be sent by site.	Decided this detail should be included in the SRM instead and was removed from protocol.
Schedule of Activities Section 12.1.3.2	Added creatinine clearance to screening assessments	To correct the omission of creatinine clearance.
Schedule of Activities Section 12.1.3.2	At the follow up visit, footnote added: If the participant dies before the first follow up, any subsequent anticancer therapy or radiotherapy should be recorded in the eCRF.	To record any subsequent therapy the participant may have received after study discontinuation, if they die before first follow up is completed.
Futility Evaluation Section 12.1.3.12	Clarify ipilimumab cohort will start at 3mg/kg dose.	To align with study strategy.
Schedule of Activities Section 12.1.3.2	Added footnote: **Pre:** predose sample to be collected prior to dosing per institutional guidance, as long as it is collected <u>prior</u> to dosing of the corresponding agent**; EOI**: End of infusion sample is in reference to EOI of the corresponding agent.	To clarify the sample collection reference for predose and EOI.
Schedule of Activities Section 12.1.3.2	Added in the TDV SOA: In the event of hypersensitivity reaction that is clinically significant and/or leads to study treatment discontinuation, an additional sample should be collected at 24 weeks post last dose of study treatment.	To correct the omission of hypersensitivity collection of ADA samples at TDV and added sample collection for feladilimab.

12.1.3.2. Schedule of Activities Specific to Ipilimumab and Feladilimab Combination

The timing and number of planned study assessments (including safety, pharmacokinetic, ADA, biomarker or other assessments) may be altered during the course of the study based on newly available data.

Table 19 Schedule of Activities – Screening: Arm 3: Ipilimumab and Feladilimab Combination

Screening Study Assessments	Screening[1]	Notes
Visit Window ≤4 Wk		
Informed Consent[1]	X	1. All screening assessments must be performed within 4 weeks (28 days) prior to first dose of study treatment unless otherwise specified. The informed consent may be signed within 45 days prior to first dose.
Participant Registration[2]	X	2. Participants will be registered in RAMOS NG at screening.
Inclusion/Exclusion Criteria	X	Review eligibility prior to randomization.
Demographics, Medical History (incl. alcohol & tobacco use), Prior Medications, Disease History[12]	X	12. All known mutations should be entered in the eCRF as disease history.
Prior Anticancer Treatment, Radiotherapy	X	
Screening Safety		
AE/SAE/AESI Assessment[3]	X	3. After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. Refer to Section 9.4 for further details.
ECOG PS	X	
Physical Examination	X	
Vital Signs, Height and Weight[4]	X	4. Vital signs include blood pressure, temperature, pulse, respiratory rate, and oxygen saturation. Height is recorded at Screening only. Record weight in kilograms.
12-lead ECG	X	
Echocardiogram or MUGA scan[5]	X	5. ECHO required at Screening within 28 days prior to first dose of study treatment, and during treatment phase if clinically indicated. MUGA scan may be used if ECHO not feasible.

Screening Study Assessments	Screening[1]	Notes
Visit Window ≤4 Wk		
Screening Local Laboratory Assessments (Safety)		
Hepatitis B and C[6]	X	
Serum β-hCG (for women of childbearing potential)	≤3d	
Clinical Chemistry[6], Coagulation[6], Hematology[6], Thyroid function[6]	X	6. Refer to Appendix 3 for a complete list of required assessments. Required within 7 days of randomization day. Not required to be tested on Day 1 if screening labs are within 72 hours from time of scheduled first dose. Must be drawn predose or up to 3 days prior to dosing. If Hepatitis B and C was performed within 3 months prior to first dose of study intervention or SoC, repeat testing at screening is not required; otherwise, this testing is mandatory.
Calculated CrCl[7]	X	7. CrCl is calculated by the CKD-EPI or Cockcroft-Gault formula. See Appendix 9.
Troponin I or Troponin T	X	
Urinalysis[6]	X	
Screening Other Laboratory Assessments		
PD-L1 expression by IHC[7]	X	7. PD-L1 expression by IHC and type of assay utilized (i.e., Ventana SP263, Ventana SP142, Dako 28-8, or Dako 22C3) must be recorded in the eCRF, if known. Note: Test is not required to be performed by the site if not previously performed.
Screening Disease Assessments		
Tumor Imaging[8]	X	8. Diagnostic quality CT scan of chest and abdomen with contrast must be obtained within 28 days of first dose. Baseline brain scan (MRI with and without IV gadolinium) should be obtained within 6 weeks of first dose if history of CNS disease or if clinically indicated. Bone scan should be obtained within 6 weeks of first dose if clinically indicated. See additional information regarding bone scans in Section 9.3.1.
Pre-Baseline scans for Tumor Growth Kinetics[9]	X	9. Upon participant consent, up to 3 pre-baseline scans (within 12 months before the baseline scan) will be collected to assess tumor growth rate to support exploratory investigation of tumor growth kinetics (See Section 9.3.2 for details on images for submission).

Screening Study Assessments	Screening[1]	Notes
Visit Window ≤4 Wk		
Screening Tumor Biopsies		
Fresh tumor tissue sample and Archival tumor[10]	X	10. Part 1: All participants are required to have tumor tissue available (archival or fresh biopsy) prior to start of study treatment. A fresh biopsy is required if archival tissue is unavailable. Following Part 1 initial safety evaluation (up to first 10 participants), for the additional participants enrolled to assess further safety as well as PK/PD, fresh tumor tissue AND archival tumor tissue samples at screening are required prior to start of study treatment. Part 2: Tumor tissue at screening (either archival or fresh biopsy if archival tissue is unavailable), is required for all participants in Part 2. Fresh tumor tissue at screening is required in addition to an archival tissue for at least 20 participants for this arm. Participants with inaccessible tumor or those participants that do not consent to the tumor biopsy procedure may be enrolled provided an archival specimen is submitted. The archival specimen may have been obtained at any time from the time of initial diagnosis to time of study entry. Note: Enrollment may become limited during the study, as required, to ensure collection of fresh tissue samples as noted.

'Abbreviations: AE = adverse event; AESI = adverse events of special interest; β-hCG = β -human chorionic gonadotropin; CKD-EPI = chronic kidney disease epidemiology collaboration; CrCl = creatinine clearance; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiography; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; IHC = Immunohistochemistry; IWRS = interactive web response system; MRI = magnetic resonance imaging; MUGA = multi-gated acquisition; SAE = serious adverse event.

Table 20 Schedule of Activities – Treatment Period: Arm 3: Ipilimumab and Feladilimab Combination

On Treatment Study Assessments												Notes
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28 - 49**	**52 - 106**	
Day	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190 - 337**	**358 - 736**	
Visit Window	**±3-day window on treatment days unless otherwise noted. (Visits occur once every 3 weeks during treatment period)**											
Inclusion/Exclusion Criteria	X											
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	
Participant Randomization[1]	X											1. Once determined to be eligible, participants must be randomized via IWRS. Drug shipments will be managed via IWRS. Sites must allow up to 7 business days for shipment of study drug. Randomization can be done prior to Day 1, but no more than 3 days prior to Day 1. (Refer to SRM).
Study treatments[1]												
Administer Feladilimab (GSK3359609)*	X	X	X	X	X	X	X	X	X	X	Q3W	*Feladilimab (GSK3359609) must be administered within ±3 days of scheduled visit unless otherwise indicated. Refer to Section 5.2 for maximum duration of study treatment. feladilimab (GSK3359609) will be administered first and ipilimumab will be administered at least 30 minutes and no longer than one hour following feladilimab (GSK3359609) EOI.
Administer Ipilimumab[2]	X	X	X	X	X	X	X	X	X	X	Q3W	2. Feladilimab (GSK3359609) will be administered first and ipilimumab will be administered at least 30 minutes and no longer than one hour following feladilimab (GSK3359609) EOI. Refer to Section 5.2 for maximum duration of study treatment. Dosing interval can be extended to Q6W for toxicity or intolerance
On Treatment Safety												
AE/SAE/AESI Assessment[3]	X	X	X	X	X	X	X	X	X	X	X	3. After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AESIs will be

On Treatment Study Assessments												Notes
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28 - 49**	**52 - 106**	
Day	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190 - 337**	**358 - 736**	
Visit Window	**±3-day window on treatment days unless otherwise noted. (Visits occur once every 3 weeks during treatment period)**											
												followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.
ECOG PS**	X	X	X	X	X	X	X	X	X	Q6W*	Q6W*	*Q6W procedures are counted starting from Week 25 (i.e. the first Q6W visit is Week 31, then Week 37, etc.), unless more frequent assessments are clinically indicated.
Physical Examination**	X	X	X	X	X	X	X	X	X	Q6W*	Q6W*	** Physical examinations and ECOG may be performed within 24 hours prior to dosing (i.e., as opposed to the day of dosing), if necessary.
Vital Signs and Weight[4]	X	X	X	X	X	X	X	X	X	X	X	4. Vital signs include blood pressure, temperature, pulse, respiratory rate, and oxygen saturation. Weight is to be recorded at every other treatment visit in kilograms. Vital signs are to be performed predose on treatment days.
On Treatment Local Laboratory Assessments (Safety) – assessments may be performed up to 3 days prior to treatment												
Serum β-hCG (for women of childbearing potential)[5]	X	X	X	X	X	X	X	X	X	X	X	5. Monthly urine pregnancy testing may also be performed as consistent with local standards however if a urine test is positive or borderline, or in the event of a missed menstrual period or suspicion of pregnancy, a serum β-hCG test will be required.
Clinical Chemistry, Hematology[6]	X	X	X	X	X	X	X	X	X	X	X	6. Refer to Appendix 3 for a complete list of required assessments. Laboratory testing may be performed one day prior to dosing if necessary. Not required to be tested on Day 1 if screening labs are within 72 hours from time of scheduled first dose.
Thyroid function tests			X		X		X		X	Q6W*	Q6W*	*Q6W procedures are counted starting from Week 25 (i.e. the first Q6W visit is Week 31, then Week 37, etc.).
Calculated CrCl[7]				X			X	X	X	X	X	7. CrCl is calculated by the CKD-EPI or Cockcroft-Gault formula. Either formula is acceptable and must be consistently utilized for each participant throughout the study. See Appendix 9.

On Treatment Study Assessments												Notes
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28 - 49**	**52 - 106**	
Day	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190 - 337**	**358 - 736**	
Visit Window	**±3-day window on treatment days unless otherwise noted. (Visits occur once every 3 weeks during treatment period)**											
Urinalysis		X	X	X	X	X	X	X	X	X	X	
On Treatment Disease Assessments												
Tumor Imaging/Response Assessment[8]			X		X		X		X	X[8]		8. Diagnostic quality CT scan of chest and abdomen with contrast is required every 6 weeks (±1 week) until Week 49 and every 12 weeks thereafter. Imaging/clinical assessments should be performed as indicated in Section 9.2. The same method of assessment is required throughout the study. Brain scan (MRI with and without IV gadolinium) and bone scan to be performed as clinically indicated during the treatment period. If a participant has achieved a PD, CR, or PR in the previous radiologic assessment, a repeat scan should be performed after at least 4 weeks to confirm the response.
On Treatment Patient-Reported Outcomes/Health-Related Quality of Life: Part 2 ONLY												
CCI [redacted]												

On Treatment Study Assessments												Notes
Week	1	4	7	10	13	16	19	22	25	28 - 49	52 - 106	
Day	1	22	43	64	85	106	127	148	169	190 - 337	358 - 736	
Visit Window	±3-day window on treatment days unless otherwise noted. (Visits occur once every 3 weeks during treatment period)											
On Treatment Biomarkers[21]												
CCI [redacted]												
On Treatment Tumor biopsies[22]												
Fresh tumor tissue sample[13]			X				X[13]					13.Part 1: For participants in the safety evaluation for each substudy, fresh biopsies at week 7 (± 8 days) is optional. Following Part 1 initial safety evaluation (up to 10 participants), the additional participants enrolled to assess further safety as well as PK/PD are required to provide a fresh biopsy obtained at week 7 (± 8 days). 22. On treatment biopsy for participants in the PK/PD cohort is no longer required for ongoing participants in this arm. Part 2: Fresh biopsy collected at week 7 (± 8 days) is optional for participants in Part 2, if tumor is amenable to biopsy and upon participant consent. However, fresh biopsy

On Treatment Study Assessments												Notes
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28 - 49**	**52 - 106**	
Day	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190 - 337**	**358 - 736**	
Visit Window	**±3-day window on treatment days unless otherwise noted. (Visits occur once every 3 weeks during treatment period)**											
												at week 7 (± 8 days) is required for at least 20 participants for this arm who also provided a fresh biopsy at screening. Additional optional fresh tumor tissue sample will be collected at Week 19 at the time of imaging assessment and at the time of confirmed PR or PD (± 8 days), upon participant consent. Note: Enrollment may become limited during the study, as required, to ensure collection of fresh tissue samples as noted.
On Treatment Pharmacokinetics and Anti-Drug Antibodies (ADA)												
Plasma Feladilimab (GSK3359609; ICOS Agonist) PK[14, 23]	X	X	X	X	X	X	X	X	X	X	X[14]	14. Draw sample (2 mL) at predose for all marked visits. Additional samples also drawn at the following time points: Week 1 (Day 1) at end of infusion (EOI) (within 15 minutes) and EOI+4h. EOI samples also drawn at Week 13 and Week 25. After Week 25, draw samples every 12 weeks at predose only. There is a +15 minutes window allowance for the EOI time points. 23. Collection of on treatment ICOS PK is no longer required for ongoing participants in this arm.
Ipilimumab PK[24]	Pre, EOI*	Pre, EOI	Pre, EOI	Pre, EOI	Pre, EOI	Pre, EOI	Pre, EOI[15]			Pre[15]	Pre[15]	*Part 1 ONLY: Additional collection time points for PKs on day 8 (± 2 days) and day 15 (± 3 days). 15. To be collected predose, EOI every 3 weeks until Week 19, then predose only every 18 weeks thereafter. If ipilimumab is given on a differing scheduling frequency, pre and EOI should be collected relative to dosing on infusion days only. 24. Collection of on treatment ipilimumab PK is no longer required for ongoing participants in this arm.

On Treatment Study Assessments												Notes
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28 - 49**	**52 - 106**	
Day	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190 - 337**	**358 - 736**	
Visit Window	**±3-day window on treatment days unless otherwise noted. (Visits occur once every 3 weeks during treatment period)**											
Serum Feladilimab (GSK3359609; ICOS Agonist) ADA[16, 25]	X	X	X	X	X	X	X	X	X	X	X[16]	16. Draw sample (4 mL) at predose on ALL treatment visits; then starting with Week 25 predose samples to be collected every 12 weeks. Draw a sample at any time during visit for non-treatment visits. Serum samples will be collected and tested for the presence of antibodies that bind to investigational agents as deemed appropriate. Feladilimab serum samples may also be tested for presence of antibodies that bind to Chinese Hamster Ovary (CHO) host cell proteins such as phospholipase B- like (PLBL2). 25. Collection of on treatment ICOS ADA is no longer required for ongoing participants in this arm.
Serum Ipilimumab ADA[17, 26]	Pre	Pre	Pre	Pre	Pre	Pre	Pre[18]			Pre[18]	Pre[18]	17. Serum samples are required to be collected prior to dosing (i.e., predose) on each dosing day and at the indicated assessment visits following study treatment discontinuation, and one sample collected 12 weeks post last dose of study treatment. In the event of hypersensitivity reaction that is clinically significant and/or leads to study treatment discontinuation, serum samples should be collected 30 days, 12 weeks, and 24 weeks post last dose of study treatment. 18. To be collected every 3 weeks until Week 19, then every 18 weeks thereafter. 26. Collection of on treatment ipilimumab ADA is no longer required for ongoing participants in this arm.
Serum: IRR lab panel[19]												19. Assessment ONLY required in participant experiencing anaphylaxis, serious hypersensitivity, or AEs related to study treatment administration that led to withdrawal from the study. Refer to Table 3 for list of analytes. Predose analysis will be performed on the serum sample collected

On Treatment Study Assessments												Notes
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28 - 49**	**52 - 106**	
Day	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190 - 337**	**358 - 736**	
Visit Window	**±3-day window on treatment days unless otherwise noted. (Visits occur once every 3 weeks during treatment period)**											
												for feladilimab (GSK3359609) and/or ipilimumab immunogenicity assessments.
On Treatment Pharmacogenetics												
Genetic research[20]	X											20. Informed consent for optional genetic research must be obtained before collecting this sample. It is recommended that the optional research sample be taken at the first opportunity after a participant has met all eligibility requirements before Day 1 or on Day 1.

Abbreviations: ADA = Anti-drug antibody; AE = Adverse event; AESI = Adverse events of special interest; β-hCG = Beta-human chorionic gonadotropin; CKD-EPI = Chronic kidney disease epidemiology collaboration; CR = complete response; CrCl = Creatinine clearance; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECOG PS = Eastern Cooperative Oncology Group performance status; EOI = End of infusion; CCI [redacted] ICOS = inducible T Cell co-stimulator; IRR = infusion related reaction; CCI [redacted]; PD = Progressive Disease; CCI [redacted] PR = Partial response; Pre = Predose; CCI [redacted]; SAE = Serious adverse event.

Pre: predose sample to be collected prior to dosing per institutional guidance, as long as it is collected prior to dosing of the corresponding agent**; EOI**: End of infusion sample is in reference to EOI of the corresponding agent.

Table 21 Schedule of Activities – Treatment Discontinuation Visit and Follow-Up: Arm 3: Ipilimumab and Feladilimab Combination

TDV and Follow Up Assessments	Treatment Discontinuation Visit	Survival Follow-Up	Notes
Visit Window	**+ 10 days**		
Anticancer Treatment		X*	* Follow up for survival is no longer required for participants in this arm.
Concomitant Medications	X		
TDV and Follow Up Safety			
AE/SAE/AESI Assessment[2]	X		2. After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. Refer to Section 9.4.1 and Section 9.4.3 for further details..
ECOG PS	X		
Physical Examination	X		
Vital Signs and Weight[3]	X		3. Vital signs include blood pressure, temperature, pulse, respiratory rate, and oxygen saturation.
TDV and Follow Up Local Laboratory Assessments			
Clinical Chemistry	X		
Serum β-hCG (for women of childbearing potential)	X		
Hematology	X		
Thyroid function tests	X		
Calculated CrCl	X		
Urinalysis	X		
TDV and Follow Up Disease Assessments			
Tumor Imaging/Response Assessment[4]	X		4. At the TDV, CT scan is required only if the last disease assessment did not show PD and was performed ≥6 weeks before TDV. For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first. See additional information in Section 9.3.1.

TDV and Follow Up Assessments	Treatment Discontinuation Visit	Survival Follow-Up	Notes
Visit Window	**+ 10 days**		
Telephone call for survival status[1a]		X*	*Follow up for survival is no longer required for participants in this arm.
TDV and Follow Up Tumor Biopsies			
Fresh tumor tissue sample	X[5]		5. If possible, obtain an optional tumor tissue sample at time of confirmed PD or PR.
TDV and Follow Up Patient-Reported Outcomes/Health-Related Quality of Life: Part 2 ONLY			
CCI [redacted]			
TDV and Follow Up Biomarkers[10]			
CCI [redacted]			
TDV and Follow Up Pharmacokinetics and Anti-Drug Antibodies (ADA)[9]			
Feladilimab (GSK3359609) ADA		X[7,8]	7. To be collected 30 days post last dose and 12 weeks post last dose. 8. In the event of hypersensitivity reaction that is clinically significant and/or leads to study treatment discontinuation, an additional sample should be collected at 24 weeks post last dose of study treatment. 9. Collection of follow up PK and ADA samples is no longer required for ongoing participants in this arm.
Feladilimab (GSK3359609) PK		X[7]	
Ipilimumab ADA		X[7,8]	
Ipilimumab PK		X[7]	

Abbreviations: ADA = Anti-drug antibody; AE = Adverse event; AESI = Adverse events of special interest; β-hCG = Beta-human chorionic gonadotropin; CR = complete response; CrCl = Creatinine clearance; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = Electronic case report form; CCI [redacted] PD = Progressive Disease; CCI [redacted], CCI [redacted]

CCI PR = Partial response; CCI ; SAE = Serious adverse event; TDV = Treatment Discontinuation Visit

12.1.3.3. Rationale for the ICOS Agonist/Ipilimumab Combination

Ipilimumab is a recombinant, human monoclonal IgG1 kappa antibody that binds to CTLA-4. CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor immune response [YERVOY Prescribing Information, 2020]. Yervoy (ipilimumab) alone and in combination with nivolumab ± platinum-based chemotherapy is indicated for the treatment of patients across a number of indications which include metastatic melanoma and NSCLC.

Inducible t-cell costimulator (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.

The rationale for targeting ICOS in cancer has been established by multiple lines of nonclinical and clinical evidence. Engagement of the ICOS pathway with an ICOS-L-Fc fusion protein is shown to have potent antitumor activity in multiple syngeneic mouse tumor models [Ara, 2003]. Emerging data from patients treated with anti-CTLA-4 antibodies suggest a positive role of ICOS+ effector T cells in mediating an antitumor immune response. Patients with metastatic melanoma [Di Giacomo, 2013], urothelial [Carthon, 2010], breast [Vonderheide, 2010] and prostate cancer [Chen, 2009] who have increased absolute counts of circulating and tumor infiltrating CD4+ICOS+ and CD8+ICOS+ T cells after ipilimumab treatment have significantly better treatment related outcomes than patients where little or no increases are observed. Importantly, it was shown that ipilimumab changes the ICOS+ T effector-to-Treg cell ratio, reversing an abundance of Tregs cell pre-treatment to a significant abundance of T effectors vs. Tregs cells relative to cells following treatment [Liakou, 2008; Vonderheide, 2010]. As evidenced by the clinical data, ICOS+ T effector cells may be a positive predictive biomarker of ipilimumab response, and activation of this population of cells with an ICOS agonist antibody may confer an advantage by mounting a more robust immune antitumor response.

The T cell activating potential of 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 feladilimab either alone or in combination with ipilimumab demonstrated a more robust pro-inflammatory cytokine response than either single agent alone. A modified allogenic mixed lymphocyte reaction (MLR) 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 feladilimab in combination with ipilimumab. Significant increases in IFNγ secretion were observed for feladilimab combined with ipilimumab as compared to either agent alone, supporting clinical evaluation of this combination.

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 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 showing that interplay between receptor induction extended to CTLA-4.

To support the combination of feladilimab with ipilimumab (anti-CTLA-4 mAb), the nonclinical toxicology findings of ipilimumab as a single agent was reviewed. The nonclinical toxicology profiles of ipilimumab is well characterized and indicates 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 feladilimab combination therapy based on these nonclinical assessments or clinical safety data are described in this protocol. In intravenous repeat-dose toxicology studies in monkeys, ipilimumab was generally well tolerated. Immune-mediated adverse reactions were observed infrequently and included colitis (which resulted in a single fatality), dermatitis and infusion reaction (possibly due to acute cytokine release resulting from a rapid injection rate) [Hanaizi, 2012]. In a monkey reproductive toxicology study, administration of ipilimumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight), and higher incidences of infant mortality in a dose-related manner. The clinical relevance of these findings are well characterized and risk mitigation measures are described in this protocol.

Refer to the GSK3359609 Investigator's Brochure (IB) [GSK Document Number 2017N319717_03; 2020] for further details.

12.1.3.4. Clinical Safety Summary

12.1.3.4.1. Feladilimab

As of the feladilimab Investigator Brochure data cutoff date of 16 March 2020, 249 participants received at least 1 dose of monotherapy feladilimab in study 204691 at the following dose levels: 0.001 mg/kg (n=1), 0.003 mg/kg (n=1), 0.01 mg/kg (n=2), 0.03 mg/kg (n=7), 0.10 mg/kg (n=25), 0.30 mg/kg (n=56), 1.0 mg/kg (n=126), 3.0 mg/kg (n=24), and 10 .0 mg/kg (n=7). In these 249 participants, the most common AEs (occurring in ≥15% of participants overall regardless of dose level or relationship) were anemia (22%), asthenia (21%), nausea (19%), fatigue (18%), diarrhea (16%), and vomiting (15%).

Refer to GSK3359609 IB [GSK Document Number 2017N319717_03] for further details.

12.1.3.4.2. Ipilimumab

The most common adverse reactions (≥5%) with ipilimumab as a single agent are fatigue, diarrhea, pruritis, rash, and colitis. The most common adverse reactions (≥20%) with ipilimumab in combination with nivolumab are fatigue, rash, pruritis, diarrhea, musculoskeletal pain, cough, pyrexia, decreased appetite, nausea, abdominal pain, arthralgia, headache, vomiting, dyspnea, dizziness, hypothyroidism, and decreased weight.

For more details on specific indications, adverse reactions and ipilimumab dosage refer to the prescribing information [YERVOY Prescribing Information, 2020].

12.1.3.5. Dose Justification

12.1.3.5.1. Feladilimab Pharmacokinetics and Pharmacodynamics

The PK of feladilimab was evaluated after 30 minutes of IV infusion at doses from 0.001 mg/kg to 10.0 mg/kg every 3 weeks (Q3W) in participants with solid tumors in Study 204691. The plasma PK samples (received prior to the 2020 IB update cutoff date of 16 March 2020) were analyzed with a validated bioanalytical method with a LLOQ of 0.1 µg/mL.

As of 16 March 2020, preliminary PK data in monotherapy cohorts were available in 1 participant at 0.003 mg/kg, 2 participants at 0.01 mg/kg, 7 participants at 0.03 mg/kg, 25 participants at 0.1 mg/kg, 52 participants at 0.3 mg/kg, 123 participants at 1.0 mg/kg, 23 participants at 3.0 mg/kg, and 7 participants at 10.0 mg/kg dose. Preliminary PK data in pembrolizumab combination cohorts were available in 5 participants at 0.01 mg/kg, 5 participants at 0.03 mg/kg, 13 participants at 0.1 mg/kg, 244 participants at 0.3 mg/kg, 38 participants at 1.0 mg/kg, and 18 participants at 3.0 mg/kg dose. Preliminary PK data in GSK3174998 combination cohorts were available in 5 participants each at 8 and 24 mg and 1 participant at 80 mg fixed dose. Preliminary PK data in chemotherapy combination

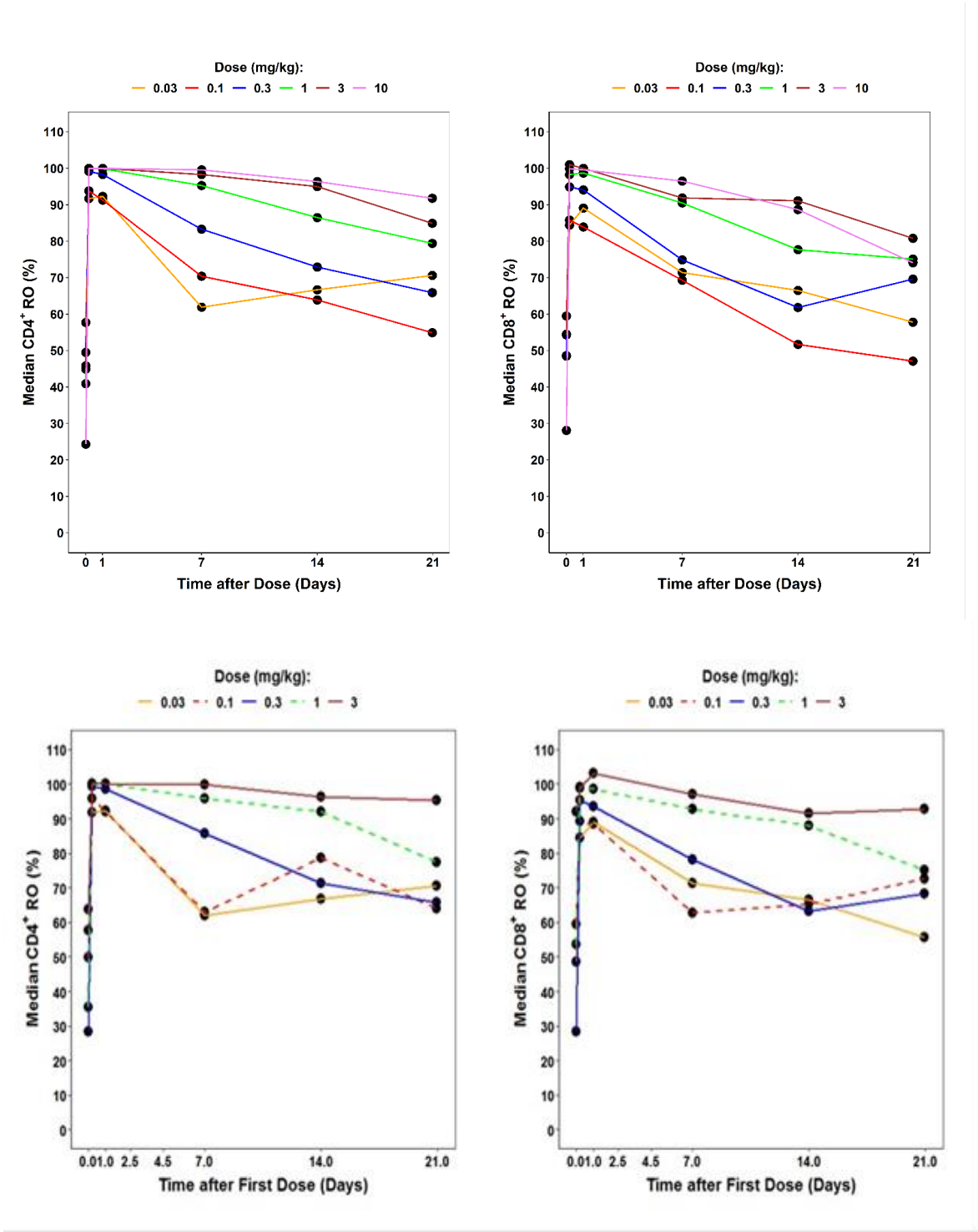
cohorts of the safety run-in were available in 55 participants at 80 mg fixed dose of feladilimab.

Based on these preliminary data, the median plasma concentration-time profiles of feladilimab exhibit a bi-exponential decline. There are no changes in feladilimab PK when co-administered at doses from 0.01 to 3.0 mg/kg with biologic or chemotherapy partners. Furthermore, median feladilimab plasma PK profiles after dosing at 8, 24, and 80 mg fixed doses were superimposable to the median PK profiles observed with 0.1, 0.3, and 1.0 mg/kg doses. Preliminary plasma PK parameters of feladilimab computed using noncompartmental analysis methods (AUC, $C\tau$, and C_{max}) calculated over the first dosing interval (up to 503 hours) exhibit approximate dose proportional increases in feladilimab exposure over the range of 0.01 to 10.0 mg/kg doses. Observed exposures (AUC and $C\tau$) from body-weight based dose of 1.0 mg/kg (combined monotherapy and combination cohorts) and corresponding fixed dose equivalent of 80 mg (chemotherapy safety run-in) overlap with each other, indicating similar exposures can be achieved with a fixed dosing regimen. Preliminary population PK estimated geometric mean systemic half-life ($t_{1/2}$) of feladilimab is approximately 19 days.

Based on the preliminary data, median CD4 and CD8 receptor occupancy was maintained at or above 70% during the dosing interval of first cycle for doses ≥0.3 mg/kg as shown in Figure 8.

Refer to GSK3359609 IB [GSK Document Number 2017N319717_03] for further details.

Figure 8 Median CD4+ and CD8+ Receptor Occupancy (%RO) During the First Cycle of Feladilimab Administration as Monotherapy



Feladilimab Dosing Frequency

The systemic half-life of feladilimab is approximately 19 days based on the preliminary population PK analysis of data from ongoing study 204691. The existing feladilimab

Q3W regimen in the ongoing clinical study is also consistent with the Q3W dosing regimen typical with other IgG4 based monoclonal antibody therapies. Thus, feladilimab will be dosed Q3W in combination with ipilimumab. Combination of feladilimab with any other treatment in other arms of this study may have a different dosing regimen as deemed appropriate.

Rationale for Fixed Dose

Therapeutic monoclonal antibodies are often dosed based on body-size due to the concept that this reduces inter-participant variability in drug exposure. However, body-weight dependency of PK parameters does not always explain all or even a majority of observed variability in the exposure of monoclonal antibodies [Zhao, 2017]. Hence, the selection of body-weight based versus fixed dosing in this study was evaluated through population PK modelling and simulation efforts.

A preliminary population PK model (N = 637 participants; March 2020), which characterized the influence of body weight, age, and other participant covariates on exposure was developed. Results of this analysis indicate a feladilimab fixed dose is appropriate for trial participants across the bodyweight spectrum. Simulations show a feladilimab body weight-based dose results in slightly higher exposure in heavier weight participants and a feladilimab fixed dose results in slightly higher exposures in lighter participants. However, the range of exposures are similar between body-weight based and fixed dosing across the entire body weight spectrum and the exposures are maintained well within established clinical boundaries of safety at doses in the range of 24 to 80 mg Q3W (the highest studied dose in monotherapy deemed tolerable was 10 mg/kg or ~800 mg). This suggests that there is no advantage of body-weight based dosing over fixed dosing and that lighter patients will not be more susceptible to treatment-related adverse events arising from marginal increases in exposure.

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

Refer to GSK3359609 IB [GSK Document Number 2017N319717_03] for further details.

12.1.3.5.2. Feladilimab Dose Rationale (Arm 3)

Based on the preliminary PK data described above in Section 12.1.3.5.1 and target engagement shown in Figure 8, median CD4 and CD8 receptor occupancy was maintained at or above 70% during the dosing interval of first cycle for doses ≥0.3 mg/kg. Sufficiently high CD4+ RO is expected at peak exposures (89% to >99% RO) as well as at trough exposures (69% to >99% RO) at steady-state with the proposed 24 mg dose in arm 3.

Collectively, based on the safety and exposure data from the Phase 1 study and the predicted target engagement, a 24-mg dose will be evaluated in combination with

ipilimumab in this study. No drug-drug interaction related changes are expected in feladilimab PK with ipilimumab co-administration. The currently planned feladilimab dose for this arm is the same as that used in the phase 2/3 studies for recurrent or metastatic (R/M) head and neck squamous cell carcinoma/cancer (HNSCC).

12.1.3.5.3. Ipilimumab Dose Rationale

The dose for ipilimumab for this study is 1 mg/kg or 3 mg/kg administered intravenously every 3 weeks.

The 1 mg/kg or 3 mg/kg doses were selected based on approvals in multiple tumor types, both as monotherapy and in combination with nivolumab. [YERVOY Prescribing Information, 2020].

12.1.3.6. Study Treatments

Table 22 Description and Administration of Arm 3 Study Treatments

Name	Ipilimumab	Feladilimab (GSK3359609; ICOS agonist)
Description	CTLA-4 inhibitor	Humanized anti-ICOS IgG4 mAb
Dosage form/strength	50 mg/ 10 mL Solution; 5 mg/mL	Solution for injection/ 10 mg/mL
Dosage	1 mg/kg, 3 mg/kg	24 mg
Route of administration	IV infusion	IV infusion[a]
Dosing instructions[a]/frequency	Administer diluted product/once Q3W (refer to SRM for infusion time)	Administer diluted product/once Q3W

[a]: The study reference manual contains the details on product handling, storage, preparation, and administration.

In the ipilimumab + feladilimab containing arm, feladilimab will be administered first as a 30minute IV infusion (infusion time may be adjusted in the event an infusion reaction occurs) under medical supervision of an investigator or designee. The administration of the ipilimumab must be started at least 30 minutes and no more than one hour following the end of the feladilimab infusion under medical supervision of an investigator or designee.

Participants should remain under observation at the study site post-study treatment infusion per the judgement of the investigator or as per institutional guidelines. Refer to Section 12.1.3.10, Table 24 for details on the management of participants experiencing infusion reactions.

The date(s), start time(s) and stop time(s) of administration of each study drug will be documented in the source documents and reported in the eCRF. 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. 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 72-hour window does not apply to completion of study treatment administration interrupted by an infusion reaction. Refer to Section 7.2.1.4 for criteria governing dose interruptions or delays.

Details on preparation and administration of feladilimab and ipilimumab are described in the study reference manual (SRM) and ipilimumab package insert, respectively.

12.1.3.7. Concomitant Therapy

Please refer to Section 7.7

12.1.3.8. Treatment of Overdose

12.1.3.8.1. Feladilimab Overdose

An overdose of feladilimab is defined as administration of a dose that is >240 mg (>10 times the 24 mg 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 and laboratory abnormalities for at least 130 days from the date of the overdose.
3. Obtain a plasma sample for PK analysis within 28 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

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

There is no specific antidote for overdose with the experimental treatments being evaluated in this study. 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.

12.1.3.8.2. Ipilimumab Overdose

According to ipilimumab prescribing information, no information is available on overdosage. In case of overdose symptomatic treatment has to be applied; there are no known antidotes for the compound.

In the event of an overdose, the investigator must:

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

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

12.1.3.9. Treatment Duration for Ipilimumab

Participants enrolled will be treated until disease progression, intolerable toxicity, informed consent withdrawal or death. Combination study treatment will continue to be administered at the indicated schedule for a maximum duration of approximately 2 years or up to 35 treatment visits, whichever comes first. Refer to Section 5.2. for additional details regarding follow up after discontinuation of study treatment.

12.1.3.10. Dose modification and Management Guidelines

The dose of feladilimab cannot be reduced or modified.

No dose reductions are allowed for ipilimumab. Dose Modification Guidelines for immune related Adverse Events are listed in Section 7.2.1.1.

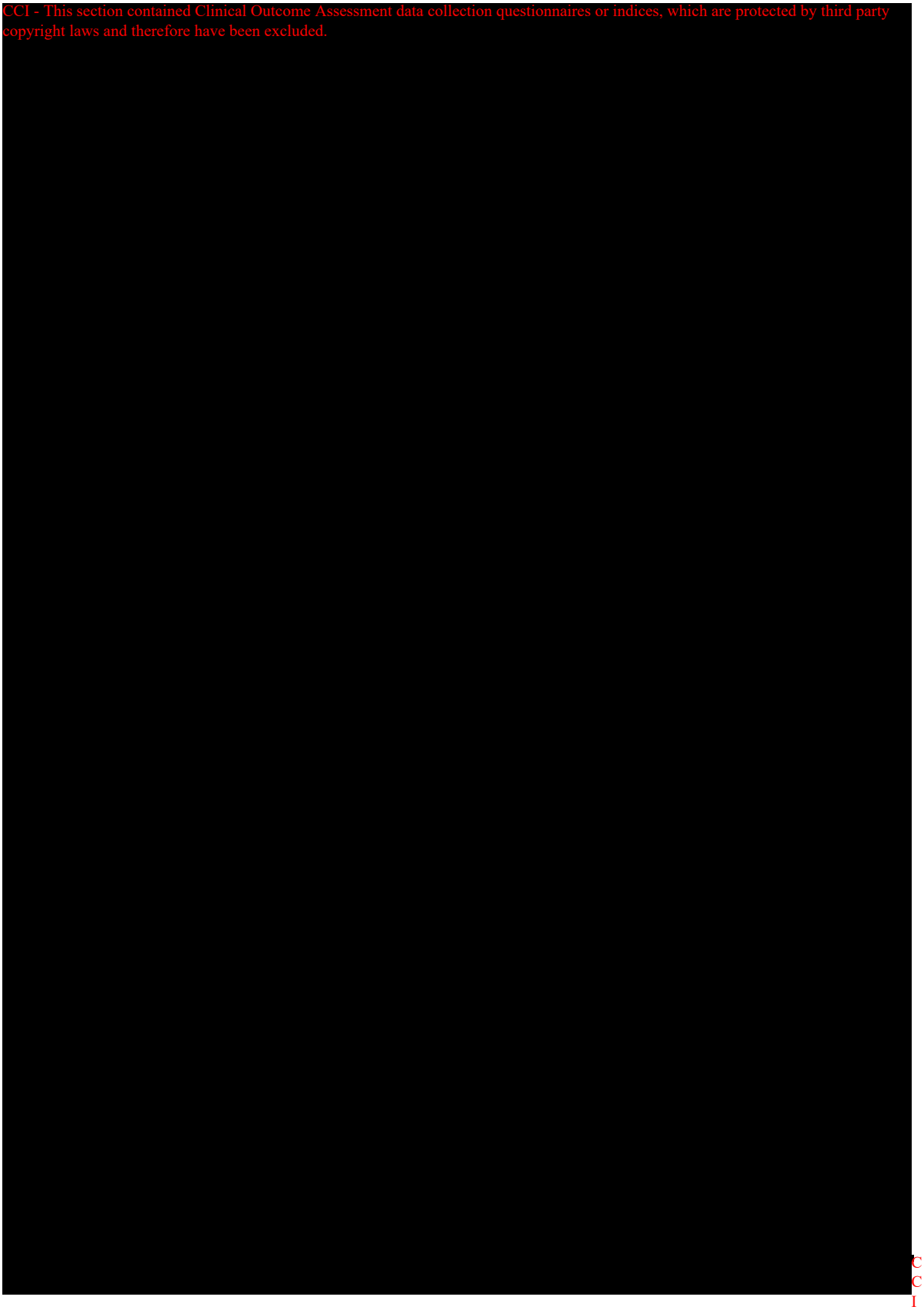
If either GSK3359606 or ipilimumab is held or discontinued for any toxicity, the other study drug must also be held or discontinued, unless discussed otherwise with Medical Monitor.

12.1.3.10.1. General Guidelines for Immune-Related Adverse Events (irAEs)

AEs associated with immunotherapy treatment may be immune-mediated. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of treatment, or during the treatment course, and may affect more than one body system simultaneously. Therefore, early recognition of and initiation of treatment for these events is critical to reduce potential complications. Based on existing data from the study 204691, most treatment-related AEs were Grade 1 or 2, managed with supportive care and if appropriate the administration of corticosteroids.
For suspected irAEs, ensure adequate evaluation to confirm the etiology or exclude other causes. Additional procedures or tests such as, but not limited to, bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue treatment and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with immunotherapies are provided in Table 23.

Table 23 Dose Modification and Toxicity Management Guidelines for Immune-Related AEs

General instructions: • Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks. • For situations where immunotherapy treatment has been withheld, treatment can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Immunotherapy treatment should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks. • For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.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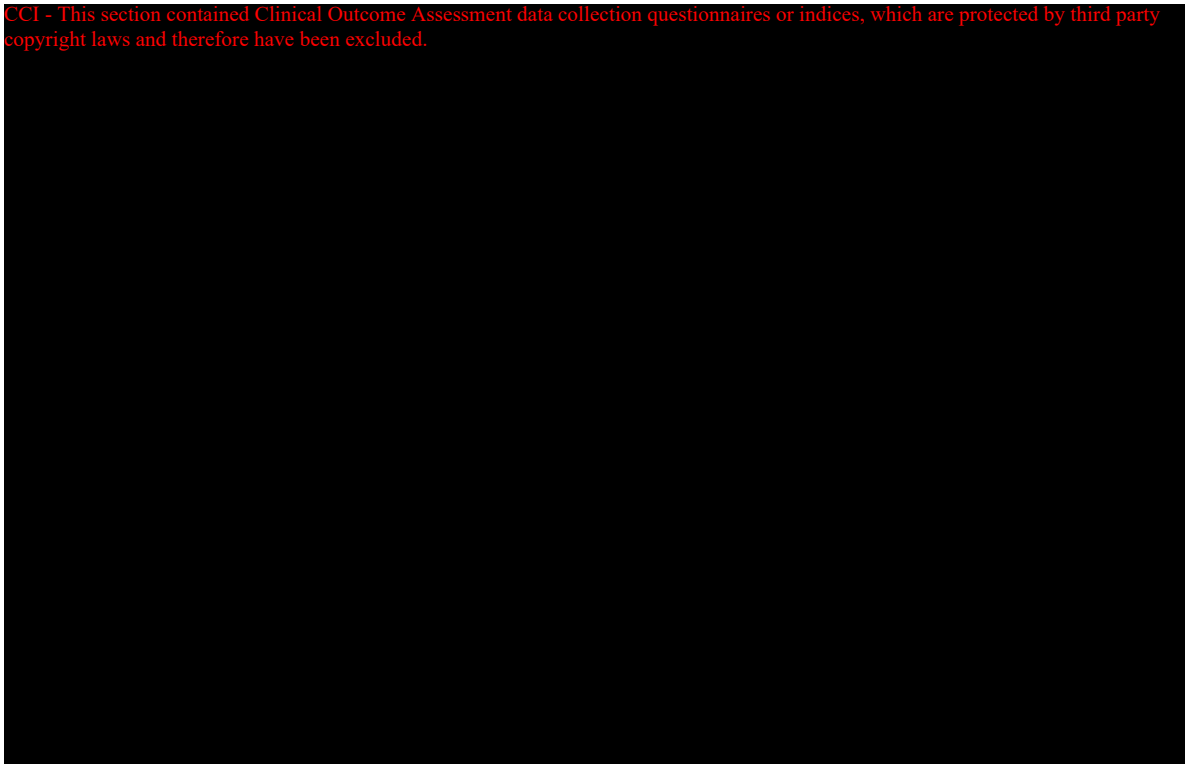
12.1.3.10.2. Dose Modification and Toxicity Management of Infusion-Reactions Related to Immunotherapy Treatment

Table 24 Immunotherapy Infusion Reaction Dose Modification and Treatment Guidelines

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

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



12.1.3.10.3. Adverse Events of Special Interest (AESI)

AESI are defined as events of potential immunologic etiology, including irAEs. Such events recently reported after treatment with other immune modulatory therapy include, but are not limited to, the following: pneumonitis, nephritis, hepatitis, colitis, immune related endocrinopathies (such as thyroiditis or hypophysitis) or immune related cutaneous toxicities, to include rashes confirmed via biopsy to be immune-mediated.

AESIs will be reported within 24 hours if the event meets the criteria for a serious event.

12.1.3.11. Safety Evaluation

All the regimen qualification activities in Part 1 are based on the premise that a proposed dose for each component, informed by prior experience, will be evaluated to go forward to Part 2. If the Part 1 regimen qualification process confirms the dose combination, the combination will proceed to Part 2. If the Part 1 regimen qualification process does not confirm the dose combination, further evaluation in the 205801 platform study of that combination will stop.

The combination cohort of feladilimab with ipilimumab will test 24 mg feladilimab in combination with either 1mg/kg ipilimumab or 3mg/kg ipilimumab. The arm assessing the combination of 24 mg feladilimab with 1 mg/kg ipilimumab will be conducted independently from the arm assessing the combination of 3 mg/kg ipilimumab with 24 mg feladilimab. There will be no dose escalation or de-escalation for either combination partner. Further evaluation of a combination demonstrated to result in toxicity as described in Table 27 at the rate defined in Table 25, will be stopped.

Safety and tolerability will be guided using a modified toxicity probability interval

(mTPI) approach with some additional modifications due to only one dose level being evaluated. 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, pT – ε1), the overdosing interval as (pT + ε2, 1), and the proper dosing interval as (pT – ε1, pT + ε2), where pT is the target toxicity rate, ε1 and ε2 are small fractions, such as 0.05, to account for the uncertainty around the true target toxicity. The three dosing intervals are associated with three different dose decisions. 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. For example, if the over-dosing interval has the largest UPM, decision will be to stop further evaluation.

Initial safety and tolerability of the combination will be evaluated within the first 21 days (DLT period). Evaluation of the available safety data over the first 21 days of treatment for each participant enrolled is required from at least 3 participants before a decision is made to enroll additional participants. The maximum number of participants assigned to either dose level will be at the discretion of the Sponsor in consultation with the investigators. If no more than one of the first three participants treated with 24 mg feladilimab + 1 mg/kg ipilimumab experience safety findings (DLTs) meeting the criteria described in Table 27, an additional 6-7 participants will be treated with 24 mg feladilimab + 1mg/kg ipilimumab.

If a participant withdraws from the study before the completion of the 21-day DLT evaluation period for reasons other than DLT, then the participant may be replaced to achieve the three-participant required minimum. The decision to declare the combination tolerable will occur following review of the safety, PK and PD data and joint discussion by the GSK Medical Monitor and investigators. Membership, roles and accountabilities, and the process for safety review and meeting frequency is outlined in the Study Reference Manual.

The mTPI design assumptions include the following:

(i) A maximum of 10 participants will complete the DLT evaluation period;
(ii) The true underlying toxicity rate for feladilimab falls within the range from 25% to 33% and targets at 30%.
(iii) Maximum probability that the dose exceeds the target toxicity is 95%; however an additional safety rule will be applied if the maximum sample size of 10 is reached whereby the dose will be considered non-tolerated if there is greater than 70% posterior probability that the true DLT rate is >30%

Participants will be enrolled in cohorts of 3-4 and decisions will be made after all patients within a cohort complete the DLT evaluation period.

The monitoring rules guiding dose decision are provided in Table 25. The tolerability decision framework using the mTPI method were generated based on a beta/binomial

model and pre-calculated before study initiation. The entries in the Dose Decision Rules table below represent dose-finding decision points at which a determination is made whether the combination remains safe for continued testing using the data generated in the cohort of interest.. In other studies utilizing mTPI, these points are often denoted as “E”, “S”, and “D”, denoting the thresholds governing escalating the dose, staying at the same dose, or de-escalating the dose, respectively. However in this study, as there is no dose escalation or de-escalation, the thresholds mark the criteria used to determine whether the doses of the combination are tolerated and therefore, permit continued treatment of additional participants at the same combination dose. If a dose combination is not tolerated per Table 25 and Table 27, further evaluation of that dose combination will be stopped without exploration of other dose levels of either or both combination partners.

As an example, the scenario in which one of the first three participants in Part 1 experience a DLT is represented in the cell marking the intersections of row ‘1’ and column ‘3’ in Table 25. According to the model underlying the mTPI, such a scenario predicts the actual rate of toxicity to be within the acceptable, predetermined range, therefore allowing treatment of additional three participants at the same dose combination. The scenario in which one of these three additional participants experience DLT, is represented in the cell marking the intersection of row ‘2’ and column ‘6’, allowing treatment of an additional four participants according to the model. If two of these four additional participants experience DLTs, the combination will not be considered as tolerated and no additional participants will be treated in this combination. not continue because of unacceptable toxicity. If the combination is considered tolerated, additional participants will be enrolled to further evaluate safety and PK/PD. No formal evaluation of DLTs will be performed after the 21 day period, however other measures of safety will continue to be monitored.

Table 25 Dose Decision Rules

	Number Treated		
#DLTs	3	6	10
0	Tolerated	Not applicable	Not applicable
1	Enroll 3	Tolerated	Tolerated
2	Stop	Enroll 4	Tolerated
3	Stop	Stop	Tolerated
4		Stop	Stop
5		Stop	Stop
6		Stop	Stop
7			Stop
8			Stop
9			Stop
10			Stop

12.1.3.12. Futility evaluation

Once an arm transitions through the initial safety evaluation as described above, additional participants will be enrolled to that arm, up to a maximum of 15 participants to provide further evaluation of safety and tolerability and:

1. Preliminary PK/pharmacodynamic characteristics (i.e., measures of target engagement and functional effects such as receptor occupancy and cytokine release) and
2. Evaluation of antitumor activity.

In these participants, tumor biopsy at Screening and Week 7 will be required (refer to SOA tables for each arm Section 12.1 or further details).

An interim evaluation of futility in terms of ORR will be conducted after the first 10 participants have had at least two post baseline RECIST assessments. A maximum of 15 participants will be enrolled to allow for 10 evaluable participants to be assessed for futility. If no objective responses are observed in 10 evaluable participants, development of the experimental regimen may be stopped. Decisions will be made after evaluation of other endpoints and will be based on the totality of data, including the Disease Control Rate endpoint.

Table 26 Planned Dose Levels for Feladilimab and Ipilimumab

Dose Level	Ipilimumab (mg/kg)	Feladilimab (GSK3356909) (mg)	Safety (n)	PK/PD (n)	Total (n)
1	1	24	3-6	6-19	9-25
2	3	24	3-10	N/A	3-10

The ipilimumab combination cohort will initiate at the 3mg/kg dose in combination with feladilimab 24 mg. If the 3mg/kg ipilimumab dose meets the dose limiting toxicity definition as described below, a second cohort of 3-10 participants will be dosed at 1mg/kg ipilimumab plus 24 mg feladilimab to explore a lower dose.

12.1.3.13. Dose Limiting Toxicity

The severity of all toxicities will be graded using National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 5.0) [NCI, 2017]. The DLT observation period is 21 days in length and begins on the day 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 27 and is considered by the investigator to be clinically relevant and attributed (probably or possibly) to the study treatment during the 21-day DLT observation period. An AE considered related to the underlying disease under study it is not defined as a DLT. A safety event can still be included for DLT consideration after the 21 day window.

Table 27 Dose-Limiting Toxicity Criteria

Toxicity	DLT Definition
Hematologic	• Febrile neutropenia as defined by CTCAE v5 • 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
	  ○ Grade 3 and Grade 4 asymptomatic electrolyte abnormalities that are corrected within 24 hours without clinical sequelae
	  ○ Grade 3 nausea, vomiting, or fatigue that resolves to Grade 1 within 7 days with optimal supportive care
	  ○ Grade 3 and Grade 4 infusion reactions in participants not receiving prophylaxis for IRRs (refer to Section 7.2.1.2 for details on IRR management)

Toxicity	DLT Definition
Other	• Toxicity that results in permanent discontinuation of feladilimab monotherapy or 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. Suggested toxicity management guidelines as described in Section 7.2.1.2 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.
CTCAE=Common Toxicity Criteria for Adverse Events; DLT = Dose-limiting toxicity; G-CSF =Granulocyte colony-stimulating factor; GSK =GlaxoSmithKline; IRR=infusion related reaction

If a participant experiences a DLT during the DLT observation period, the participant may resume dosing provided the toxicity did not meet study treatment discontinuation criteria and following approval by the Sponsor. In cases where retreatment is considered, refer to Section 12.1.3.10.1 for selection of the dose and schedule of ipilimumab in combination with feladilimab. Participants may reduce the dose intensity of ipilimumab one or two times.

Toxicity management and dose modification guidelines described in Section 7.2.1.2 are provided 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 feladilimab and ipilimumab.

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 as ipilimumab and pembrolizumab.

If there is a delay in administration of study treatment, refer to Section 7.2.1.4 for guidance on planning of subsequent study visits.

12.1.3.14. Risk-Benefit Assessment for Ipilimumab combined with Feladilimab

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 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 IFN 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.

Although there is no clinical experience with the combination of feladilimab with ipilimumab, given the currently available safety data and the low likelihood of drug-drug interactions between feladilimab with ipilimumab, combination therapy may have an acceptable safety profile. Additionally, the combination may provide anti-tumor effect in participants with advanced NSCLC. The current nonclinical and clinical safety information for feladilimab and ipilimumab, used as single agents, provide support for their use in combination in the target patient population.

This is the first study testing the combination of feladilimab with ipilimumab in participants with advanced NSCLC that have been treated with standard therapies. Study participants may benefit from medical tests and screening performed during the study. Any potential benefit of the addition of ipilimumab to feladilimab is unknown. Data obtained in this study may help identify individuals more likely to benefit or have side-effects from ipilimumab plus feladilimab.

Based on the status of ipilimumab as a marketed product with documented anticancer activity and an acceptable safety profile and feladilimab as an agent with close to a one thousand patient experience with preliminary signals of activity in NSCLC and a manageable toxicity profile, the potential benefit to risk is favorable to proceed with the combination in the context of a controlled monitored study with an initial safety clearance and rule out futility screening to confirm the potential risks and benefits.

The following sub sections outline the risks and mitigation strategies for this protocol for ipilimumab. Refer to the latest ipilimumab US product insert (USPI) and the EU SmPC for additional details. Feladilimab risk assessment and mitigation strategies are in the master protocol (Section 3.3).

Table 28 Risk Assessment and Mitigation Strategy: Ipilimumab

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. (refer to the latest SmPC and/or USPI for YERVOY)	• Participants with the following medical history are ineligible for this study ○ Toxicity (Grade 3) related to prior immunotherapy leading to study treatment discontinuation ○ Active autoimmune disease (refer to Section 6.2 exclusion criterion 6) ○ Severe hypersensitivity to another mAb • Established management algorithms for immune-related adverse events (irAEs) • Refer to Section 7.2.1.1 for further details on the identification, evaluation, and management of toxicities with a potential immune etiology.
Infusion and hypersensitivity reactions and potential CRS	• Risk for infusion reactions and hypersensitivity is inherent to many mAbs [Brennan, 2010] (refer to the latest SmPC and/or USPI for YERVOY)	• 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 7.2.1.2 for further details on management of infusion reactions. • Refer to Section 7.2.1.2 for further details on management of CRS
Immune complex disease	• Immune complex formation and deposition findings (refer to the latest SmPC and/or USPI for YERVOY)	• Clinical laboratory safety assessments and immunogenicity testing

Table 29 below provides an outline of the risk assessment and mitigation strategy for GSK3359609 (feladilimab). More detailed information about the known and expected benefits and risks and reasonably expected adverse events of feladilimab may be found in the IB [GSK Document Number 2017N319717_03].

Table 29 Risk Assessment and Mitigation Strategy GSK3359609 (feladilimab)

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 ○ Toxicity (≥Grade 3) related to prior immunotherapy leading to study treatment discontinuation ○ Active autoimmune disease (refer to Section 6.2 exclusion criterion 6) ○ Severe hypersensitivity to another mAb • Established management algorithms for immune-related adverse events (irAEs) • Refer to Section 7.2.1.1 for further details on the identification, evaluation, and management of toxicities with a potential immune etiology.
Infusion-related reactions (IRRs) which include hypersensitivity and potential cytokine release syndrome (CRS)	• Risk for infusion reactions and hypersensitivity is inherent to many mAbs [Brennan, 2010] • The overall rate of IRRs with feladilimab is low and there have been no cases of CRS observed across the clinical program of feladilimab [GSK Document Number 2017N319717_03, 2020].	• 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 7.2.1.2 for further details on management of infusion reactions and details on CRS management.
Immune complex disease	• Immune complex formation and deposition findings in nonclinical safety studies [GSK Document Number 2017N319717_03, 2020]	• Clinical laboratory safety assessments and immunogenicity testing

Abbreviations: AE = adverse event; IB = Investigator's Brochure; ICOS = inducible T-cell co-stimulator; LPS = lipopolysaccharide; mAb = monoclonal antibody; TCR = T-cell receptor.

12.1.3.15. Additional Study Population Criteria: Arm 3

None.

12.1.3.16. References

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12.1.4. Arm 4: GSK4428859A (Anti-TIGIT) and Dostarlimab (Anti-PD-1) Combination

12.1.4.1. Protocol Amendment 9 Summary of Changes Specific to GSK4428859A and Dostarlimab Arm

Section # and Name	Description of Change	Brief Rationale
Schedule of Activities Section 12.1.4.2 (Table 30, Table 31 and Table 32) Dose modification and Management Guidelines (Section 12.1.4.11 and Table 34)	Addition of text to clarify that the following investigations will require a Cardiologist or locally appropriate specialist review; 1. CCI [redacted] Addition of text to clarify that the Sponsor will need to be informed regarding these participants Addition of text to clarify that investigators are required to review all safety laboratory assessments before dosing..	Modifications were made to provide additional monitoring requirements and management of cardiac abnormalities in the event of CCI [redacted]
Section 12.1.4.15 and Table 38	CCI [redacted]	CCI [redacted]

Protocol Amendment 8 Summary of Changes Specific to GSK4428859A and Dostarlimab Arm

Section # and Name	Description of Change	Brief Rationale
Schedule of Activities Section 12.1.4.2 (Table 30, Table 31 and Table 32)	CCI [redacted]	
Schedule of Activities Section 12.1.4.2 (Table 31 and Table 32)		
Dose modification and Management Guidelines (Section 12.1.4.11 and Table 34)		

Protocol Amendment 7 Summary of Changes Specific to GSK4428859A and Dostarlimab Arm

Section # and Name	Description of Change	Brief Rationale
Schedule of Activities Section 12.1.4.2 (Table 31 and Table 32)	CCI [redacted]	

Protocol Amendment 6 Summary of Changes Specific to GSK4428859A and Dostarlimab Arm

Section # and Name	Description of Change	Brief Rationale
Schedule of Activities Section 12.1.4.2 (Table 31)	Removed the timing between infusions	Moved details of timing between infusions to the Pharmacy Manual to allow flexibility as new data from ongoing studies become available
Schedule of Activities Section 12.1.4.2 (Table 31)	Updated assessment title/heading of whole blood to specify flow cytometry	To clarify the intent for the whole blood sample
Schedule of Activities Section 12.1.4.2 (Table 31)	Updated note # 17, under the IRR sample	To clarify when an IRR sample is required to be taken
Schedule of Activities Section 12.1.4.2 (Table 32)	Included a 60 day and 90 day after last dose safety lab assessments during follow up	To address request from regulatory agency to include safety lab assessments during follow up
Schedule of Activities Section 12.1.4.2 (Table 32)	Updated the time window for treatment discontinuation visit to specify it is within	To clarify the time window and align with the footnote included in the SOA

Section # and Name	Description of Change	Brief Rationale
	30 days of study treatment discontinuation	
Clinical Safety Summary: GSK4428859A Section 12.1.4.4.1	Added number of participants CCI), showing favorable results in Phase 1 dose-finding study of GSK4428859A	To include omitted data
Dose Justification: GSK4428859A Pharmacokinetics and Pharmacodynamics Section 12.1.4.6.1	Corrected t1/2 range of GSK4428859A	To correct typo
Study Treatments Section 12.1.4.7	Removed the timing for observation after completion of study treatment administration	Moved details of observation period to the Pharmacy Manual to allow flexibility as new data from ongoing studies become available
Dose Modification and Management Guidelines Section 12.1.4.10	CCI [redacted]	To include the most recent safety data from the ongoing FTIH study
Dose Modification and Management Guideline Section 12.1.4.11	Table 34: Corrected Grade 0 for AEs to AEs resolved	To align with grading of AEs as there is no Grade 0
GSK4428859A Dose Rationale (Arm 4) Section 12.1.4.6.2	Updated language around the dose rationale for in vitro evaluation of GSK4428859	Corrected prior error in information reported to align with Investigator Brochure
Dose Limiting Toxicity Section 12.1.4.14	CCI [redacted]	To clarify that the time window is after completion of the DLT period

Section # and Name	Description of Change	Brief Rationale
Risk-Benefit Assessment of GSK4428859A and Dostarlimab combined 12.1.4.15	CCI [redacted]	To clarify protocol requirements to collect sample in the case of an infusion reaction
Additional Inclusion Criteria: Arm 4 Section 12.1.4.16.1	Added inclusion criteria: -Male contraception is not required for this arm	To update contraception requirements for males participating in this arm
All Sections	Defined abbreviations	Added abbreviations that were omitted in error

12.1.4.2. Schedule of Activities Specific to the GSK4428859A and Dostarlimab Combination

The timing and number of planned study assessments (including safety, pharmacokinetic, ADA, biomarker or other assessments) may be altered during the course of the study based on newly available data.

Table 30 Schedule of Activities – Screening Arm 4: GSK4428859A and Dostarlimab Combination

Screening Study Assessments	Screening[1]	Notes
Visit Window	≤4 Wks	
Informed Consent[1]	X	1. All screening assessments must be performed within 4 weeks (28 days) prior to first dose of study treatment unless otherwise specified. The informed consent may be signed within 45 days prior to first dose.
Participant Registration[2]	X	2. Participants will be registered in RAMOS NG at screening.
Inclusion/Exclusion Criteria	X	Review eligibility prior to randomization.
Demographics, Medical History (including alcohol and tobacco use), Prior Medications, Disease History[12]	X	12. All known mutations should be entered in the eCRF as disease history.
Prior Anticancer Treatment, Radiotherapy	X	
Screening Safety		
AE/SAE/AESI Assessment[3]	X	3. Any AESI or SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study. After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. Refer to Section 9.4 for further details.
ECOG PS	X	
Physical Examination	X	
Vital Signs, Height and Weight[4]	X	4. Vital signs include blood pressure, temperature, pulse, respiratory rate, and oxygen saturation. Height is recorded at Screening only. Record weight in kilograms.
12-lead ECG	X	Consider cardiologist or locally appropriate specialist review for participants with potentially significant ECG abnormalities such as AV block (except for first degree), new cardiac arrhythmias, or frequent PVCs. Please inform the Sponsor regarding these participants.
Echocardiogram or MUGA scan[5]	X	5. ECHO required at Screening within 28 days prior to first dose of study treatment, and during treatment phase if clinically indicated. MUGA scan may be used if ECHO not feasible.
Screening Local Laboratory Assessments (Safety)		
Hepatitis B and C[6]	X	
Serum β-hCG (for women of childbearing potential)	≤3d	

Screening Study Assessments	Screening[1]	Notes
Visit Window	≤4 Wks	
Clinical Chemistry[6], Coagulation[6], Hematology[6], Thyroid function[6]	X	6. Refer to Appendix 3 for a complete list of required assessments. Required within 7 days of randomization day. Not required to be tested on Day 1 if screening labs are within 72 hours from time of scheduled first dose. Must be drawn predose or up to 3 days prior to dosing. If Hepatitis B and C was performed within 3 months prior to first dose of study intervention or SoC, repeat testing at screening is not required; otherwise, this testing is mandatory.
Calculated CrCl[7]	X	7. CrCl is calculated by the CKD-EPI or Cockcroft-Gault formula. See Appendix 9.
CCI [redacted]		
Urinalysis[6]	X	
Screening Other Laboratory Assessments		
PD-L1 expression by IHC[8]	X	8. PD-L1 expression by IHC and type of assay utilized (i.e., Ventana SP263, Ventana SP142, Dako 28-8, or Dako 22C3) must be recorded in the eCRF, if known. Note: Test is not required to be performed by the site if not previously performed.
Screening Disease Assessments		
Tumor Imaging[9]	X	9. Diagnostic quality CT scan of chest and abdomen with contrast must be obtained within 28 days of first dose. Baseline brain scan (MRI with and without IV gadolinium) should be obtained within 6 weeks of first dose if history of CNS disease or if clinically indicated. Bone scan should be obtained within 6 weeks of first dose if clinically indicated. See additional information regarding bone scans in Section 9.3.1.
Pre-Baseline scans for Tumor Growth Kinetics[10]	X	10. Upon participant consent, up to 3 pre-baseline scans (within 12 months before the baseline scan) will be collected to assess tumor growth rate to support exploratory investigation of tumor growth kinetics (See Section 9.3.2 for details on images for submission).

Screening Study Assessments	Screening[1]	Notes
Visit Window	≤4 Wks	
Screening Tumor Biopsies		
Fresh tumor tissue sample and Archival tumor[11]	X	CCI [redacted]

Abbreviations: AE = adverse event; AESI = adverse events of special interest; β-hCG = β -human chorionic gonadotropin; BNP = B-type natriuretic peptide; CKD-EPI = chronic kidney disease epidemiology collaboration; CrCl = creatinine clearance; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiography; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; IHC = Immunohistochemistry; IWRS = interactive web response system; MRI = magnetic resonance imaging; MUGA = multi-gated acquisition; NT-pro-BNP = N-terminal pro-hormone BNP; SAE = serious adverse event.

Table 31 Schedule of Activities – Treatment Period Experimental Arm 4: GSK4428859A (Anti-TIGIT) and Dostarlimab (Anti-PD-1) Combination

On Treatment Study Assessments												Notes
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28 - 49**	**52 - 106**	
Day	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190 - 337**	**358 - 736**	
Visit Window	**±3-day window on treatment days (Visits occur once every 3 weeks during treatment period)**											
Inclusion/Exclusion Criteria	X											
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	
Participant Randomization[1]	X											1. Once determined to be eligible, participants must be randomized via IWRS. Drug shipments will be managed via IWRS. Sites must allow up to 7 business days for shipment of study drug. Randomization can be done prior to Day 1, but no more than 3 days prior to Day 1. (Refer to SRM).
Study treatments[1]												
Administer Dostarlimab[2]	X	X	X	X	X	X	X	X	X	X	Q3W	CCI [redacted]
CCI [redacted]												Refer to Section 5.2 for maximum duration of study treatment.
On Treatment Safety												
AE/SAE/AESI Assessment[3]	X	X	X	X	X	X	X	X	X	X	X	3. After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. Refer to Section 9.4.1 for further details.
ECOG PS**	X	X	X	X	X	X	X	X	X*	Q6W*	Q6W*	*Q6W procedures are counted starting from Week 25 (i.e. the first Q6W visit is Week 31,

On Treatment Study Assessments												Notes
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28 - 49**	**52 - 106**	
Day	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190 - 337**	**358 - 736**	
Visit Window	**±3-day window on treatment days (Visits occur once every 3 weeks during treatment period)**											
												then Week 37, etc.) unless more frequent assessments are clinically indicated.
Physical Examination**	X	X	X	X	X	X	X	X	X	Q6W*	Q6W*	** Physical examinations and ECOG may be performed within 24 hours prior to dosing (i.e., as opposed to the day of dosing), if necessary.
Vital Signs and Weight[4]	X	X	X	X	X	X	X	X	X	X	X	4. Vital signs include blood pressure, temperature, pulse, respiratory rate, and oxygen saturation. Weight is to be recorded at every other treatment visit in kilograms. Vital signs are to be performed predose on treatment days. Refer to Section 9.5.3. If a participant experiences an infusion-related reaction, refer to Section 12.1.4.11.1 for guidance on vital signs monitoring.
12-lead ECG*	X	X	X	X	X	X	X	X	X	X	X*	* Perform at every dosing visit (may be performed within 24 hours prior to dosing). Results must be reviewed before dosing Cardiologist or locally appropriate specialist review may be required if abnormal results are obtained and confirmed as described in Table 34 .
On Treatment Local Laboratory Assessments (Safety) – assessments may be performed up to 3 days prior to treatment												
Serum β-hCG (for women of childbearing potential)[5]	X	X	X	X	X	X	X	X	X	X	X	5. Monthly urine pregnancy testing may also be performed as consistent with local standards however if a urine test is positive or borderline, or in the event of a missed menstrual period or suspicion of pregnancy, a serum β-hCG test will be required.
Clinical Chemistry, Hematology, Coagulation[6]	X	X	X	X	X	X	X	X	X	X	X	6. Refer to Appendix 3 for a complete list of required assessments. Laboratory testing may be performed one day prior to dosing if necessary. Not required to be tested on Day

On Treatment Study Assessments												Notes
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28 - 49**	**52 - 106**	
Day	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190 - 337**	**358 - 736**	
Visit Window	**±3-day window on treatment days (Visits occur once every 3 weeks during treatment period)**											
												1 if screening labs are within 72 hours from time of scheduled first dose.
CCI [redacted]												
Thyroid function tests			X		X		X		X*	Q6W*	Q6W*	*Q6W procedures are counted starting from Week 25 (i.e. the first Q6W visit is Week 31, then Week 37, etc.).
Calculated CrCl[7]	X	X	X	X	X	X	X	X	X	X	X	7. CrCl is calculated by the CKD-EPI or Cockcroft-Gault formula. Either formula is acceptable and must be consistently utilized for each participant throughout the study. See Appendix 9.
Urinalysis		X	X	X	X	X	X	X	X	X	X	
On Treatment Disease Assessments												
Tumor Imaging/Response Assessment[8]			X		X		X		X	X[8]		8. Diagnostic quality CT scan of chest and abdomen with contrast is required every 6 weeks (±1 week) until Week 49 and every 12 weeks thereafter. Imaging/clinical assessments should be performed as indicated in Section 9.2. The same method of assessment is required throughout the study. Brain scan (MRI with and without IV gadolinium) and bone scan to be performed

On Treatment Study Assessments												Notes
Week	1	4	7	10	13	16	19	22	25	28 - 49	52 - 106	
Day	1	22	43	64	85	106	127	148	169	190 - 337	358 - 736	
Visit Window	±3-day window on treatment days (Visits occur once every 3 weeks during treatment period)											
												as clinically indicated during the treatment period. If a participant has achieved a PD, CR, or PR in the previous radiologic assessment, a repeat scan should be performed after at least 4 weeks to confirm the response.
On Treatment Patient-Reported Outcomes/Health-Related Quality of Life: Part 2 ONLY												
CCI [redacted]												

On Treatment Study Assessments												Notes
Week	1	4	7	10	13	16	19	22	25	28 - 49	52 - 106	
Day	1	22	43	64	85	106	127	148	169	190 - 337	358 - 736	
Visit Window	±3-day window on treatment days (Visits occur once every 3 weeks during treatment period)											
On Treatment Biomarkers												
CCI	[redacted]											

On Treatment Study Assessments												Notes
Week	1	4	7	10	13	16	19	22	25	28 - 49	52 - 106	
Day	1	22	43	64	85	106	127	148	169	190 - 337	358 - 736	
Visit Window	±3-day window on treatment days (Visits occur once every 3 weeks during treatment period)											
On Treatment Tumor biopsies												
Fresh tumor tissue sample[13]			X[13]				X[19]					CCI [redacted]
On Treatment Pharmacokinetics and Anti-Drug Antibodies (ADA)												
GSK4428859A PK*[14]	CCI [redacted]											

On Treatment Study Assessments												Notes
Week	1	4	7	10	13	16	19	22	25	28 - 49	52 - 106	
Day	1	22	43	64	85	106	127	148	169	190 - 337	358 - 736	
Visit Window	±3-day window on treatment days (Visits occur once every 3 weeks during treatment period)											
CCI [redacted]												
CCI [redacted]												17. Assessment required in participant experiencing anaphylaxis, serious hypersensitivity, or in the occurrence of an infusion reaction/CRS of any grade. Samples should be drawn during the occurrence of the event. Only if not possible to collect at the occurrence of the event, samples should be drawn as soon as possible after the event and within 24 hours (Refer to Section 7.2.1.2).Refer to Table 3

On Treatment Study Assessments												Notes
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28 - 49**	**52 - 106**	
Day	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190 - 337**	**358 - 736**	
Visit Window	**±3-day window on treatment days (Visits occur once every 3 weeks during treatment period)**											
												for list of analytes. Predose analysis will be performed on the serum sample collected for GSK4428859A and/or dostarlimab immunogenicity assessments.
On Treatment Pharmacogenetics												
Genetic research[18]	X											18. Informed consent for optional genetic research must be obtained before collecting this sample. It is recommended that the optional research sample be taken at the first opportunity after a participant has met all eligibility requirements before Day 1 or on Day 1.

Abbreviations: ADA = Anti-drug antibody; AE = Adverse event; AESI = Adverse events of special interest; β-hCG = Beta-human chorionic gonadotropin; BNP = B-type natriuretic peptide; CKD-EPI = Chronic kidney disease epidemiology collaboration; CR = complete response; CrCl = Creatinine clearance; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = Electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOI = End of infusion; CCI [redacted] IRR = infusion related reaction; CCI [redacted]; NT-pro-BNP = N-terminal pro-hormone BNP; CCI [redacted]; PD = Progressive Disease; CCI [redacted]; PR = Partial response; Pre =Predose; CCI [redacted] SAE = Serious adverse event.

Pre: predose sample to be collected prior to dosing per institutional guidance, as long as it is collected prior to dosing of the corresponding agent; **EOI**: End of infusion sample is in reference to EOI of the corresponding agent.

Table 32 Schedule of Activities – Treatment Discontinuation Visit and Follow-Up Arm 4: GSK4428859A (Anti-TIGIT) and Dostarlimab (Anti-PD-1) Combination

TDV and Follow Up Assessments	Treatment Discontinuation Visit[1]	Survival Follow-Up[1a]	Notes
Visit Window	**within 30 days of study treatment discontinuation**		
Anticancer Treatment		Q12W*	*If the participant dies before the first follow up, any subsequent anticancer therapy or radiotherapy should be recorded in the eCRF.
Concomitant Medications	X		
TDV and Follow Up Safety			
AE/SAE/AESI Assessment[2]	X		2. After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. Refer to Section 9.4.1 and Section 9.4.3 for further details.
ECOG PS	X		
Physical Examination	X		
Vital Signs and Weight[3]	X		3. Vital signs include blood pressure, temperature, pulse, respiratory rate, and oxygen saturation.
TDV and Follow Up Local Laboratory Assessments			
Clinical Chemistry	X	X^	Refer to Appendix 3 for a complete list of required laboratory assessments. ^Safety laboratory assessments should be collected at TDV (within 30 days of last dose of study treatment) and at 60 and 90 days after last dose of study treatment, unless the participant has started a new anti-cancer therapy within the 90 day follow-up period, in which case safety laboratory assessments are not applicable.
Serum β-hCG (for women of childbearing potential)	X		
Hematology	X	X^	
Coagulation	X		
Thyroid function tests	X	X^	
Calculated CrCl	X		
Urinalysis	X		
CCI [redacted]			
12-lead ECG[a]	X		
TDV and Follow Up Disease Assessments			

TDV and Follow Up Assessments	Treatment Discontinuation Visit[1]	Survival Follow-Up[1a]	Notes
Visit Window	**within 30 days of study treatment discontinuation**		
Tumor Imaging/Response Assessment[4]	X		4. At the TDV, CT scan is required only if the last disease assessment did not show confirmed PD and was performed ≥6 weeks before TDV. For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first. See additional information in Section 9.3.1
Telephone call for survival status[1a]		Q12W	
TDV and Follow Up Tumor Biopsies			
Fresh tumor tissue sample	X[5]		5. If possible, obtain an optional tumor tissue sample at time of confirmed PR or PD.
TDV and Follow Up Patient-Reported Outcomes/Health-Related Quality of Life: Part 2 ONLY			
CCI [redacted]			
TDV and Follow Up Biomarkers			
CCI [redacted]			
TDV and Follow Up Pharmacokinetics and Anti-Drug Antibodies (ADA)			
CCI [redacted]			

Abbreviations: ADA = Anti-drug antibody; AE = Adverse event; AESI = Adverse events of special interest; β-hCG = Beta-human chorionic gonadotropin; BNP = B-type natriuretic peptide; CR = complete response; CrCl = Creatinine clearance; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events;ECG = Electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = Electronic case report form; CCI [redacted]; NT-pro-BNP = N-terminal pro-hormone BNP; PBMC = peripheral mononuclear cells; PD = Progressive Disease; CCI [redacted]; CCI [redacted]; SAE = Serious adverse event; TDV = Treatment Discontinuation Visit

1. The assessments required at the study treatment discontinuation visit must be completed within 30 days from the date study treatment was discontinued and must occur prior to the start of subsequent anticancer therapy. If participant attends clinic for scheduled visit and decision is made to discontinue treatment, site can use this visit as the TDV and complete all assessments.

1a. Survival Follow-Up is the Observational Phase of the study. Participants will be followed for survival and subsequent anticancer therapy every 12 weeks after the last dose of study treatment, via telephone contact. Participants will be contacted every 12 weeks (±7 days) until death or participant's withdrawal from further contact. Subsequent anticancer treatment and death date will be documented in the eCRF

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12.1.4.3. Rationale for the GSK4428859A (Anti-TIGIT) and Dostarlimab (Anti-PD-1) Combination

Multiple immune checkpoints in addition to PD-(L)1 may regulate T cell anergy and modulate antitumor immunity [Topalian, 2011; Mellman, 2011]. Co-regulatory receptors expressed on T cells can induce stimulatory or inhibitory signaling cascades that modulate T cell proliferation, cytokine production, and cytotoxic T cell activation. Proteins of the nectin and nectin-like (Necl1) family, including TIGIT (T cell immunoglobulin and immunoreceptor tyrosine-based inhibition motif domain), PVRIG (Poliovirus Receptor-related Immunoglobulin Domain Containing), and CD96, have emerged as immune-suppressing candidates that may prevent immune reactivation after PD-(L)1 blockade. These co-regulatory receptors modulate the CD226 immune checkpoint, which is one of the major activating receptors for natural killer (NK) cells.

TIGIT interaction with the ligand CD155 downregulates cytotoxic T and NK cells and is a critical regulator of antitumor T cell immunity [Harjunpää, 2020]. TIGIT may regulate antitumor immunity through a variety of mechanisms: by inhibiting NK cells from releasing tumor antigens, impairing T cell priming by dendritic cells, or inhibiting CD8+ effector tumor cell killing [Harjunpää, 2020; Johnston, 2014; Joller, 2014]. The interaction of TIGIT with its complementary costimulatory receptor, CD226, is analogous to the interaction of CTLA-4 and CD28. TIGIT competes with CD226 for its main ligand, CD155 [Stengel, 2012; Johnston, 2014], modulating antitumor immunity through multiple mechanisms. Binding of TIGIT on T cells with CD155 ligand on dendritic cells impairs CD4+ T cell function [Chauvin, 2020]. In addition, binding of TIGIT prevents homodimerization and activation of CD226 on CD8+ T cells [Johnston, 2014]. TIGIT also interacts weakly with other co-regulatory inhibitors of the CD226 pathway including CD112, CD113, and CD114.

TIGIT is highly expressed on murine and human tumor infiltrating T cells [Johnston, 2014]. In human tumor specimens from the Cancer Genome Atlas (TCGA [NCI, 2021]), TIGIT expression is upregulated in a broad range of solid tumors [Johnston, 2014]. TIGIT is upregulated on tumor infiltrating CD8+ T cells and a population of infiltrating CD4+ T cells in solid tumors in comparison to peripheral T cells from patients and normal donors. CD8+ and CD4+ TIGIT-expressing T cells also co-express PD-1.

In NSCLC, TIGIT was expressed in tumor-infiltrating CD8+ and CD4+ T cells and was co-expressed with PD-1 [Johnston, 2014]. Peripheral CD8+ and CD4+ T cells from NSCLC tumor donors had higher levels of TIGIT compared with healthy donors. In addition, in patients with NSCLC, the expression of PD-1 was higher in TIGIT+ cells than in TIGIT- cells in both circulating CD8+ T cells and tumor infiltrating CD8+ T cells [Hu, 2020]. TIGIT could act as a checkpoint inhibitor in exhausted tumor-infiltrating T cells.

EOS884448 (also known as EOS-448; hereafter referred to as GSK4428859A) is a fully human IgG1 mAb that prevents TIGIT-ligand binding. As an IgG1, GSK4428859A also displays a potent affinity for the FcγRs with the potential to mediate antibody-dependent cellular cytotoxicity/phagocytosis (ADCC/P) against TIGIT expressing cells. Binding of GSK4428859A to TIGIT was shown to increase T cell activation by competing with

TIGIT ligands. GSK4428859A (or its mouse surrogate for rodent studies) mediates ADCC/P of immunosuppressive cells by preferentially targeting immunosuppressive Tregs that express a high level of TIGIT relative to cytotoxic CD8 or NK cells, resulting in an increased ratio of effector CD8+/immunosuppressive Treg cells. Moreover, this effect was abrogated in mice lacking FcγRs, further suggesting the requirement for an ADCC/P effect to fully induce tumor growth inhibition. Overall, these data demonstrate that GSK4428859A restores antitumor immunity by preventing the activation of TIGIT by its natural ligands, PVR/CD155 and Nectin2/CD112, and induces a strong immune response mediated by Treg depletion and ADCC/P [Preillon, 2021].

Dostarlimab (formerly referred to as TSR-042) is an IgG4-k humanized monoclonal antibody that binds with high affinity to PD-1 resulting in inhibition of binding to PD-L1 and PD-L2. This antibody was generated based on a proprietary platform that utilizes affinity maturation to select antibodies with desired functional characteristics. The functional antagonist activity of dostarlimab was confirmed in an MLR demonstrating enhanced interleukin-2 production upon addition of dostarlimab. Dostarlimab is an anti-PD1 agent so nonclinical safety data is expected to be similar toa large extent to what was seen with data supporting pembrolizumab combinations. To support combination with dostarlimab, the principal nonclinical toxicology findings associated with dostarlimab were reviewed. A toxicology program including single-dose and repeat-dose IV toxicity studies in cynomolgus monkeys for up to 13 weeks indicated that dostarlimab was well tolerated with no signs of adverse effects, except for potential immune-related reactions in tissues, such as the skin, heart, liver, and kidney.

Pharmacological inhibition of TIGIT with antagonist antibodies inhibits tumor growth in murine tumor models, either alone or in combination with immune checkpoint inhibitors like anti-PD-(L)1 [Johnston, 2014; Zhang, 2018; Hung, 2018; Guillerey, 2018; Dixon, 2018; Minnie, 2018; Minnie, 2019]. Activation of PD-1 signaling dephosphorylates and inactivates CD226 via an intracellular SH2-containing protein tyrosine phosphatase 2 domain. Combined blockade of TIGIT and PD-1 can synergize to promote antitumor immune response and overcome resistance to immunotherapy in a variety of tumor types in nonclinical model systems. In a nonclinical mouse model system of CT26 CRC, anti-TIGIT or anti-PD-L1 antibodies alone were insufficient to decrease tumor burden, however the combination of anti-PD-1 and anti-TIGIT blocking antibodies caused tumor regression with the majority of mice achieving a complete response [Johnston, 2014]. Mice bearing CT26 tumors treated with anti-TIGIT and anti-PD-L1 agents in combination had improved survival compared with control or monotherapy treated mice. Combined TIGIT and PD-1 blockade in mice with established MC38 CRC demonstrated tumor regression and tumor clearance compared with monotherapy and control treatment [Dixon, 2018]. Combination treatment with anti-TIGIT and anti-PD-1 agents resulted in increased production of inflammatory cytokines including IL-2, IFNγ, and TNFα by CD4+ and CD8+ tumor infiltrating lymphocytes compared with either therapy alone, suggesting that combined blockade of TIGIT and PD-1 enhances TIL function and associated OS. These findings suggest the potential for synergy between anti-PD-(L)1 and anti-TIGIT agents to overcome T cell anergy and stimulate antitumor immunity.

To support combination with GSK4428859A, the principal nonclinical toxicology findings associated with GSK4428859A were reviewed. A program including a battery of nonclinical toxicity studies was completed to evaluate the potential repeat-dose toxicities, immunotoxicity, potential for cytokine release, tissue cross-reactivity and safety pharmacology. All studies, including single-dose and repeat-dose IV toxicity studies in cynomolgus monkeys for up to 4 weeks indicated that GSK4428859A was well tolerated with no signs of adverse effects, and a NOAEL that was the highest tested dose of CCI mg/kg.

12.1.4.4. Clinical Safety Summary

12.1.4.4.1. GSK4428859A

Several mAbs targeting TIGIT are in various stages of clinical development. These agents include tiragolumab, vibostolimab, domvanalimab, etigilimab, and GSK4428859A, among an increasing number of others.

A Phase 1b study of vibostolimab monotherapy in participants with advanced solid tumor types previously treated with anti-PD-(L)1 therapy reported a 3% ORR and 35% DCR [Golan, 2018]. In a Phase 1a/Phase 1b study of tiragolumab as a single agent and in combination with atezolizumab in advanced solid tumors, there were no objective responses in 24 participants treated with tiragolumab monotherapy [Bendell, 2020]. The 24 participants enrolled in the tiragolumab monotherapy arm included primary cancer history types such as colon, rectum, breast, ovarian, endometrial, melanoma, and other cancer diagnosis [Bendell, 2020]. The ORR for etigilimab in the dose-escalation phase was 0%, with a DCR of 30% in a Phase 1a/Phase 1b study of etigilimab in participants with advanced solid tumors [Sharma, 2018]. A Phase 1 dose-finding study of GSK4428859A, monotherapy demonstrated favorable tolerability and modest preliminary efficacy in 20 participants with advanced solid tumors, with an ORR of 5% [Van den Mooter, 2021].

The safety profile of anti-TIGIT mAbs has been tolerable and comparable to that of other single-agent immune checkpoint inhibitors. In the vibostolimab Phase 1b study of immune checkpoint inhibitor-experienced participants, 59% of participants experienced any treatment-related adverse event (TRAE) with Grade ≥3 TRAEs in 15% of participants in the vibostolimab monotherapy arm. The most common TRAEs reported were fatigue (22%) and rash (20%). One participant (2%) had a TRAE that led to discontinuation and none experienced a fatal TRAE [Golan, 2018]. In the Phase 1a dose-escalation phase of the tiragolumab study in 24 patients, there were no DLTs [Bendell, 2020]. TRAEs occurred in 67% of participants, Grade ≥3 TRAEs in 4% (Grade 3 blood creatinine increase) and the most common AE reported was fatigue (38%). There were 6 SAEs reported (25%) with no AEs leading to study withdrawal or death [Bendell, 2020].

CCI

CCI

[redacted]

12.1.4.4.2. Dostarlimab

CCI

[redacted]

- Treatment-emergent SAEs regardless of causality were reported in [CCI]% of participants; the most frequently reported [CCI]% of participants) were abdominal pain [CCI]%), pneumonia [CCI]%), and dyspnoea [CCI]%). Treatment-related SAEs were reported in 8.5% of participants; the most frequently reported [CCI]% of participants) were pneumonitis [CCI]%), adrenal insufficiency [CCI]%), and pyrexia [CCI]%).
- TEAEs leading to treatment discontinuation regardless of causality were reported in [CCI]% of participants; the most frequently reported [CCI]% of participants) were alanine aminotransferase increased [CCI]%), aspartate aminotransferase increased [CCI]%), pneumonitis [CCI]%), and transaminases increased [CCI]%). Treatment-related events leading to discontinuation were reported in [CCI]% of participants; the most frequently reported [CCI]% of participants) were alanine aminotransferase increased [CCI]%), aspartate aminotransferase increased [CCI]%), pneumonitis [CCI]%), and transaminases increased [CCI]%).
- TEAEs leading to death regardless of causality were reported in [CCI]% of participants with respiratory failure the only event reported in >1 participant [CCI]participants [CCI]%]); [CCI]% of the deaths were due to treatment-related TEAEs (completed suicide, hepatic ischaemia).

Of the [CCI] participants, [CCI]% who received dostarlimab monotherapy experienced at least 1 immune-related TEAE (irAE). The most frequent [CCI]%) irAEs were hypothyroidism, diarrhea, alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased, hyperglycemia and amylase increased. [CCI] participants [CCI]%) who received dostarlimab monotherapy experienced at least 1 irAE with severity of ≥Grade 3. For [CCI] participants with ≥Grade 3 irAEs, the AE was assessed as study drug related by investigators.

The safety profile of monotherapy dostarlimab in participants with advanced or recurrent solid tumors was generally similar to the reported safety profiles of other mAbs blocking the PD-1 interactions (KEYTRUDA USPI, 2021; KEYTRUDA, SmPC, 2021; OPDIVO USPI, 2021; OPDIVO, SmPC, 2021).

12.1.4.5. Anti-TIGIT and Anti-PD-1/PD-L1 Monoclonal Antibody Combinations in Clinical Studies

Combinations with anti-TIGIT mAbs and anti-PD-1/PD-L1 mAbs have demonstrated improved antitumor efficacy while preserving acceptable side effect profiles. The combination of vibostolimab with pembrolizumab (an anti-PD-1 mAb) demonstrated a confirmed ORR of 24%, DCR of 36%, and a median DOR that was not reached (95% CI: 4 to 17+ months) in participants with a variety of advanced solid tumors who were naïve to anti-PD-(L)1 therapy [Niu, 2020]. Notably, even in participants who had previously received anti-PD-(L)1 therapy, the DCR was 50%, driven mostly by disease stabilization [Ahn, 2020]. In a Phase 1b dose-escalation study, the combination of tiragolumab with atezolizumab (an anti-PD-L1 mAb) showed an ORR of 9% in participants with advanced solid tumors. In an expansion cohort of anti-PD(L)1-naïve participants with PD-L1+ NSCLC, an ORR of 46% and a DCR of 85% were observed [Bendell, 2020].

The results from the aforementioned Phase 1b study led to the Phase 2 CITYSCAPE study, a randomized, double-blind study of tiragolumab plus atezolizumab versus placebo plus atezolizumab in participants with PD-L1+ (TPS ≥1%), treatment-naïve, locally advanced or metastatic NSCLC. In the CITYSCAPE study, a confirmed ORR of 37% for the combination arm compared with 21% for the placebo/atezolizumab arm in the intent-to-treat population (n=135) was reported [Rodríguez-Abreu, 2020]. Median PFS was improved from 3.88 months (range: 2.73 to 4.53 months) with atezolizumab to 5.5 months (range: 4.2 to 10.4 months; HR: 0.58, 95% CI: 0.38, 0.89) for the combination. In 58 participants with PD-L1-high (TPS ≥50%) tumors, the confirmed ORR was 66% for the combination compared with 24% in the atezolizumab arm. The median PFS was not reached with the combination (95% CI: 5.49 to not evaluable [NE]) compared with 4.11 months (95% CI: 2.07, 4.73) for the atezolizumab arm (HR for PFS: 0.3; 95% CI: 0.15. 0.61). For participants with PD-L1 TPS 1-49%, the ORR and PFS were similar across both arms (ORR: 18% with atezolizumab vs 16% with tiragolumab and atezolizumab; PFS: 3.58 months and 4.04 months, respectively [HR:0.89; 95% CI: 0.53, 1.49]). The rates of TEAEs (99% vs 96%), Grade ≥3 AEs (48% vs 44%), Grade 5 AEs (5% vs 7%), SAEs (37% vs 35%), and AEs leading to treatment withdrawal (10% vs 9%) were all similar between the combination and placebo/atezolizumab arms, respectively; there was a modest increase in AEs leading to dose modification in the combination arm (40% vs 28%). The overall rate of immune-mediated AEs (69% vs 47%) and Grade 3 or 4 immune-mediated AEs (18% vs 13%) were higher in the combination arm [Rodríguez-Abreu, 2020].

Similar results have been observed with other anti-TIGIT mAbs and anti-PD-(L)1 combinations, suggesting anti-TIGIT mAbs promote enhanced antitumor immune responses without a substantial increased risk of toxicity over single-agent immune checkpoint blockade [Niu, 2020]. Vibostolimab in combination with pembrolizumab has demonstrated responses in participants with advanced NSCLC naïve to anti-PD-(L)1 therapy both with and without PD-L1 expression [Niu, 2020]. As a result, multiple Phase 3 clinical studies are underway evaluating anti-TIGT and anti-PD(L)1 combination therapy in PD-L1+ NSCLC (NCT04738487; NCT04746924; NCT04262856; NCT04294810; NCT04736173).

The combination of GSK4428859A and dostarlimab is supported by the reported clinical safety profiles of similar TIGIT-targeting agents administered alone or in combination with anti-PD-(L)1 agents. In the dose-escalation phase, tiragolumab (an anti-TIGIT mAb) was administered at 2, 8, 30, 100, 400, 600, 1200 mg Q3W in combination with the anti-PD-L1 agent, atezolizumab (1200 mg Q3W). No DLTs were observed across all doses (N=49). TRAEs occurred in 59% of participants and the most frequently reported TRAEs were Grade 1 pruritus, Grade 1-2 fatigue, Grade 1-2 rash, Grade 1 diarrhea, and Grade 1 arthralgia. Two Grade 3 TRAEs were reported in the combination: 1 hyperlipasemia and 1 lymphocyte count decreased. Infusion reactions were seen in 8% of participants, most were Grade 1/2. A higher rate of immune-related AEs (irAEs) was observed with the combination than with tiragolumab monotherapy [Bendell, 2020]. In the Phase 2 CITYSCAPE study, the addition of tiragolumab at 600 mg Q3W to first-line atezolizumab at 1200 mg Q3W in PD-L1–selected metastatic NSCLC demonstrated good tolerability with a safety profile similar to placebo plus atezolizumab [Rodríguez-Abreu, 2020]. Vibostolimab (an anti-TIGIT mAb) demonstrated a tolerable safety profile across

the various doses tested alone and in combination with pembrolizumab (anti-PD-1, 200 mg Q3W) in the Phase 1b study (see Rationale Section 12.1.4.3 for further details).

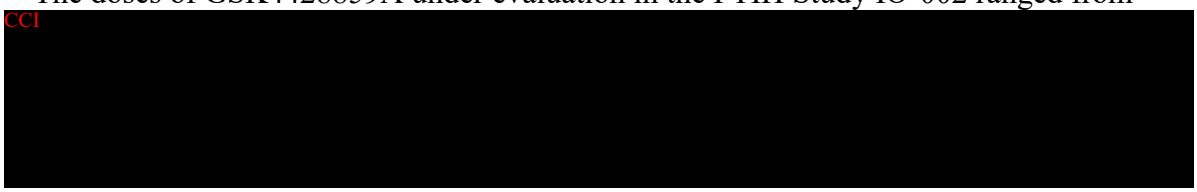
12.1.4.6. Dose Justification

12.1.4.6.1. GSK4428859A Pharmacokinetics and Pharmacodynamics

12.1.4.6.2. GSK4428859A Dose Rationale (Arm 4)

The GSK4428859A RP2D of CCI mg CCI is based on the preliminary safety, PK/PD, and efficacy data available from the Phase 1/Phase 2a clinical Study IO-002 (NCT04335253), as well as observations from other clinical studies evaluating anti-TIGIT mAbs which generally have similar properties [Bendell, 2020; Rodríguez-Abreu, 2020; Niu, 2020]. Additionally, Study TIG-006 is currently evaluating the safety, tolerability, PK, PD, and anti-tumor activity of GSK4428859A in combination with pembrolizumab in participants with advanced solid tumors. The starting dose level of GSK4428859A will be CCI mg CCI in combination with pembrolizumab.

The doses of GSK4428859A under evaluation in the FTIH Study IO-002 ranged from



CCI [redacted]

In vitro evaluation shows that GSK4428859A competes with CD155 for TIGIT binding with a saturating effect noted at 4.22 to 133 nM (0.623 to 20.0 µg/mL) [Refer to Section 5.1.1.1.4 of the iTeos EOS884448 [EOS-448] IB, 2021]. This target level has been confirmed in multiple functional assays, including ADCC, and translates to in vivo mouse studies [Refer to Section 5.1.1.1.8 and Section 5.1.1.2.3 of the iTeos EOS884448 [EOS-448] IB, 2021]. Assuming a tumor tissue dilution of 20-fold [Shah, 2013] and CCI [redacted] dosing, CCI [redacted] µg/mL would result in tumor concentrations that would saturate TIGIT binding in the tumor. A preliminary population PK analysis of GSK4428859A FTIH data was conducted and simulations were performed to evaluate a variety of GSK4428859A doses and regimens for future studies. The simulated minimum serum concentration after the first dose and at steady state following CCI [redacted] mg CCI [redacted] is CCI [redacted] µg/mL and CCI [redacted] µg/mL, respectively [Refer to Table 16 of the iTeos EOS884448 [EOS-448] IB, 2021], both of which are within the range estimated to result in tumor concentrations that would saturate TIGIT binding.

Based on these data, GSK4428859A CCI [redacted] mg is considered an appropriate starting dose to combine with dostarlimab to minimize the risk of unacceptable toxicity and maximize the potential benefit to participants with NSCLC. Moreover, CCI [redacted]

12.1.4.6.3. Dostarlimab Dose Rationale

CCI

No reduction in dostarlimab dose is allowed given that the safety and efficacy profile of the included dose regimen for dostarlimab is considered acceptable, whereas the efficacy of lower doses is not fully characterized.

12.1.4.7. Study Treatments

Table 33 Description and Administration of Arm 4 GSK4428859A plus Dostarlimab (Anti-PD-1) Study Treatments

CCI

CCI [redacted] (see pharmacy manual for administration instructions).

All participants should remain under observation at the study site after the completion of study treatment administration (refer to SRM for details). Section 12.1.4.11, Table 35 for details on the management of participants experiencing infusion reactions. Refer to Section 5.2 for information on the duration of study treatment.

The date and time of administration will be documented in the source documents and reported in the eCRF. 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). Both drugs should be administered on the same day. The 72-hour window does not apply to completion of study treatment administration interrupted by an infusion reaction. Refer to Section 7.2.1.4 for criteria governing dose interruptions or delays.

Details on preparation and administration of GSK4428859A and dostarlimab are described in the pharmacy manual.

12.1.4.8. Concomitant Therapy

Please refer to Section 7.7

12.1.4.9. Treatment of Overdose

12.1.4.9.1. GSK4428859A Overdose

An overdose of GSK4428859A is defined as administration of a dose that is above CCI [redacted] mg.

In the event of an overdose, the investigator must:

1 Contact the Medical Monitor immediately.
2 Closely monitor the participant for adverse events and laboratory abnormalities for at least 120 days.
3 Obtain a sample for PK analysis within 28 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4 Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

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

There is no specific antidote for overdose with the experimental treatments being evaluated in this study. 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.

12.1.4.9.2. Dostarlimab Overdose

Human data on overdose are not available. There is no known antidote for dostarlimab.

An overdose of dostarlimab is defined as any dose that is ≥20% than [redacted] mg [redacted]

In the event of an overdose, the investigator must:

1 Contact the Medical Monitor immediately.
2 Closely monitor the participant for adverse events and laboratory abnormalities for at least 120 days.
3 Obtain a sample for PK analysis within 28 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4 Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

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

There is no specific antidote for overdose with the experimental treatments being evaluated in this study. 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.

12.1.4.10. Treatment Duration for GSK4428859A and Dostarlimab

Participants enrolled will be treated until disease progression, intolerable toxicity, informed consent withdrawal or death. Combination study treatment will continue to be administered at the indicated schedule for a maximum duration of up to 35 treatment visits or approximately 2 years, whichever comes first. Refer to Section 5.2 for additional details regarding follow up after discontinuation of study treatment.

12.1.4.11. Dose modification and Management Guidelines

No dose reductions are allowed for dostarlimab. No dose reductions are allowed for GSK4428859A at the participant level. Dose modification guidelines for immune related adverse events are listed in Table 34. If study drugs must be held or discontinued for any

toxicity, all study drugs must be held or discontinued, unless discussed otherwise with Medical Monitor.

In case of any unforeseen toxicities for GSK4428859A occurring at the [redacted] mg [redacted] dose cohort in combination, de-escalation to [redacted] mg or a lower dose [redacted] may be considered at the cohort level, if needed.

In addition to the immune-related adverse events listed in Table 34, immunotherapy may be associated with other irAEs, including events which may be less commonly associated with PD-(L)1 inhibitors but can similarly result from activation of cellular immune response. For these events, most current professional guidelines (e.g.: National Comprehensive Cancer Network [NCCN], National Comprehensive Cancer Network [SITC]) should be considered. Patients should receive appropriate supportive care measures as deemed necessary by the treating Investigator, including but not limited to the items outlined below:

Table 34 Dose Modification and Toxicity Management Guidelines for Immune-Related AEs

General instructions:

- Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
- For situations where immunotherapy treatment has been withheld, treatment can be resumed after AE has been reduced to Grade 1 or resolved and corticosteroid has been tapered. Immunotherapy treatment should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks.
- For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Severity grade or conditions (CTCAEv5.0)	Action taken	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Respiratory				
Pneumonitis	[redacted]			

Immune-related AEs	Severity grade or conditions (CTCAEv5.0)	Action taken	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Gastrointestinal				
Diarrhea / colitis	CCI [redacted]			
Hepatobiliary				
Hepatitis with no tumor involvement of the liver	CCI [redacted]			

Immune-related AEs	Severity grade or conditions (CTCAEv5.0)	Action taken	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
	CCI [redacted]			
Hepatitis with tumor involvement of the liver**				
Endocrine				
Type 1 diabetes mellitus (T1DM) or Hyperglycemia				
Endocrinopathies (e.g. hypophysitis, hypo-/hyperthyroidism, adrenal insufficiency)				
Renal				
Nephritis with renal dysfunction				
Cardiovascular				

Immune-related AEs	Severity grade or conditions (CTCAEv5.0)	Action taken	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Cardiac Investigations i) ECG changes and/or ii) troponin and/ or NT-proBNP/BNP elevations	CCI [redacted]			

Immune-related AEs	Severity grade or conditions (CTCAEv5.0)	Action taken	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
	CCI			
Myocarditis				
Other				
Neurological Events (myasthenia gravis, Guillain-Barré syndrome, encephalitis, transverse myelitis)				
All other immune-related AEs				
Skin Toxicities[1]				
Rash				

Immune-related AEs	Severity grade or conditions (CTCAEv5.0)	Action taken	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
	CCI			
Pruritis				
Exfoliative dermatologic conditions (e.g. SJS, TEN, DRESS)				

Immune-related AEs	Severity grade or conditions (CTCAEv5.0)	Action taken	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
	CCI [redacted]			

NOTES:
*Resume in patients with complete resolution or partial resolution to Grade 1 after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg/day (or equivalent) within 12 weeks of initiating steroids.

**If AST and ALT are less than or equal to ULN at baseline in patients with liver involvement, withhold or permanently discontinue based on recommendations for hepatitis with no liver involvement.
***Abnormal troponin and proNTBNP/BNP at screening is defined as any value >ULN at screening

1. For any grade skin toxicities, recent alcohol intake or other potentially related concomitant exposures per Investigator assessment, should be recorded in the eCRF. Please refer to SRM for additional details.

Abbreviations: BNP = B-type natriuretic peptide; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; DRESS = drug reaction with eosinophilia and systemic symptoms.

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

Table 35 Immunotherapy Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Please refer to the pharmacy manual for administration details.	Participant may be premedicated 1h (± 30 minutes) prior to infusion of study drugs with: Diphenhydramine 50 mg (or equivalent dose of antihistamine) and/or acetaminophen 325-1000 mg (or equivalent dose of analgesic)
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	Participant may be premedicated 1h (± 30 minutes) prior to infusion of study drugs with: Diphenhydramine 50 mg (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg (or equivalent dose of analgesic). If necessary, corticosteroids (up to 25mg of hydrocortisone or equivalent) may be used and adaptation of the infusion rate should be discussed with Medical

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
	If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr), unless otherwise specified in the pharmacy manual. Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment. Please refer to the pharmacy manual for administration details.	Monitor.
Grades 3 or 4 Grade 3: Prolonged (e.g. not rapidly responsive to symptomatic medication and/or interruption of infusion; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment. Please refer to the pharmacy manual for administration details.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

Abbreviations: NSAIDs = non-steroidal anti-inflammatory drugs.

If a participant has an infusion related reaction, vital signs will be obtained every 15 minutes (± 5 minutes) at the start of symptoms until the participant is deemed medically stable in the opinion of the investigator; pulse oximetry should be performed in conjunction with vital signs.

Adverse Events of Special Interest (AESI)

Refer to Section 7.2.1.1 for details. In addition, for AESIs of immune related cutaneous toxicities of any grade, recent alcohol intake or other potentially related concomitant exposures per Investigator assessment, should be recorded in the eCRF. Please refer to SRM for additional details.

12.1.4.12. Safety Evaluation

If a participant withdraws from the study before the completion of the 21-day DLT evaluation period for reasons other than DLT or becomes non-evaluable during the DLT period, then the participant may be replaced to achieve the three-participant required minimum. The decision to declare the combination tolerable will occur following review of the safety, PK and PD data (if available) and joint discussion by the GSK Medical Monitor and investigators. Membership, roles and accountabilities, and the process for safety review and meeting frequency is outlined in the Study Reference Manual.

The mTPI design assumptions include the following:

(i)

(ii)

The monitoring rules guiding dose decision are provided in Table 36. The tolerability decision framework using the mTPI method were generated based on a beta/binomial model and pre-calculated before study initiation. The rules in Table 36 utilize the mTPI method along with additional rules as following:

CCI

[redacted]

CCI

CCI

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12.1.4.14. Dose Limiting Toxicity

The severity of all toxicities will be graded using National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 5.0) [NCI, 2017]. The DLT observation period is 21 days in length and begins on the day study treatment is first

administrated to the participant.

A DLT is defined as an AE that meets at least one of the criteria listed in Table 37 and is considered by the investigator to be clinically relevant and attributed (probably, or possibly) to the study treatment during the 21-day DLT observation period. An AE considered related to the underlying disease under study it is not defined as a DLT. A safety event can still be included for DLT consideration after the 21 day window. See Section 10.4 for the definition of a DLT evaluable participant.

Table 37 Dose-Limiting Toxicity Criteria

Toxicity	DLT Definition (Grading per CTCAE v5)
Hematologic	• Grade 4 neutropenia of any duration or febrile neutropenia • Grade 4 anemia of any duration • Grade 4 thrombocytopenia of any duration or Grade 3 thrombocytopenia with bleeding
Non- hematologic	• Grade 2 uveitis, episcleritis, iritis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to G1 severity or requires systemic treatment. • Grade 2 colitis or diarrhea that persists without resolution to ≤ Grade 1 for ≥ 7 days despite adequate immunosuppressive therapy • Grade 3 diarrhea/colitis lasting ≥72h regardless of medical intervention or G4 diarrhea/colitis • Grade 3 pneumonitis • Grade 3 rash if no resolution to ≤Grade 2 or baseline within 2 weeks with use of systemic steroids or anti-inflammatory agents per standard of care • Grade 3 hypersensitivity or IRR • ALT ≥ 3x ULN plus bilirubin ≥ 2x ULN (>35% direct) or plus INR >1.5, if measured[a] (possible Hy's Law) • Grade 3 toxicity that does not resolve to ≤Grade 1 or baseline within 3 days despite optimal supportive care[b] or any Grade 4 toxicity • Following events are not considered DLTs o ≥ Grade 3 electrolyte abnormalities that are corrected to ≤ Grade 1 or baseline within 72 hours without clinical sequelae o Grade 3 nausea or vomiting that resolves to ≤Grade 1 or baseline within 7 days o ≥Grade 3 fatigue ≤7 days o ≥Grade 3 lymphopenia o Grade 3 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis
Other	• Toxicity that results in permanent discontinuation of either agent in combination • Any other toxicity considered to be dose-limiting that occurs after the completion of the DLT observation period 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. Not applicable to participants taking anticoagulants.
b. Suggested toxicity management guidelines as described in Section 12.1.4.11 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.

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

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

Toxicity management and dose modification guidelines provided in Section 12.1.4.11 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.

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 12.1.4.11. These guidelines are based on the experience of irAE management following the development of immune check-point inhibitors such as ipilimumab and pembrolizumab. Guidelines are also provided for infusion reactions or severe cytokine release (Section 12.1.4.11.1). The joint ASCO and NCCN guidelines for the diagnosis and management of irAEs treated with immune checkpoint inhibitor therapy may be used as a supplement to the guidance provided in Section 12.1.4.11.

If there is a delay in administration of study treatment, refer to Section 12.1.4.11 for guidance on planning of subsequent study visits.

12.1.4.15. Risk-Benefit Assessment of GSK4428859A and Dostarlimab combined

Table 38 Risk Assessment and Mitigation Strategy: Dostarlimab and GSK4428859A

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Immune-related AEs (irAEs)	• Inflammatory AEs such as diarrhea/colitis, pneumonitis, nephritis, myocarditis 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. • An anti-PD-1 checkpoint inhibitor (dostarlimab) will be used in combination with an anti-TIGIT mAb (GSK4428859A). • Based on the safety profile of anti PD-1 antibodies, administered alone or in combination, the anticipated adverse reactions may be primarily immune mediated. Based on emerging data from anti-TIGIT mAbs, administered alone or in combination, the anticipated adverse reactions are similarly immune mediated.	• Participants with the following medical history are ineligible for this study ○ Toxicity (≥Grade 3) related to prior immunotherapy leading to study treatment discontinuation ○ Active autoimmune disease (refer to Section 6.2 exclusion criterion 6) ○ Severe hypersensitivity to another mAb • Established management algorithms for immune-related adverse events (irAEs) • Refer to Section 12.1.4.11 for further details on the identification, evaluation, and management of toxicities with a potential immune etiology.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Infusion and hypersensitivity reactions and potential CRS	• Risk for infusion reactions and hypersensitivity is inherent to many mAbs [Brennan, 2010] **Dostarlimab**: • The frequency of IRRs with dostarlimab is labelled as common CCI [redacted] **GSK4428859A** • CCI [redacted] See Investigator's Brochures for dostarlimab, and GSK4428859A [iTeos EOS884448 [EOS-448] IB, 2021] for details.	• 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 12.1.4.11 for further details on management and monitoring of infusion reactions. • Refer to Section 12.1.4.11 for further details on management of CRS • Refer to Protocol Section 7.2.1.2; Table 3 for details of blood panel collection for all participants experiencing any grade of infusion reaction or CRS • For severe (Grade 3) or life-threatening (Grade 4) IRRs associated with GSK4428859A or dostarlimab, infusion should be stopped, and treatment should be permanently discontinued.
ADA and Immune complex disease	• Immune complex deposition may cause clinical symptoms, most commonly renal, skin, or vasculitis pathology. • For nonclinical immune complex formation and deposition findings (refer to individual product Investigator's Brochure [IBs]) • GSK4428859A is a fully human IgG1 mAb with a wild-type Fc domain. Based on the characteristics of the molecules and active pharmaceutical ingredients, the risk of immunogenicity in humans is considered to be low and similar to other mAbs.	• Clinical laboratory safety assessments and immunogenicity testing
Reproductive toxicity	• Animal studies assessing reproductive toxicity have not yet been conducted. • Immune-checkpoint inhibitors (such as dostarlimab) have been shown to have potential to disrupt maternal-fetal tolerance leading to failure of implantation or spontaneous abortion. A similar risk will be assumed for GSK4428859A.	• Inclusion of contraception guidelines for WOCBP (Section 6.1). • Exclusion of lactating or pregnant women (Section 6.2). • Pregnancy testing for WOCBP during Screening and throughout the Treatment period, as specified in the SoA (Section 12.1.4.1).

Abbreviations: AE = adverse event; IB = Investigator's Brochure; irAEs= immune-related adverse events; IRR= infusion-related reactions; mAb = monoclonal antibody.

12.1.4.16. Additional Study Population Criteria: Arm 4

12.1.4.16.1. Additional Inclusion Criteria: Arm 4

1. Male contraception is not required for this arm.

12.1.4.16.2. Additional Exclusion Criteria: Arm 4

1. Known hypersensitivity to dostarlimab and/or GSK4428859A components or excipients.
2. Has received prior antibodies or drugs targeting TIGIT, CD96, PVRIG, or other therapies targeting the CD226 axis pathway.

12.1.4.17. References

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12.1.5. Arm 5: GSK4428859A (Anti-TIGIT) plus Dostarlimab (Anti-PD-1) plus GSK6097608 (Anti-CD96) Combination

12.1.5.1. Protocol Amendment 9 Summary of Changes Specific to GSK4428859A and Dostarlimab and GSK6097608 Arm

Section # and Name	Description of Change	Brief Rationale
Schedule of Activities Section 12.1.5.2 (Table 30, Table 40 and Table 41) Dose modification and Management Guidelines (Section 12.1.5.11 and Table 34)	Addition of text to clarify that the following investigations will require a Cardiologist or locally appropriate specialist review; CCI [redacted] Addition of text to clarify that the Sponsor will need to be informed regarding these participants Addition of text to clarify that investigators are required to review all safety laboratory assessments before dosing..	CCI [redacted]
Section 12.1.5.15 and Table 50	CCI [redacted]	

Protocol Amendment 8 Summary of Changes Specific to GSK4428859A and Dostarlimab and GSK6097608 Arm

Section # and Name	Description of Change	Brief Rationale
Schedule of Activities Section 12.1.5.2 (Table 39, Table 40 and Table 41)	CCI [redacted]	
Schedule of Activities Section 12.1.5.2 (Table 40 and Table 41)		
CCI [redacted]		

Protocol Amendment 7 Summary of Changes Specific to GSK4428859A and Dostarlimab and GSK6097608 Arm

Section # and Name	Description of Change	Brief Rationale
Schedule of Activities Section 12.1.5.2 (Table 40 and Table 41)	[redacted]	
[redacted]		

12.1.5.2. Schedule of Activities Specific to the GSK4428859A (Anti-TIGIT) plus Dostarlimab (Anti-PD-1) plus GSK6097608 (Anti-CD96) Combination

The timing and number of planned study assessments (including safety, pharmacokinetic, ADA, biomarker or other assessments) may be altered during the course of the study based on newly available data.

Table 39 Schedule of Activities – Screening: Arm 5: GSK4428859A (Anti-TIGIT) plus Dostarlimab (Anti-PD-1) plus GSK6097608 (Anti-CD96) Combination

Screening Study Assessments	Screening[1]	Notes
Visit Window	≤4 Wks	
Informed Consent[1]	X	1. All screening assessments must be performed within 4 weeks (28 days) prior to first dose of study treatment unless otherwise specified. The informed consent may be signed within 45 days prior to first dose.
Participant Registration[2]	X	2. Participants will be registered in RAMOS NG at screening.
Inclusion/Exclusion Criteria	X	Review eligibility prior to randomization.
Demographics, Medical History (including alcohol and tobacco use), Prior Medications, Disease History[12]	X	12. All known mutations should be entered in the eCRF as disease history.
Prior Anticancer Treatment, Radiotherapy	X	
Screening Safety		
AE/SAE/AESI Assessment[3]	X	3. Any AESI or SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study. After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. Refer to Section 9.4 for further details.
ECOG PS	X	
Physical Examination	X	
Vital Signs, Height and Weight[4]	X	4. Vital signs include blood pressure, temperature, pulse, respiratory rate, and oxygen saturation. Height is recorded at Screening only. Record weight in kilograms.
12-lead ECG	X	Consider cardiologist or locally appropriate specialist review for participants with potentially significant ECG abnormalities such as AV block (except for first degree), new cardiac arrhythmias, or frequent PVCs. Please inform the Sponsor regarding these participants.
Echocardiogram or MUGA scan[5]	X	5. ECHO required at Screening within 28 days prior to first dose of study treatment, and during treatment phase if clinically indicated. MUGA scan may be used if ECHO not feasible.
Screening Local Laboratory Assessments (Safety)		
Hepatitis B and C[6]	X	

Screening Study Assessments	Screening[1]	Notes
Visit Window	≤4 Wks	
Serum β-hCG (for women of childbearing potential)	≤3d	
Clinical Chemistry[6], Coagulation[6], Hematology[6], Thyroid function[6]	X	6. Refer to Appendix 3 for a complete list of required assessments. Required within 7 days of randomization day. Not required to be tested on Day 1 if screening labs are within 72 hours from time of scheduled first dose. Must be drawn predose or up to 3 days prior to dosing. If Hepatitis B and C was performed within 3 months prior to first dose of study intervention or SoC, repeat testing at screening is not required; otherwise, this testing is mandatory.
Calculated CrCl[7]	X	7. CrCl is calculated by the CKD-EPI or Cockcroft-Gault formula. See Appendix 9.
CCI [redacted]		
Urinalysis[6]	X	
Screening Other Laboratory Assessments		
PD-L1 expression by IHC[8]	X	8. PD-L1 expression by IHC and type of assay utilized (i.e., Ventana SP263, Ventana SP142, Dako 28-8, or Dako 22C3) must be recorded in the eCRF, if known. Note: Test is not required to be performed by the site if not previously performed.
Screening Disease Assessments		
Tumor Imaging[9]	X	9. Diagnostic quality CT scan of chest and abdomen with contrast must be obtained within 28 days of first dose. Baseline brain scan (MRI with and without IV gadolinium) should be obtained within 6 weeks of first dose if history of CNS disease or if clinically indicated. Bone scan should be obtained within 6 weeks of first dose if clinically indicated. See additional information regarding bone scans in Section 9.3.1.
Pre-Baseline scans for Tumor Growth Kinetics[10]	X	10. Upon participant consent, up to 3 pre-baseline scans (within 12 months before the baseline scan) will be collected to assess tumor growth rate to support exploratory investigation of tumor growth kinetics (See Section 9.3.2 for details on images for submission).

Screening Study Assessments	Screening[1]	Notes
Visit Window	≤4 Wks	
Screening Tumor Biopsies		
Fresh tumor tissue sample and Archival tumor[11]	X	CCI [redacted]

Abbreviations: AE = adverse event; AESI = adverse events of special interest; β-hCG = β -human chorionic gonadotropin; BNP = B-type natriuretic peptide CKD-EPI = chronic kidney disease epidemiology collaboration; CrCl = creatinine clearance; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiography; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; IHC = Immunohistochemistry; IWRS = interactive web response system; MRI = magnetic resonance imaging; MUGA = multi-gated acquisition; NT-pro-BNP = N-terminal pro-hormone BNP ;SAE = serious adverse event.

Table 40 Schedule of Activities – Treatment Period Experimental Arm 5: GSK4428859A (Anti-TIGIT) plus Dostarlimab (Anti-PD-1) plus GSK6097608 (Anti-CD96) Combination

On Treatment Study Assessments												Notes
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28 - 49**	**52 - 106**	
Day	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190 - 337**	**358 - 736**	
Visit Window	**±3-day window on treatment days (Visits occur once every 3 weeks during treatment period)**											
Inclusion/Exclusion Criteria	X											
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	
Participant Randomization[1]	X											1. Once determined to be eligible, participants must be randomized via IWRS. Drug shipments will be managed via IWRS. Sites must allow up to 7 business days for shipment of study drug. Randomization can be done prior to Day 1, but no more than 3 days prior to Day 1. (Refer to SRM).
Study treatments[1]												
Administer Dostarlimab[2]	X	X	X	X	X	X	X	X	X	X	Q3W	CCI [redacted]
CCI [redacted]												
On Treatment Safety												
AE/SAE/AESI Assessment[3]	X	X	X	X	X	X	X	X	X	X	X	3. After the initial AE/SAE report, the investigator is required to proactively follow

On Treatment Study Assessments												Notes
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28 - 49**	**52 - 106**	
Day	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190 - 337**	**358 - 736**	
Visit Window	**±3-day window on treatment days (Visits occur once every 3 weeks during treatment period)**											
												each participant at subsequent visits/contacts. Refer to Section 9.4.1 for further details.
ECOG PS**	X	X	X	X	X	X	X	X	X*	Q6W*	Q6W*	*Q6W procedures are counted starting from Week 25 (i.e. the first Q6W visit is Week 31, then Week 37, etc.) unless more frequent assessments are clinically indicated.
Physical Examination**	X	X	X	X	X	X	X	X	X	Q6W*	Q6W*	** Physical examinations and ECOG may be performed within 24 hours prior to dosing (i.e., as opposed to the day of dosing), if necessary.
Vital Signs and Weight[4]	X	X	X	X	X	X	X	X	X	X	X	4. Vital signs include blood pressure, temperature, pulse, respiratory rate, and oxygen saturation. Weight is to be recorded at every other treatment visit in kilograms. Vital signs are to be performed predose on treatment days. Refer to Section 9.5.3. If a participant experiences an infusion-related reaction, refer to Section 12.1.4.11.1 for guidance on vital signs monitoring.
12-lead ECG	X	X	X	X	X	X	X	X	X	X	X*	*Perform at every dosing visit (may be performed within 24 hours prior to dosing). Results must be reviewed before dosing Cardiologist or locally appropriate specialist review may be required if abnormal results are obtained and confirmed as described in Table 46.
On Treatment Local Laboratory Assessments (Safety) – assessments may be performed up to 3 days prior to treatment												
Serum β-hCG (for women of childbearing potential)[5]	X	X	X	X	X	X	X	X	X	X	X	5. Monthly urine pregnancy testing may also be performed as consistent with local standards however if a urine test is positive or borderline, or in the event of a missed menstrual period or suspicion of pregnancy, a serum β-hCG test will be required.

On Treatment Study Assessments												Notes
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28 - 49**	**52 - 106**	
Day	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**190 - 337**	**358 - 736**	
Visit Window	**±3-day window on treatment days (Visits occur once every 3 weeks during treatment period)**											
Clinical Chemistry, Hematology, Coagulation[6]	X	X	X	X	X	X	X	X	X	X	X	6. Refer to Appendix 3 for a complete list of required assessments. Laboratory testing may be performed one day prior to dosing if necessary. Not required to be tested on Day 1 if screening labs are within 72 hours from time of scheduled first dose.
CCI												
Thyroid function tests			X		X		X		X*	Q6W*	Q6W*	*Q6W procedures are counted starting from Week 25 (i.e. the first Q6W visit is Week 31, then Week 37, etc.).
Calculated CrCl[7]	X	X	X	X	X	X	X	X	X	X	X	7. CrCl is calculated by the CKD-EPI or Cockcroft-Gault formula. Either formula is acceptable and must be consistently utilized for each participant throughout the study. See Appendix 9.
Urinalysis		X	X	X	X	X	X	X	X	X	X	
On Treatment Disease Assessments												
Tumor Imaging/Response Assessment[8]			X		X		X		X	X[8]		8. Diagnostic quality CT scan of chest and abdomen with contrast is required every 6 weeks (±1 week) until Week 49 and every 12 weeks thereafter. Imaging/clinical assessments should be performed as indicated in Section 9.2. The same method

On Treatment Study Assessments												Notes
Week	1	4	7	10	13	16	19	22	25	28 - 49	52 - 106	
Day	1	22	43	64	85	106	127	148	169	190 - 337	358 - 736	
Visit Window	±3-day window on treatment days (Visits occur once every 3 weeks during treatment period)											
												of assessment is required throughout the study. Brain scan (MRI with and without IV gadolinium) and bone scan to be performed as clinically indicated during the treatment period. If a participant has achieved a PD, CR, or PR in the previous radiologic assessment, a repeat scan should be performed after at least 4 weeks to confirm the response.
On Treatment Patient-Reported Outcomes/Health-Related Quality of Life: Part 2 ONLY												
CCI [redacted]												

On Treatment Study Assessments												Notes
Week	1	4	7	10	13	16	19	22	25	28 - 49	52 - 106	
Day	1	22	43	64	85	106	127	148	169	190 - 337	358 - 736	
Visit Window	±3-day window on treatment days (Visits occur once every 3 weeks during treatment period)											
On Treatment Biomarkers												
CCI	[redacted]											

On Treatment Study Assessments												Notes
Week	1	4	7	10	13	16	19	22	25	28 - 49	52 - 106	
Day	1	22	43	64	85	106	127	148	169	190 - 337	358 - 736	
Visit Window	±3-day window on treatment days (Visits occur once every 3 weeks during treatment period)											
On Treatment Tumor biopsies												
Fresh tumor tissue sample[13]			X[13]				X[19]					CCI [redacted]
On Treatment Pharmacokinetics and Anti-Drug Antibodies (ADA)												
CCI [redacted]												

On Treatment Study Assessments												Notes
Week	1	4	7	10	13	16	19	22	25	28 - 49	52 - 106	
Day	1	22	43	64	85	106	127	148	169	190 - 337	358 - 736	
Visit Window	±3-day window on treatment days (Visits occur once every 3 weeks during treatment period)											

CCI

[redacted]

On Treatment Study Assessments												Notes
Week	1	4	7	10	13	16	19	22	25	28 - 49	52 - 106	
Day	1	22	43	64	85	106	127	148	169	190 - 337	358 - 736	
Visit Window	±3-day window on treatment days (Visits occur once every 3 weeks during treatment period)											
												21. To be collected at Week 25 and every 12 weeks thereafter.
CCI [redacted]												
Serum: IRR lab panel[17]												17. Assessment required in participant experiencing anaphylaxis, serious hypersensitivity, or in the occurrence of an infusion reaction/CRS of any grade. Samples should be drawn during the occurrence of the event. Only if not possible to collect at the occurrence of the event, samples should be drawn as soon as possible after the event and within 24 hours (Refer to Section 7.2.1.2). Refer to Table 3 for list of analytes. Predose analysis will be performed on the serum sample collected for GSK4428859A and/or dostarlimab and/or GSK6097608 immunogenicity assessments.

On Treatment Study Assessments												Notes
Week	1	4	7	10	13	16	19	22	25	28 - 49	52 - 106	
Day	1	22	43	64	85	106	127	148	169	190 - 337	358 - 736	
Visit Window	±3-day window on treatment days (Visits occur once every 3 weeks during treatment period)											
On Treatment Pharmacogenetics												
Genetic research[18]	X											18. Informed consent for optional genetic research must be obtained before collecting this sample. It is recommended that the optional research sample be taken at the first opportunity after a participant has met all eligibility requirements before Day 1 or on Day 1.

Abbreviations: ADA = Anti-drug antibody; AE = Adverse event; AESI = Adverse events of special interest; β-hCG = Beta-human chorionic gonadotropin; BNP = B-type natriuretic peptide ; CKD-EPI = Chronic kidney disease epidemiology collaboration; CR = complete response; CrCl = Creatinine clearance; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events;ECG = Electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOI = End of infusion; CCI [redacted] IRR = infusion related reaction; CCI [redacted]; NT-pro-BNP = N-terminal pro-hormone BNP; PBMC = peripheral mononuclear cells; PD = Progressive Disease; CCI [redacted]; PR = Partial response; Pre =Predose; CCI [redacted] – Physical Function; SAE = Serious adverse event.

Pre: predose sample to be collected prior to dosing per institutional guidance, as long as it is collected prior to dosing of the corresponding agent; **EOI**: End of infusion sample is in reference to EOI of the corresponding agent.

Table 41 Schedule of Activities – Treatment Discontinuation Visit and Follow-Up Arm 5: GSK4428859A (Anti-TIGIT) plus Dostarlimab (Anti-PD-1) plus GSK6097608 (Anti-CD96) Combination

TDV and Follow Up Assessments	Treatment Discontinuation Visit[1]	Survival Follow-Up[1a]	Notes
Visit Window	**within 30 days of study treatment discontinuation**		
Anticancer Treatment		Q12W*	*If the participant dies before the first follow up, any subsequent anticancer therapy or radiotherapy should be recorded in the eCRF.
Concomitant Medications	X		
TDV and Follow Up Safety			
AE/SAE/AESI Assessment[2]	X		2. After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. Refer to Section 9.4.1 and Section 9.4.3 for further details.
ECOG PS	X		
Physical Examination	X		
Vital Signs and Weight[3]	X		3. Vital signs include blood pressure, temperature, pulse, respiratory rate, and oxygen saturation.
TDV and Follow Up Local Laboratory Assessments			
Clinical Chemistry	X	X^	Refer to Appendix 3 for a complete list of required laboratory assessments. ^Safety laboratory assessments should be collected at TDV (within 30 days of last dose of study treatment) and at 60 and 90 days after last dose of study treatment, unless the participant has started a new anti-cancer therapy within the 90 day follow-up period, in which case safety laboratory assessments are not applicable. Refer to Appendix 3 for the specific laboratory assessments. CCI [redacted]
Serum β-hCG (for women of childbearing potential)	X		
Hematology	X	X^	
Coagulation	X		
Thyroid function tests	X	X^	
Calculated CrCl	X		
Urinalysis	X		
CCI [redacted]			
12-lead ECG[a]	X		
TDV and Follow Up Disease Assessments			

TDV and Follow Up Assessments	Treatment Discontinuation Visit[1]	Survival Follow-Up[1a]	Notes
Visit Window	**within 30 days of study treatment discontinuation**		
Tumor Imaging/Response Assessment[4]	X		4. At the TDV, CT scan is required only if the last disease assessment did not show confirmed PD and was performed ≥6 weeks before TDV. For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first. See additional information in Section 9.3.1
Telephone call for survival status[1a]		Q12W	
TDV and Follow Up Tumor Biopsies			
Fresh tumor tissue sample	X[5]		5. If possible, obtain an optional tumor tissue sample at time of confirmed PR or PD.
TDV and Follow Up Patient-Reported Outcomes/Health-Related Quality of Life: Part 2 ONLY			
CCI			
TDV and Follow Up Biomarkers			
CCI			
TDV and Follow Up Pharmacokinetics and Anti-Drug Antibodies (ADA)			
CCI			

TDV and Follow Up Assessments	Treatment Discontinuation Visit[1]	Survival Follow-Up[1a]	Notes
Visit Window	**within 30 days of study treatment discontinuation**		
CCI [redacted]			

Abbreviations: ADA = Anti-drug antibody; AE = Adverse event; AESI = Adverse events of special interest; β-hCG = Beta-human chorionic gonadotropin; BNP = B-type natriuretic peptide CR = complete response; CrCl = Creatinine clearance; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events;ECG = Electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = Electronic case report form; CCI [redacted]; NT- pro- BNP =N-terminal pro-hormone BNP CCI [redacted]; PD = Progressive Disease; CCI [redacted]; PR = Partial response; CCI [redacted] SAE = Serious adverse event; TDV = Treatment Discontinuation Visit.

1. The assessments required at the study treatment discontinuation visit must be completed within 30 days from the date study treatment was discontinued and must occur prior to the start of subsequent anticancer therapy. If participant attends clinic for scheduled visit and decision is made to discontinue treatment, site can use this visit as the TDV and complete all assessments. See Section 9.4.1 for details on collecting AE and SAE information.

1a. Survival Follow-Up is the Observational Phase of the study. Participants will be followed for survival and subsequent anticancer therapy every 12 weeks after the last dose of study treatment, via telephone contact. Participants will be contacted every 12 weeks (±7 days) until death or participant's withdrawal from further contact. Subsequent anticancer treatment and death date will be documented in the eCRF.

12.1.5.3. Study Design Arm 5: GSK4428859A (Anti-TIGIT) plus Dostarlimab (Anti-PD-1) plus GSK6097608 (Anti-CD96) Combination

CCI [redacted]

GSK4428859A will be evaluated at a CCI [redacted], in accordance to the mTPI dose decision rules presented in Table 48 Section 12.1.5.12 (see Figure 9). A maximum of 9 evaluable participants will be assigned to DLT cohorts for each dose combination per mTPI. Further evaluation of a combination dose demonstrated to result in unacceptable toxicity as described in Table 48 will be stopped.

After the combinations mentioned above are determined to be tolerated per the mTPI rules in Section 12.1.5.12 (Table 48), there is an option to open PK/PD cohorts to further evaluate safety and PK/PD. If PK/PD cohorts are opened, CCI [redacted]

12.1.5.4. Rationale for the GSK4428859A (Anti-TIGIT) plus Dostarlimab (Anti-PD-1) plus GSK6097608 (Anti-CD96) Combination

Anti-TIGIT and Anti-PD-1/PD-L1 Monoclonal Antibody Combinations in Clinical Studies

Combinations with anti-TIGIT mAbs and anti-PD-1/PD-L1 mAbs have demonstrated improved antitumor efficacy while preserving acceptable side effect profiles. The combination of vibostolimab (an anti-TIGIT mAb) with pembrolizumab (an anti-PD-1 mAb) demonstrated a confirmed ORR of 24%, DCR of 36%, and a median DOR that was not reached (95% CI: 4 to 17+ months) in participants with a variety of advanced solid tumors who were naïve to anti-PD-(L)1 therapy [Niu, 2020]. Notably, even in

participants who had previously received anti-PD-(L)1 therapy, the DCR was 50%, driven mostly by disease stabilization [Ahn, 2020]. Vibostolimab demonstrated a tolerable safety profile across the various doses tested alone and in combination with pembrolizumab (anti-PD-1, 200 mg Q3W) in the Phase 1b study (see Rationale Section 12.1.5.3 for further details).

In the dose escalation phase, tiragolumab (an anti-TIGIT mAb) was administered at 2, 8, 30, 100, 400, 600, 1200 mg Q3W in combination with the anti-PDL1 agent, atezolizumab (1200 mg Q3W). No DLTs were observed across all doses (N=49). TRAEs occurred in 59% of participants and the most frequently reported TRAEs were Grade 1 pruritus, Grade 1 to 2 fatigue, Grade 1 to 2 rash, Grade 1 diarrhea, and Grade 1 arthralgia. Two Grade 3 TRAEs were reported in the combination: 1 hyperlipasemia and 1 lymphocyte count decreased. Infusion reactions were seen in 8% of participants, most were Grade 1/2. A higher rate of immune-related AEs (irAEs) was observed with the combination than with tiragolumab monotherapy [Bendell, 2020]. In a Phase 1b dose escalation study, the combination of tiragolumab with atezolizumab (an anti-PD-L1 mAb) showed an ORR of 9% in participants with advanced solid tumors. In an expansion cohort of anti-PD(L)1naïve participants with PD-L1+ NSCLC, an ORR of 46% and a DCR of 85% were observed [Bendell, 2020]. The results from the aforementioned Phase 1b study led to the Phase 2 CITYSCAPE study, a randomized, double-blind study of tiragolumab plus atezolizumab versus placebo plus atezolizumab in participants with PD-L1+ (TPS ≥1%), treatment-naïve, locally advanced or metastatic NSCLC. In the CITYSCAPE study, a confirmed ORR of 37% for the combination arm compared with 21% for the placebo/atezolizumab arm in the intent-to-treat population (n=135) was reported [Rodríguez-Abreu, 2020]. Median PFS was improved from 3.88 months (range: 2.73 to 4.53 months) with atezolizumab to 5.5 months (range: 4.2 to 10.4 months; HR: 0.58, 95% CI: 0.38, 0.89) for the combination. In 58 participants with PD-L1 high (TPS ≥50%) tumors, the confirmed ORR was 66% for the combination compared with 24% in the atezolizumab arm. The median PFS was not reached with the combination (95% CI: 5.49 to not evaluable [NE]) compared with 4.11 months (95% CI: 2.07, 4.73) for the atezolizumab arm (HR for PFS: 0.3; 95% CI: 0.15. 0.61). For participants with PD-L1 TPS 1-49%, the ORR and PFS were similar across both arms (ORR: 18% with atezolizumab vs 16% with tiragolumab and atezolizumab; PFS: 3.58 months and 4.04 months, respectively [HR:0.89; 95% CI: 0.53, 1.49]). The rates of TEAEs (99% vs 96%), Grade ≥3 AEs (48% vs 44%), Grade 5 AEs (5% vs 7%), SAEs (37% vs 35%), and AEs leading to treatment withdrawal (10% vs 9%) were all similar between the combination and placebo/atezolizumab arms, respectively; there was a modest increase in AEs leading to dose modification in the combination arm (40% vs 28%). The overall rate of immune-mediated AEs (69% vs 47%) and Grade 3 or 4 immune mediated AEs (18% vs 13%) were higher in the combination arm [Rodríguez-Abreu, 2020].

As a result, multiple Phase 3 clinical studies are underway evaluating anti-TIGIT and anti-PD(L)1 combination therapy in PD-L1+ NSCLC (NCT04738487; NCT04746924; NCT04262856; NCT04294810; NCT04736173).

Triplet Combination of GSK4428859A plus Dostarlimab plus GSK6097608

Multiple immune checkpoints in addition to PD-(L)1 may regulate T cell anergy and modulate antitumor immunity [Topalian, 2011; Mellman, 2011]. Co-regulatory receptors expressed on T cells can induce stimulatory or inhibitory signaling cascades that modulate T cell proliferation, cytokine production, and cytotoxic T cell activation. Proteins of the nectin and nectin-like (Necl1) family, including TIGIT, PVRIG (poliovirus receptor-related immunoglobulin domain), and CD96, have emerged as immune-suppressing candidates that may prevent immune reactivation after PD(L)1 blockade. These co-regulatory receptors modulate the CD226 immune checkpoint, which is one of the major activating receptors for NK cells.

CD96, TIGIT and CD226 (DNAM-1) are cell-surface receptors in the Ig superfamily and are known to interact with nectin and nectin-like ligands. CD155 is the primary ligand for all 3 receptors (CD96, TIGIT, and CD226). CD226 has been reported to potentiate NK-cell cytotoxicity against cancer cells, and is critical for tumor immunosurveillance [Gilfillan, 2008; Iguchi-Manaka , 2008; Lakshmikanth, 2009; Chan, 2010]. Conversely, both CD96 [Chan , 2014] and TIGIT [Li , 2018]

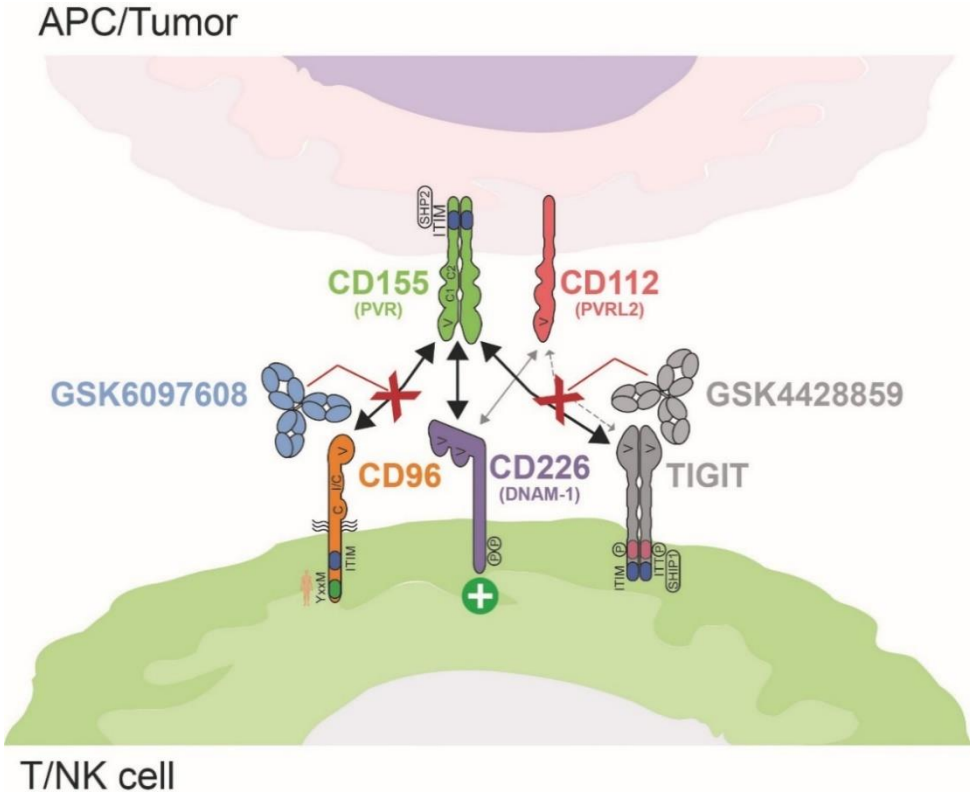
[Lozano , 2012] are known to dampen immune responses through inhibition of NK- and/or T-cell function. Binding of CD96 and TIGIT with CD155 prevents homodimerization and activation of CD226 on CD8+ T cells [Johnston, 2014].

In the tumor microenvironment, CD96 is expressed by NK cells, effector T cells, and regulatory T cells (Tregs). TIGIT is highly expressed on murine and human tumor infiltrating T cells [Johnston, 2014]. In human tumor specimens from the Cancer Genome Atlas (TCGA [NCI, 2021]), TIGIT expression is upregulated in a broad range of solid tumors [Johnston, 2014]. TIGIT is upregulated on tumor infiltrating CD8+ T cells and a population of infiltrating CD4+ T cells in solid tumors in comparison to peripheral T cells from patients and normal donors. CD8+ and CD4+ TIGIT-expressing T cells also co-express PD-1.

CCI [redacted] [GSK Document Number 2019N420882_00]. In NSCLC, TIGIT was expressed in tumor-infiltrating CD8+ and CD4+ T cells and was co-expressed with PD-1 [Johnston, 2014]. Peripheral CD8+ and CD4+ T cells from NSCLC tumor donors had higher levels of TIGIT compared with healthy donors. In addition, in patients with NSCLC, the expression of PD-1 was higher in TIGIT+ cells than in TIGIT-negative cells in both circulating CD8+ T cells and tumor-infiltrating CD8+ T cells [Hu, 2020]. TIGIT could act as a checkpoint inhibitor in exhausted tumor-infiltrating T cells.

CD96 and TIGIT represent novel immune checkpoint receptor targets. As depicted schematically in Figure 10, engagement of CD96 and TIGIT with CD155 functions as an ‘off switch,’ or immune checkpoint, to downregulate immune responses.

Figure 10 Mechanism of Action for CD226 Axis



Abbreviations: APC = antigen-presenting cell; CD = cluster of differentiation; NK = natural killer; TIGIT = T-cell immunoglobulin and immunoreceptor tyrosine-based inhibition motif domain.

EOS884448 (also known as EOS-448; hereafter referred to as GSK4428859A) is a fully human IgG1 mAb that prevents TIGIT-ligand binding. As an IgG1, GSK4428859A also displays a potent affinity for the fragment crystallizable (Fc) gamma receptors (FcγRs) with the potential to mediate ADCC/P against TIGIT expressing cells. Binding of GSK4428859A to TIGIT was shown to increase T cell activation by competing with TIGIT ligands. GSK4428859A (or its mouse surrogate for rodent studies) mediates ADCC/P of immunosuppressive cells by preferentially targeting immunosuppressive regulatory T cells that express a high level of TIGIT relative to cytotoxic CD8 or NK cells, resulting in an increased ratio of effector CD8+/immunosuppressive regulatory T cell cells. Moreover, this effect was abrogated in mice lacking FcγRs, further suggesting the requirement for an ADCC/P effect to fully induce tumor growth inhibition. Overall, these data demonstrate that GSK4428859A restores antitumor immunity by preventing the activation of TIGIT by its natural ligands, PVR/CD155 and Nectin2/CD112, and induces a strong immune response mediated by regulatory T cell depletion and ADCC/P [Preillon, 2021].

GSK6097608 is a fully human IgG1 mAb checkpoint inhibitor designed to modulate this axis by forming a high-affinity complex with CD96, disrupting CD96 binding to CD155, and subsequently redirecting CD155-mediated costimulatory signaling through the activating receptor CD226 to increase T-cell and NK-cell antitumor activity. Modulation

of this axis via inhibition or deletion of CD96 has resulted in antitumor activity in mouse tumor models both alone and in combination with PD-1 inhibition [Blake, 2016; Harjunpää, 2018].

Dostarlimab (formerly referred to as TSR-042) is an IgG4-k humanized monoclonal antibody that binds with high affinity to PD-1 resulting in inhibition of binding to PD-L1 and PD-L2. This antibody was generated based on a proprietary platform that utilizes affinity maturation to select antibodies with desired functional characteristics. The functional antagonist activity of dostarlimab was confirmed in an MLR demonstrating enhanced interleukin-2 production upon addition of dostarlimab. Dostarlimab is an anti-PD1 agent so nonclinical safety data is expected to be similar toa large extent to what was seen with data supporting pembrolizumab combinations. To support combination with dostarlimab, the principal nonclinical toxicology findings associated with dostarlimab were reviewed. CCI [redacted].

As a proof of concept, co-inhibition of CD96 and PD-(L)1 has proven efficacious in several nonclinical tumor models. For example, dual genetic ablation of *CD96* and *Pdcd1* (PD-1) significantly suppressed SM1WT1 (melanoma) tumor growth in mice relative to single knockout approaches (i.e., *CD96-/-* or *Pdcd1-/-*) without overt perturbations in immune homeostasis beyond what has been reported for PD-1-deficient mice [Harjunpää, 2018]. Combinations of anti-CD96 antibodies with anti-CTLA-4 or anti-PD-1 antibodies have also been shown to be more effective than anti-CD96 alone with regards to mouse survival [Blake, 2016]. Similar improvements in antitumor responses have been observed in mice following antibody-mediated co-blockade of CD96 and PD-1 or PD-L1 [Blake, 2016; Li, 2018; Mittal, 2019]. Likewise, in nonclinical models, the combination of anti-PD-L1 and anti-TIGIT agents synergistically improved tumor control over either antibody alone [Johnston, 2014]. Finally, and most importantly, triple combination of anti-CD96, -TIGIT, and -PD-1 has been shown to further improve antitumor responses in multiple tumor models [Mittal, 2019]. Therefore, approaches that block the binding of both CD96 and TIGIT to CD155 could have therapeutic benefit. Thus, combined blockade of CD96 and TIGIT may potentiate the activity of dostarlimab.

CCI [redacted]. Monoclonal antibodies, such as GSK6097608 and dostarlimab, are not substrates for cytochrome P450 or drug transporters. Although treatments are checkpoint inhibitors and are not expected to increase the potential for CRS based on in vitro cytokine release assays (CRAs) and toxicology studies of each individual inhibitor, a combination CRA is being conducted and the data will be available to support dosing of the triplet. For additional nonclinical toxicology data for GSK6097608, dostarlimab, and GSK4428859A refer to the individual Investigator Brochures[see the iTeos EOS884448 [EOS-448] IB, 2021; Dostarlimab IB, 2021; GSK6097608 IB, 2021].

12.1.5.5. Clinical Safety Summary

12.1.5.5.1. GSK4428859A

Several mAbs targeting TIGIT are in various stages of clinical development. These agents include tiragolumab, vibostolimab, domvanalimab, etigilimab, and GSK4428859A, among an increasing number of others.

A Phase 1b study of vibostolimab monotherapy in participants with advanced solid tumor types previously treated with anti-PD-(L)1 therapy reported a 3% ORR and 35% DCR [Golan, 2018]. In a Phase 1a/Phase 1b study of tiragolumab as a single agent and in combination with atezolizumab in advanced solid tumors, there were no objective responses in 24 participants treated with tiragolumab monotherapy [Bendell, 2020]. The 24 participants enrolled in the tiragolumab monotherapy arm included primary cancer history types such as colon, rectum, breast, ovarian, endometrial, melanoma, and other cancer diagnosis [Bendell, 2020]. The ORR for etigilimab in the dose-escalation phase was 0%, with a DCR of 30% in a Phase 1a/Phase 1b study of etigilimab in participants with advanced solid tumors [Sharma, 2018]. A Phase 1 dose-finding study of GSK4428859A, monotherapy demonstrated favorable tolerability and modest preliminary efficacy in 20 participants with advanced solid tumors, with an ORR of 5% [Van den Mooter, 2021].

The safety profile of anti-TIGIT mAbs has been tolerable and comparable to that of other single-agent immune checkpoint inhibitors. In the vibostolimab Phase 1b study of immune checkpoint inhibitor-experienced participants, 59% of participants experienced any treatment-related adverse event (TRAE) with Grade ≥3 TRAEs in 15% of participants in the vibostolimab monotherapy arm. The most common TRAEs reported were fatigue (22%) and rash (20%). One participant (2%) had a TRAE that led to discontinuation and none experienced a fatal TRAE [Golan, 2018]. In the Phase 1a dose-escalation phase of the tiragolumab study in 24 patients, there were no DLTs [Bendell, 2020]. TRAEs occurred in 67% of participants, Grade≥3 TRAEs in 4% (Grade 3 blood creatinine increase) and the most common AE reported was fatigue (38%). There were 6 SAEs reported (25%) with no AEs leading to study withdrawal or death [Bendell, 2020].

CCI [redacted] There were no AEs that led to treatment discontinuations or any TEAEs leading to death. TRAEs were reported by CCI % of participants, with CCI % of participants having Grade ≥3 TRAEs, and CCI % having serious TRAEs. The most frequent TRAEs included pruritus (n=CCI %]), infusion-related reaction (n=CCI %]), fatigue (n=CCI %]), and pyrexia (n=CCI %]); at least CCI skin

disorder (all confounded) was reported in [redacted] participants (for additional details, see the iTeos EOS884448 [EOS-448] IB, 2021).

Overall, the early data from this Phase 1 study [redacted].

12.1.5.5.2. Dostarlimab

A total of [redacted] participants with advanced or recurrent solid tumors received at least one dose of monotherapy dostarlimab [redacted] prior to the data cut-off date of 1 November 2020 in study 4010-01-001 (GARNET).

The data from participants treated with monotherapy dostarlimab in Study 4010-01-001 demonstrated an acceptable safety profile with manageable toxicity in participants with advanced or recurrent solid tumors:

- Treatment-emergent adverse events (TEAEs) regardless of causality were reported in [redacted]% of participants, and [redacted]% of participants had treatment related events. The most common reported TEAEs [redacted]%) were anemia [redacted]%), fatigue [redacted]0%), nausea [redacted]%), and diarrhea [redacted]%).
- Grade ≥3 TEAEs regardless of causality were reported in [redacted]% of participants; the most frequently reported [redacted]% of participants) were anaemia [redacted]%), dyspnoea [redacted]%), abdominal pain [redacted]%), and hyponatraemia [redacted]%). Treatment-related Grade ≥3 events were reported in [redacted]% of participants; the most frequently reported [redacted]% of participants) were anaemia [redacted]%), fatigue [redacted]%), alanine aminotransferase increased ([redacted]%), and lipase increased [redacted]%).
- Treatment-emergent SAEs regardless of causality were reported in [redacted]% of participants; the most frequently reported [redacted]% of participants) were abdominal pain [redacted]%), pneumonia [redacted]%), and dyspnoea [redacted]%). Treatment-related SAEs were reported in [redacted]% of participants; the most frequently reported [redacted]% of participants) were pneumonitis [redacted]%), adrenal insufficiency [redacted]%), and pyrexia [redacted]%).
- TEAEs leading to treatment discontinuation regardless of causality were reported in [redacted]% of participants; the most frequently reported [redacted]% of participants) were alanine aminotransferase increased [redacted]%), aspartate aminotransferase increased [redacted]%), pneumonitis [redacted]%), and transaminases increased [redacted]%). Treatment-related events leading to discontinuation were reported in [redacted]% of participants; the most frequently reported [redacted]% of participants) were alanine aminotransferase increased [redacted]%), aspartate aminotransferase increased [redacted]%), pneumonitis [redacted]%), and transaminases increased [redacted]%).
- TEAEs leading to death regardless of causality were reported in [redacted]% of participants with respiratory failure the only event reported in >1 participant [redacted] participants [redacted]%]); [redacted]% of the deaths were due to treatment-related TEAEs (completed suicide, hepatic ischaemia).

Of the [redacted] participants, [redacted]% who received dostarlimab monotherapy experienced at least 1 immune-related TEAE (irAE). The most frequent [redacted]%) irAEs were hypothyroidism, diarrhea, alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased, hyperglycemia and amylase increased. [redacted] participants[redacted]%) who received dostarlimab monotherapy experienced at least 1 irAE with severity of ≥Grade 3. For [redacted] participants with ≥Grade 3 irAEs, the AE was assessed as study drug related by investigators.

The safety profile of monotherapy dostarlimab in participants with advanced or recurrent solid tumors was generally similar to the reported safety profiles of other mAbs blocking the PD-1 interactions (KEYTRUDA USPI, 2021; KEYTRUDA, SmPC, 2021; OPDIVO USPI, 2021; OPDIVO, SmPC, 2021).

12.1.5.5.3. GSK6097608

An ongoing Phase 1 FTIH study (Study 212214; NCT04446351) in advanced solid tumors is assessing the safety, tolerability, PK, PD, and preliminary anticancer activity of GSK6097608. The study design allows for the assessment of GSK6097608 as monotherapy and in combination with dostarlimab.

Arm A consists of dose escalation to determine the RP2D of GSK6097608 as a single agent, and Arm B consists of dose escalation in combination with dostarlimab. Results from Arm A and Arm B will be used to establish the RP2Ds for monotherapy and combination therapy.

As of the preliminary data cut-off date of 05 November 2021, [redacted] participants have received GSK6097608 in Study 212214. [redacted] participants have received at least 1 dose of GSK6097608 monotherapy (Arm A) and [redacted] participants have received at least 1 dose of GSK6097608 in combination with dostarlimab (Arm B). Participants in the Arm A population (GSK6097608 monotherapy; n[redacted] were enrolled at the following dose levels: [redacted] mg (n=[redacted] mg (n=[redacted] mg (n=[redacted] mg (n [redacted] mg (n=[redacted] mg (n=[redacted] and [redacted] mg (n=[redacted] Participants in the Arm B population (GSK6097608 in combination with dostarlimab; n [redacted] were enrolled in dose-escalation cohorts and received GSK6097608 at the [redacted] mg (n=[redacted] mg (n=[redacted] and [redacted] mg (n=[redacted] and [redacted] mg (n=[redacted] dose levels. In the study, [redacted] deaths were reported; [redacted] deaths were considered treatment-related.

Arm A (GKS6097608 Monotherapy) – Ongoing: [redacted]%) participants have experienced at least 1 treatment-emergent AE (TEAE). The most frequently reported TEAEs (n>2) across all dose levels were fatigue (n=[redacted]%); nausea (n=[redacted] [redacted]%); constipation (n=[redacted]%); diarrhoea (n=[redacted]%); chills, vomiting (n=[redacted]%] each); dizziness, anaemia, and anorexia (n=[redacted]%] each). Of the [redacted] participants enrolled acros [redacted] dose level [redacted] participants experienced [redacted] SAEs [redacted] event [urinary tract infection] at [redacted] mg [redacted] vents [disease progression and cerebrovascular accident] a [redacted] mg, [redacted] event [failure to thrive] at [redacted] mg; [redacted] events [pulmonary hemorrhage and hypovolemic shock] at [redacted] mg; and [redacted] event [pneumonia] at [redacted] mg). No SAEs were noted as treatment

related. Of the TRAEs reported as of 05 November 2021 (Table 42), the majority [redacted] %) Grade 1 or Grade 2 events. [redacted] DLTs have been observed to date.

[redacted]

Arm B (GSK6097608 in Combination with Dostarlimab) – Ongoing: [redacted] participants [redacted] %) have experienced at least 1 TEAE. Table 43 presents TRAEs for Arm B as of the 05 November 2021. [redacted] participants experienced 4 serious adverse events (hyponatremia, tumor hemorrhage, meningitis and CNS necrosis) as a result of disease progression. [redacted] DLTs have been reported. Of the TRAEs reported [redacted] were Grade 1 or 2 events.

[redacted]

CCI [redacted]

12.1.5.6. Dose Justification

12.1.5.6.1. GSK4428859A Pharmacokinetics and Pharmacodynamics

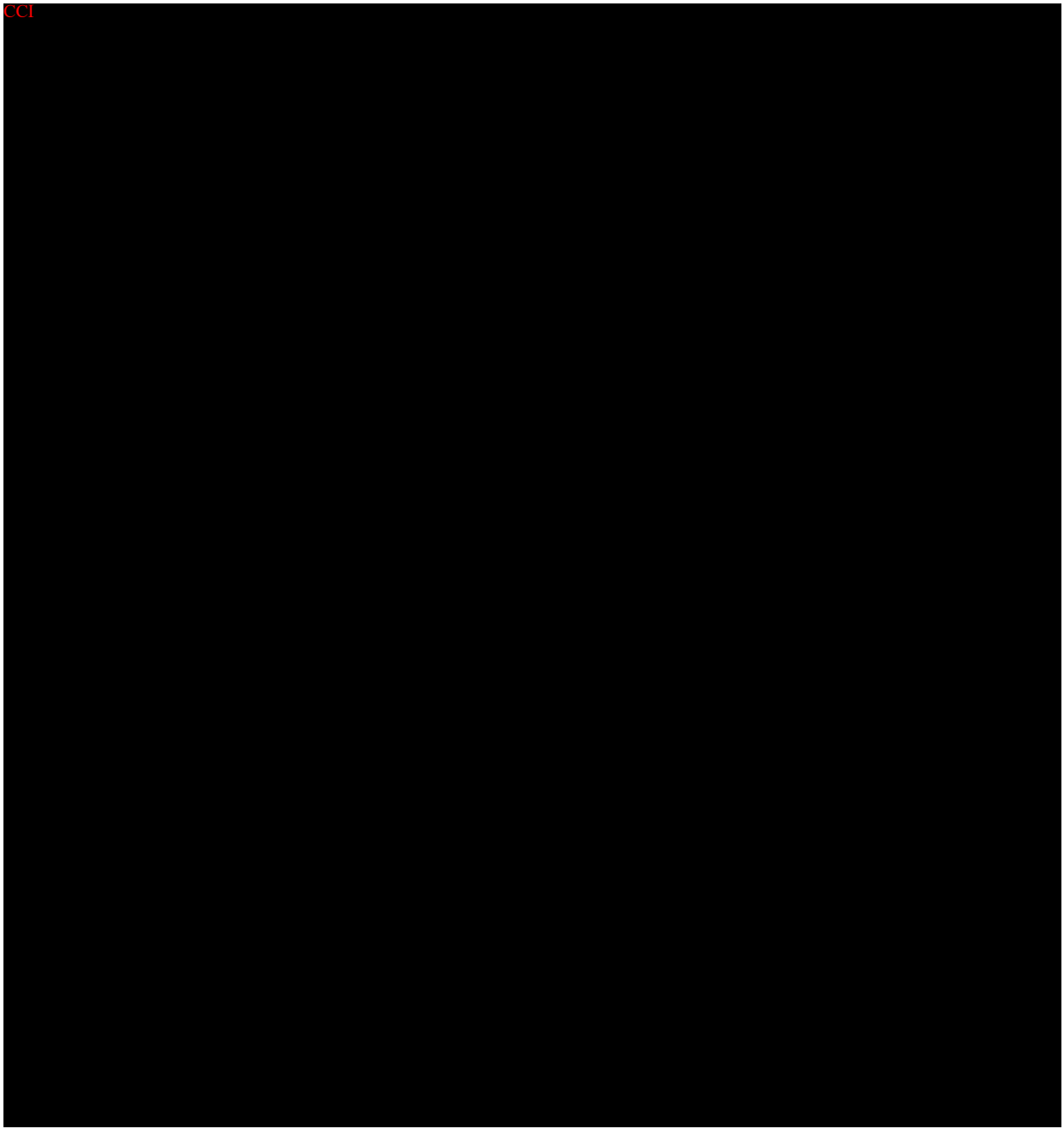
CCI [redacted]. PK data obtained at Cycle 1 are summarized in the iTeos EOS884448 [EOS-448] IB, 2021.

CCI [redacted]

12.1.5.6.2. GSK4428859A Dose Rationale (Arm 5)

The GSK4428859A RP2D of CCI mg CCI is based on the preliminary safety, PK/PD, and efficacy data available from the Phase 1/Phase 2a clinical Study IO-002 (NCT04335253), as well as observations from other clinical studies evaluating anti-TIGIT mAbs which generally have similar properties [Bendell, 2020; Rodríguez-Abreu, 2020; Niu, 2020]. Additionally, Study TIG-006 is currently evaluating the safety, tolerability, PK, PD, and anti-tumor activity of GSK4428859A in combination with pembrolizumab in participants with advanced solid tumors. The starting dose level of GSK4428859A is CCI mg CCI in combination with pembrolizumab in study IO-006 (NCT05060432). Furthermore, GSK4428859A CCI mg CCI will also be tested in combination with dostarlimab in Arm 4 of this platform study and will inform the safety/tolerability profile of this doublet (see Section 12.1.4).

CCI



CCI [redacted]

CCI [redacted] TRAEs were Grade 1 pruritus, Grade 1-2 fatigue, Grade 1-2 rash, diarrhea, and arthralgia. Two Grade 3 TRAEs were reported in the group receiving combination treatment: 1 event of hyperlipasemia and 1 event of lymphocyte count decreased. Infusion reactions were seen in 8% of participants. A higher rate of irAEs was observed with the combination than with tiragolumab monotherapy [Bendell, 2020]. In the Phase 2 CITYSCAPE study, the addition of tiragolumab at 600 mg Q3W to first-line atezolizumab at 1200 mg Q3W in PD-L1–selected metastatic NSCLC demonstrated good tolerability, with a safety profile similar to placebo plus atezolizumab [Rodríguez-Abreu, 2020]. Vibostolimab (an anti-TIGIT mAb) has also demonstrated a good safety and tolerability profile across the various doses tested alone and in combination with pembrolizumab (an anti-PD-1 mAb, 200 mg Q3W) in the Phase 1b study [Ahn, 2020; Niu, 2020].

12.1.5.6.3. Dostarlimab Dose Rationale

The anti-PD-1 mAb dostarlimab will be administered in combination with GSK4428859A and GSK6097608 as a flat dose of CCI [redacted] mg CCI [redacted]

Dostarlimab has been approved in the US and the EU for the treatment of adult patients with dMMR/MSI-H (the latter in the EU only) recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen. As determined in the GARNET study, the recommended clinical dose of dostarlimab deemed safe and effective is CCI [redacted] mg CCI [redacted] for 4 cycles, followed by CCI [redacted] mg CCI [redacted]

To facilitate combination with the other study intervention regimens of this study, dostarlimab dosing CCI [redacted]

CCI [redacted]

No reduction in dostarlimab dose is allowed given that the safety and efficacy profile of the included dose regimen for dostarlimab is considered acceptable, whereas the efficacy of lower doses is not fully characterized.

12.1.5.6.4. GSK6097608 Pharmacokinetics and Pharmacodynamics

CCI [redacted] Preliminary pharmacokinetic summary statistics are presented in Table 44 below.

CCI [redacted]

CCI

[redacted]

12.1.5.6.5. GSK6097608 Dose Rationale

See associated text under Section 12.1.5.6.4 and Section 12.1.5.5.3 for details regarding preliminary pharmacokinetic and clinical safety data from the FTIH Study.

CCI

[redacted]

CCI

[redacted]

12.1.5.7. Study Treatments

Table 45 Description and Administration of Arm 5 GSK4428859A plus Dostarlimab plus GSK6097608 Study Treatments

Name	Dostarlimab	GSK4428859A	GSK6097608
CCI			

In the dostarlimab + GSK4428859A + GSK6097608 combination arm, dostarlimab CCI mg will be administered first as an IV infusion CCI GSK4428859A CCI mg will be administered as an IV infusion CCI after completion of dostarlimab infusion. Lastly (3rd agent to be infused), GSK6097608 CCI mg, CCI mg or CCI mg will be administered as an IV infusion CCI after completion of GSK4428859A infusion (see pharmacy manual for administration instructions).

All participants should remain under observation at the study site after the completion of study treatment administration (refer to SRM for details). Section 12.1.5.11, Table 47 for details on the management of participants experiencing infusion reactions. Refer to Section 5.2 for information on the duration of study treatment.

The date and time of administration will be documented in the source documents and reported in the eCRF. 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). All drugs should be administered on the same day. The 72-hour window does not apply to completion of study treatment administration interrupted by an infusion reaction. Refer to Section 7.2.1.4 for criteria governing dose interruptions or delays.

Details on preparation and administration of GSK4428859A, dostarlimab, and GSK6097608 are described in the pharmacy manual.

12.1.5.8. Concomitant Therapy

Refer to Section 7.7.

12.1.5.9. Treatment of Overdose

12.1.5.9.1. GSK4428859A Overdose

An overdose of GSK4428859A is defined as administration of a dose that is above CCI mg.

In the event of an overdose, the investigator must:

1 Contact the Medical Monitor immediately.
2 Closely monitor the participant for adverse events and laboratory abnormalities for at least 120 days.
3 Obtain a sample for PK analysis within 28 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4 Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

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

There is no specific antidote for overdose with the experimental treatments being evaluated in this study. 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.

12.1.5.9.2. Dostarlimab Overdose

Human data on overdose are not available. There is no known antidote for dostarlimab.

An overdose of dostarlimab is defined as any dose that is ≥20% than CCI mg CCI

In the event of an overdose, the investigator must:

1 Contact the Medical Monitor immediately.
2 Closely monitor the participant for adverse events and laboratory abnormalities for at least 120 days.
3 Obtain a sample for PK analysis within 28 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4 Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

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

There is no specific antidote for overdose with the experimental treatments being evaluated in this study. 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.

12.1.5.9.3. GSK6097608 Overdose

There is no specific information on overdose of GSK6097608. GSK does not recommend specific treatment for an overdose of GSK6097608. An overdose of GSK6097608 is defined as administration of more than the protocol-specified dose.

In the event of an overdose, the investigator must:

1 Contact the Medical Monitor immediately.
2 Closely monitor the participant for adverse events and laboratory abnormalities for at least 120 days.
3 Obtain a sample for PK analysis within 28 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4 Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

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

There is no specific antidote for overdose with the experimental treatments being evaluated in this study. 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.

12.1.5.10. Treatment Duration for GSK4428859A, Dostarlimab, and GSK6097608

Participants enrolled will be treated until disease progression, intolerable toxicity, informed consent withdrawal or death. Combination study treatment will continue to be administered at the indicated schedule for a maximum duration of up to 35 treatment visits or approximately 2 years, whichever comes first. Refer to Section 5.2 for additional details regarding follow up after discontinuation of study treatment.

12.1.5.11. Dose modification and Management Guidelines

No dose reductions are allowed for GSK4428859A, dostarlimab, or GSK6097608 at the participant level. Dose modification guidelines for immune related adverse events are listed in Table 46. If study treatment must be held or discontinued for any toxicity, all

three study drugs must be held or discontinued, unless discussed otherwise with Medical Monitor.

CCI [redacted]

In addition to the immune-related adverse events listed in Table 46, immunotherapy may be associated with other irAEs, including events which may be less commonly associated with PD-(L)1 inhibitors but can similarly result from activation of cellular immune response. For these events, most current professional guidelines (e.g.: NCCN, SITC) should be considered. Patients should receive appropriate supportive care measures as deemed necessary by the treating Investigator, including but not limited to the items outlined below:

Table 46 Dose Modification and Toxicity Management Guidelines for Immune-Related AEs

General instructions: • Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks. • For situations where immunotherapy treatment has been withheld, treatment can be resumed after AE has been reduced to Grade 1 or resolved and corticosteroid has been tapered. Immunotherapy treatment should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks. • For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.				
Immune-related AEs	**Severity grade or conditions (CTCAEv5.0)**	**Action taken**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Respiratory				
Pneumonitis	CCI [redacted]			
Gastrointestinal				

Diarrhea / colitis	CCI [redacted]
Hepatobiliary	
Hepatitis with no tumor involvement of the liver	
Hepatitis with tumor involvement of the liver**	

	CCI [redacted]
Endocrine	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	
Endocrinopathies (e.g. hypophysitis, hypo-/hyperthyroidism, adrenal insufficiency)	
Renal	
Nephritis with renal dysfunction	
Cardiovascular	
Cardiac Investigations i) ECG changes and/or ii) troponin and/ or NT-proBNP/BNP elevations	

	CCI [redacted]
Myocarditis	
Other	
Neurological Events (myasthenia gravis, Guillain-Barré syndrome, encephalitis, transverse myelitis)	

	CCI [redacted]
All other immune-related AEs	
Skin Toxicities[1]	
Rash	
Pruritis	

	CCI [redacted]
Exfoliative dermatologic conditions (e.g. SJS, TEN, DRESS)	

NOTES:
*Resume in patients with complete resolution or partial resolution to Grade 1 after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg/day (or equivalent) within 12 weeks of initiating steroids.

**If AST and ALT are less than or equal to ULN at baseline in patients with liver involvement, withhold or permanently discontinue based on recommendations for hepatitis with no liver involvement.
***Abnormal troponin and proNTBNP/BNP at screening is defined as any value >ULN at screening

1. For any grade skin toxicities, recent alcohol intake or other potentially related concomitant exposures per Investigator assessment, should be recorded in the eCRF. Please refer to SRM for additional details.

Abbreviations: BNP = B-type natriuretic peptide; NT-pro-BNP = N-terminal pro-hormone BNP; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; DRESS = drug reaction with eosinophilia and systemic symptoms.

;

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

Table 47 Immunotherapy Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Please refer to the pharmacy manual for administration details.	Participant may be premedicated 1h (± 30 minutes) prior to infusion of study drugs with: Diphenhydramine 50 mg (or equivalent dose of antihistamine) and/or acetaminophen 325-1000 mg (or equivalent dose of analgesic)
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr), unless otherwise specified in the pharmacy manual. Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment. Please refer to the pharmacy manual for administration details.	Participant may be premedicated 1h (± 30 minutes) prior to infusion of study drugs with: Diphenhydramine 50 mg (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg (or equivalent dose of analgesic). If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used and adaptation of the infusion rate should be discussed with Medical Monitor.
Grades 3 or 4 Grade 3: Prolonged (e.g. not rapidly responsive to symptomatic medication and/or interruption of infusion; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
impairment, pulmonary infiltrates)) Grade 4: Life-threatening; pressor or ventilatory support indicated	Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment. Please refer to the pharmacy manual for administration details.	
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

Abbreviations: NSAIDs = non-steroidal anti-inflammatory drugs.

If a participant has an infusion related reaction, vital signs will be obtained every 15 minutes (± 5 minutes) at the start of symptoms until the participant is deemed medically stable in the opinion of the investigator; pulse oximetry should be performed in conjunction with vital signs.

Adverse Events of Special Interest (AESI)

Refer to Section 7.2.1.1 for details. In addition, for AESIs of immune related cutaneous toxicities of any grade, recent alcohol intake or other potentially related concomitant exposures per Investigator assessment, should be recorded in the eCRF. Please refer to SRM for additional details.

12.1.5.12. Safety Evaluation

CCI

CCI [redacted]

If a participant withdraws from the study before the completion of the 21-day DLT evaluation period for reasons other than DLT or becomes non-evaluable during the DLT period, then the participant may be replaced to achieve the three-participant required minimum. The decision to declare the combination tolerable will occur following review of the safety, PK and PD data (if available) and joint discussion by the GSK Medical Monitor and investigators. Membership, roles and accountabilities, and the process for safety review and meeting frequency is outlined in the Study Reference Manual.

The mTPI design assumptions include the following:

(iii) CCI [redacted]

(iv)

The monitoring rules guiding dose decision are provided in Table 48. The tolerability decision framework using the mTPI method were generated based on a beta/binomial model and pre-calculated before study initiation. The rules in Table 48 utilize the mTPI method along with additional rules as following:

- A maximum of CCI [redacted] DLT evaluable participants will be enrolled for DLT evaluation for each dose combination.
- To avoid exposing participants to excessive toxicities, if CCI [redacted] or more DLTs occur at a dose combination, that dose combination will stop enrolling more participants and will de-escalate to lower dose combination (where applicable).
- Re-escalate to a dose combination is not allowed if that dose has been evaluated and the mTPI rule indicates “D” or “DU”.

The entries in the dose decision rules in Table 48 below represent dose-finding decision points at which a determination is made whether the combination remains safe for continued testing using the data generated in the cohort of interest. These points are often denoted as “E”, “S”, “D” and “DU”, denoting the thresholds governing escalating the dose, staying at the same dose, de-escalating the dose, or de-escalating and no longer re-visit, respectively. To note, there is no “D” in Table 48 due to the above additional rules that re-escalation is not allowed. If a dose combination is not tolerated per Table 48, further evaluation of that dose combination will be stopped.

CCI [redacted]

additional participants experience DLTs, the rule indicates "DU" so this combination will not be considered acceptable and no additional participants will be treated with this combination because of unacceptable toxicity. However, if none of these additional participants experience DLTs, the rule indicates "S" with a DLT rate of CCI% CCIDLTs out of CCIparticipants), hence the combination will be considered tolerated.

If a combination is considered tolerated and the observed DLT rate is CCI%, additional participants may be enrolled to further evaluate safety and PK/PD. No formal evaluation of DLTs will be performed after the 21 day period, however other measures of safety will continue to be monitored.

CCI

CCI

CCI

[redacted]

12.1.5.14. Dose Limiting Toxicity

The severity of all toxicities will be graded using National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 5.0) [NCI, 2017]. The DLT observation period is 21 days in length and begins on the day study treatment is first administrated to the participant.

A DLT is defined as an AE that meets at least one of the criteria listed in Table 49 and is considered by the investigator to be clinically relevant and attributed (probably, or possibly) to the study treatment during the 21-day DLT observation period. An AE considered related to the underlying disease under study it is not defined as a DLT. A safety event can still be included for DLT consideration after the 21 day window. See Section 10.4 for the definition of a DLT evaluable participant.

Table 49 Dose-Limiting Toxicity Criteria

Toxicity	DLT Definition (Grading per CTCAE v5)
Hematologic	• Grade 4 neutropenia of any duration or febrile neutropenia • Grade 4 anemia of any duration • Grade 4 thrombocytopenia of any duration or Grade 3 thrombocytopenia with bleeding
Non- hematologic	• Grade 2 uveitis, episcleritis, iritis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to G1 severity or requires systemic treatment. • Grade 2 colitis or diarrhea that persists without resolution to ≤ Grade 1 for ≥7 days despite adequate immunosuppressive therapy • Grade 3 diarrhea/colitis lasting ≥72h regardless of medical intervention or G4 diarrhea/colitis • Grade 3 pneumonitis • Grade 3 rash if no resolution to ≤Grade 2 or baseline within 2 weeks with use of systemic steroids or anti-inflammatory agents per standard of care • Grade 3 hypersensitivity or IRR • ALT ≥ 3x ULN plus bilirubin ≥ 2x ULN (>35% direct) or plus INR >1.5, if measured[a] (possible Hy's Law) • Grade 3 toxicity that does not resolve to ≤Grade 1 or baseline within 3 days despite optimal supportive care[b] or any Grade 4 toxicity • Following events are not considered DLTs ○ ≥ Grade 3 electrolyte abnormalities that are corrected to ≤ Grade 1 or baseline within 72 hours without clinical sequelae ○ Grade 3 nausea or vomiting that resolves to ≤Grade 1 or baseline within 7 days ○ ≥Grade 3 fatigue ≤7 days ○ ≥Grade 3 lymphopenia ○ Grade 3 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis
Other	• Toxicity that results in permanent discontinuation of any agent in combination • Any other toxicity considered to be dose-limiting that occurs after the completion of the DLT observation period 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. Not applicable to participants taking anticoagulants.
b. Suggested toxicity management guidelines as described in Section 12.1.5.12 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.

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

If a participant experiences a DLT during the DLT observation period, the participant may resume dosing provided the toxicity did not meet study treatment discontinuation criteria in Table 46 and following approval by the Sponsor.

Toxicity management and dose modification guidelines provided in Section 12.1.5.11 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.

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 12.1.5.11. These guidelines are based on the experience of irAE management following the development of immune check-point inhibitors such as ipilimumab and pembrolizumab. Guidelines are also provided for infusion reactions or severe cytokine release (Section12.1.5.11.1). The joint ASCO and NCCN guidelines for the diagnosis and management of irAEs treated with immune checkpoint inhibitor therapy may be used as a supplement to the guidance provided in Section 12.1.5.11.

If there is a delay in administration of study treatment, refer to Section 12.1.5.11 for guidance on planning of subsequent study visits.

12.1.5.15. Risk-Benefit Assessment of GSK4428859A, GSK6097608 and Dostarlimab combined

Table 50 Risk Assessment and Mitigation Strategy: GSK4428859A, GSK6097608 and Dostarlimab

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Immune-related AEs (irAEs)	• Inflammatory AEs such as diarrhea/colitis, pneumonitis, nephritis, myocarditis 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. • An anti-PD-1 checkpoint inhibitor (dostarlimab) will be used in combination with an anti-TIGIT mAb (GSK4428859A) and anti-CD96 (GSK6097608). • Based on the safety profile of anti PD-1 antibodies, administered alone or in combination, the anticipated adverse reactions may be primarily immune mediated. Based on emerging data from anti-TIGIT mAbs, administered alone or in combination, the anticipated adverse reactions are similarly immune mediated.	• Participants with the following medical history are ineligible for this study ○ Toxicity (≥Grade 3) related to prior immunotherapy leading to study treatment discontinuation ○ Active autoimmune disease (refer to Section 6.2 exclusion criterion 6) ○ Severe hypersensitivity to another mAb • Established management algorithms for immune-related adverse events (irAEs) • Refer to Section 12.1.5.12 for further details on the identification, evaluation, and management of toxicities with a potential immune etiology.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Infusion and hypersensitivity reactions and potential CRS	• Risk for infusion reactions and hypersensitivity is inherent to many mAbs [Brennan, 2010] **GSK6097608:** • Manageable infusion reactions have been observed with GSK6097608 in the ongoing Phase 1 clinical study. **Dostarlimab**: • The frequency of IRRs with dostarlimab is labelled as common CCI [redacted] **GSK4428859A:** • CCI [redacted] See Investigator's Brochures for dostarlimab, GSK6097608 and GSK4428859A [iTeos EOS884448 [EOS-448] IB, 2021] for details.	• 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 12.1.5.12 for further details on management and monitoring of infusion reactions. • Refer to Section 12.1.5.12 for further details on management of CRS • Refer to Protocol Section 7.2.1.2; Table 3 for details of blood panel collection for all participants experiencing any grade of infusion reaction or CRS • For severe (Grade 3) or life-threatening (Grade 4) IRRs associated with GSK6097608, GSK4428859A or dostarlimab, infusion should be stopped, and treatment should be permanently discontinued.
ADA and Immune complex disease	• Immune complex deposition may cause clinical symptoms, most commonly renal, skin, or vasculitis pathology. • For nonclinical immune complex formation and deposition findings (refer to individual product Investigator's Brochure [IBs]) • GSK4428859A and GSK6097608 are fully human IgG1 mAb with a wild-type Fc domain. Based on the characteristics of the molecules and active pharmaceutical ingredients, the risk of immunogenicity in humans is considered to be low and similar to other mAbs.	• Clinical laboratory safety assessments and immunogenicity testing
Reproductive toxicity	• CCI [redacted] • Immune-checkpoint inhibitors (such as dostarlimab) have been shown to have potential to disrupt maternal-fetal tolerance leading to failure of implantation or spontaneous abortion. A similar risk will be assumed for GSK6097608 and GSK4428859A.	• Inclusion of contraception guidelines for WOCBP (Section 6.1). • Exclusion of lactating or pregnant women (Section 6.2). • Pregnancy testing for WOCBP during Screening and throughout the Treatment period, as specified in the SoA (Section 12.1.4.2 and Section 12.1.5.2).

Abbreviations: AE = adverse event; IB = Investigator's Brochure; irAEs= immune-related adverse events; IRR= infusion-related reactions; mAb = monoclonal antibody.

12.1.5.16. Additional Study Population Criteria: Arm 5

12.1.5.16.1. Additional Inclusion Criteria: Arm 5

1. Male contraception is not required for this arm.

12.1.5.16.2. Additional Exclusion Criteria: Arm 5

1. Known hypersensitivity to components or excipients of dostarlimab, GSK6097608, and/or GSK4428859A .

2. Has received prior antibodies or drugs targeting TIGIT, CD96, PVRIG, or other therapies targeting the CD226 axis pathway.

12.1.5.17. References

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12.2. Appendix 2: Abbreviations and Trademarks

Abbreviation	Definition
β-hCG	Beta-human chorionic gonadotropin
ADA	Anti-drug antibodies
ADCC/P	Antibody-dependent cellular cytotoxicity/phagocytosis
AE	Adverse event
AESI	Adverse events of special interest
AKT	V-AKT murine thymoma viral oncogene
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the concentration time curve
$AUC_{(0-\tau)}$	Area under the concentration-time curve over the dosing interval
BAL	Bronchoalveolar lavage
BARC	Breast Cancer gene
BCG	Bacillus calmette-guérin
BNP	B-type natriuretic peptide
cfDNA	Cell-free DNA
CHO	Chinese hamster ovary
CIOMS	Council for international organizations of medical sciences
CKD-EPI	Chronic kidney disease epidemiology collaboration
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration;
CNS	Central nervous system
CONSORT	Consolidated standards of reporting trials
CPK	Creatine phosphokinase
CPMS	Clinical pharmacology modeling and simulation
CR	Complete response
CRA	Cytokine release assays
CRC	Colorectal carcinoma
CrCl	Calculated creatinine clearance
CRF	Case report form
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
ct-DNA	Circulating tumor DNA
CTLA-4	Cytotoxic t-lymphocyte-associated protein 4
CV	Cardiovascular
DCR	Disease control rate
DILI	Drug-induced liver injury
dL	Deciliter
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
DRESS	Drug reaction with eosinophilia and systemic symptoms
EC	Effective concentration
ECG	Electrocardiogram(s)
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOI	End of infusion

Abbreviation	Definition
CCI [redacted]	
Fc	Fragment crystallizable
FcγR	Fc-gamma receptor
FcR	Fc region receptor
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose positron emission tomography
FSH	Follicle stimulating hormone
FTIH	First-time-in-human
GCP	Good clinical practice
%GCV	Percent geometric coefficient of variation
G-CSF	Granulocyte colony-stimulating factor
GI	Gastrointestinal
GM	Geometric mean
GSK	GlaxoSmithKline
HIPAA	Health insurance portability and accountability act
HLA	Human leukocyte antigen
HPLC	High performance liquid chromatography
HR	Hazard ratio
HRD	Homologous recombination deficiency
HRQL	Health related quality of life
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International council on harmonization of technical requirements for registration of pharmaceuticals for human use
ICOS	Inducible t-cell costimulator
iCPD	iRECIST Confirmed disease progression
IDMC	Independent Data Monitoring Committee
IEC	Independent ethics committees
IFNγ	Interferon, gamma
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin
INR	International normalized ratio
IO	Immunotherapy
irAE	Immune-related adverse event
IRB	Institutional review board
iRECIST	Modified RECIST 1.1 for immune-based therapeutics
IRR	Infusion-related reactions
ITT	Intent to treat
IV	Intravenous
IWRS	Interactive web response system
L	Litre
LDH	Lactate dehydrogenase
LFT	Liver function test
LLOQ	Lower limit of quantitation
LPS	Lipopolysaccharide
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody

Abbreviation	Definition
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MLR	Mixed lymphocyte reaction
mmol	Millimolar
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant Staphylococcus Aureus
MTD	Maximum tolerated dose
mTPI	Modified toxicity probability interval
MUGA	Multigated acquisition scan
NA	Not applicable
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NCCN	National Comprehensive Cancer Network
NE	Not evaluable
NIH	National Institutes for Health
NK	Natural killer
nM	Nanomolar(s)
NSAIDs	Non-steroidal anti-inflammatory drugs
CCI [redacted]	
NT-pro-BNP	N-terminal pro-hormone BNP
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
OTC	Over the counter
PARP	Poly(ADP-ribose) polymerase
PBMC	Peripheral blood mononuclear cells
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PET	Positron emission tomography
PFS	Progression-free survival
CCI [redacted]	
PI	Principal investigator
PK	Pharmacokinetics
PoS	Predictive probability of success
PR	Partial response
PRO	Patient-reported outcome
CCI [redacted]	
PS	Performance status
PVRIG	Poliovirus Receptor-related Immunoglobulin Domain Containing
Q1W	Every 1 week
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QLQ	Quality of life questionnaire
QoL	Quality of life
QTc	Corrected QT interval duration
QTcF	QT duration corrected for heart rate by Fridericia's formula
RANKL	Receptor activator of nuclear factor-kappaB ligand
RAP	Reporting and analysis plan

Abbreviation	Definition
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
RO	Receptor occupancy
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SCCHN	Squamous cell carcinoma of head and neck
SD	Stable disease
SGPT	Serum glutamic pyruvic transaminase
SITC	Society for Immunotherapy of Cancer
SJS	Stevens-Johnson syndrome
SmPC	Summary of product characteristics
SoA	Schedule of activities
SoC	Standard of care
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reactions
T1DM	Type 1 Diabetes Mellitus
TCR	T-cell receptor
TDV	Treatment discontinuation visit
TEAE	Treatment emergent adverse events
TEN	Toxic epidermal necrolysis
TIGIT	T-cell immunoglobulin and immunoreceptor tyrosine-based inhibition motif domain
TIL	Tumor infiltrating lymphocytes
TIM-3	T cell immunoglobulin and mucin-domain containing-3
TMDD	Target-mediated drug disposition
TNF	Tumor necrosis factor
TPS	Tumor proportion score
TRAE	Treatment related adverse event
Tregs	Regulatory t-cells
TSH	Thyroid stimulating hormone
TTR	Time to response
ULN	Upper limit of normal
UPM	Unit probability mass
WHO	World Health Organization
WOCBP	Woman of childbearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
FluMist
Keytruda
Opdivo
Taxotere
Yervoy (ipilimumab)

12.3. Appendix 3: Clinical Laboratory Tests

Table 51 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	RBC Indices	WBC count with Differential		Platelets
	Hemoglobin	Neutrophils		
	Hematocrit	Lymphocytes		
	RBC count	Monocytes		
		Eosinophils		
		Basophils		
Clinical Chemistry	BUN[a]	Potassium	Bilirubin	AST (SGOT)
	Creatinine[b]	Sodium	Total protein	ALT (SGPT)
	Glucose	Calcium	Albumin	Alkaline phosphatase
	LDH	Amylase	Lipase	
Coagulation[d]	PT/INR			
	PTT/aPTT			
Cardiac Function	Troponin I or Troponin T (Troponin I is preferred over Troponin T. High sensitivity assays are preferred where available) BNP or NT-pro-BNP (NT-pro-BNP is preferred)			
Thyroid Function	Thyroid stimulating hormone Free T4 Free T3 (when clinically indicated)			
Routine Urinalysis	Specific gravity pH, glucose, protein, blood and ketones by dipstick (Note: routine urinalysis by method other than dipstick is acceptable, in accordance with local practice).			
Other Screening Tests	Hepatitis B surface antigen (HBsAg) Hepatitis C (Hep C antibody)[c] Serum β-hCG Pregnancy test (for women of child bearing potential)			

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta-human chorionic BNP = B-type natriuretic peptide; 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 = triiodothyronine; T4 = thyroxine; WBC = white blood cells; INR = International Normalized Ratio; NT-pro-BNP = N-terminal pro-hormone BNP; PT = Prothrombin Time; aPTT = Activated Partial Thromboplastin Time

a. Required if local laboratory testing is available

b. Creatinine clearance is also required to be calculated using the formula provided in Appendix 9.

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.

d. Coagulation factors (PT/INR and aPTT/PTT) should be tested per the SOA under each study arm in Section 12.1 for all participants. Any participant receiving anticoagulant therapy should have coagulation factors monitored closely throughout the study.

12.4. Appendix 4: Study Governance Considerations

Regulatory and Ethical Considerations

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

Financial Disclosure

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

Informed Consent Process

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

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

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

Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

  The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Committees Structure

As indicated in Section 5.5.1, a Steering Committee will convene to provide recommendations at key decision points during the conduct of the study. Details describing the administrative structure for the Steering Committee are located in the Steering Committee Charter.

As indicated in Section 5.1, an IDMC will convene for review of efficacy and safety results at appropriate intervals. Additional details of the IA will be provided in an IDMC Charter.

Publication Policy

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

Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the 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.
- The Sponsor will comply with the requirements for publication of study results and will publish the results of each substudy within 12 months of the primary completion date (last participant last visit date).

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.
- Quality tolerance limits (QTLs) will be pre-defined in the QTL plan to identify systematic issues that can impact participant reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

Source Documents

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

Study and Site Closure

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

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

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

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

12.5. Appendix 5: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

Recording AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Severity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign a grade according to the NCI-CTCAE v5.0 [NCI, 2017].

Assessment of Causality
• The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very**

important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by telephone.
- Contacts for SAE reporting can be found in the SRM on the Sponsor/Medical Monitor Contact Information page.

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the SAE coordinator to OAX37649@gsk.com. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the SRM.

12.6. Appendix 6: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

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

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

Contraception Guidance

Male participants (if required)

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 6.1:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
  - Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 52 when having penile-vaginal intercourse with a woman of childbearing potential

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for the duration of the study and for at least 120 days after the last dose of study treatment.
- In addition, male participants must refrain from donating sperm for duration of study and for at least 120 days after the last dose of study treatment.
- If the participant is randomized to the SoC regimen only, then the duration of contraception is at least 3 days after the last dose of study treatment (or per institutional standard).

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 52.

Table 52 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*

Highly Effective Methods That Are User Independent
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case 2 highly effective methods of contraception should be utilized during the treatment period and for at least 120 days after the last dose of study treatment. However, if the participant is randomized to the SoC regimen only, then the duration of contraception is at least 3 days after the last dose of study treatment.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum β-hCG test
- Additional pregnancy testing should be performed at monthly intervals as indicated in the SoA during the treatment period and at for at least 120 days after the last dose of study treatment and as required locally. If the participant is randomized to the SoC regimen only, then the duration of contraception is at least 3 days after the last dose of study treatment.

  Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected. Pregnancy testing (serum β-hCG) will be performed by the certified local laboratory.

Collection of Pregnancy Information.

Male participants with partners who become pregnant

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

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 5. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will be discontinued from study treatment.

12.7. Appendix 7: Genetics

CCI

[redacted]

12.8. Appendix 8: 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.

1. [Oken, 1982]

12.9. Appendix 9: CKD-EPI and Cockcroft-Gault Formulas

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.

Cockcroft-Gault Formula

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

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

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

Cockcroft-Gault Formula for serum creatinine in mmol/L

CrCl (mL/min)=	Q X (140-age [years]) X ideal body weight (kg)[a] / 72 X serum creatinine (mmol/L)
Q=0.85 for females Q=1.0 for males	
a. Calculation of Ideal Body Weight Using the Devine Formula [Devine, 1974]	
Male participants:	
	50.0 kg + (2.3 kg X each inch over 5 feet) or 50.0 kg + (0.906 kg X each cm over 152.4 cm)
Female participants:	
	45.5 kg + (2.3 kg X each inch over 5 feet) or 45.5 kg + (0.906 kg X each cm over 152.4 cm)

Cockcroft-Gault Formula for serum creatinine in mg/dL

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

For example:

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

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

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

12.10. Appendix 10: Liver Safety: Required Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Phase 2 liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

12.10.1. For Participants with ALT up to 2.5 X ULN at Baseline:

Phase 2 Liver Chemistry Stopping Criteria and Required Follow-Up Assessments

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

Required Actions and Follow-up Assessments Following ANY Liver Stopping Event*	
Actions	**Follow-Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow-up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** participant with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and may continue participant in the study for any protocol specified follow-up assessments **MONITORING:**	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5]. • Blood sample for pharmacokinetic (PK) analysis, obtained 48 hours after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia

For bilirubin or INR criteria: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	• 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 immunoglobulin G (IgG or gamma globulins) • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease: complete Liver Imaging and/or Liver Biopsy CRF forms

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

12.10.2. For Participants with Documented Liver Metastases and ALT up to 5 X ULN at Baseline:

Phase 2 Liver Chemistry Stopping Criteria and Required Follow-Up Assessments

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

Required Actions and Follow-up Assessments following ANY Liver Stopping Event*	
Actions	**Follow-up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow-up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** participant with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and may continue participant in the study for any protocol specified follow-up assessments **MONITORING:** **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24 hrs**	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5] • Blood sample for pharmacokinetic (PK) analysis, obtained 48 hours after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin ≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications

• Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	• Record alcohol use on the liver event alcohol intake case report form **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins) • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease: complete Liver Imaging and/or Liver Biopsy CRF forms

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

12.10.3. Phase 2 Liver Chemistry Increased Monitoring Criteria with Continued Therapy

In the event a participant has an increase in ALT, bilirubin, and/or INR that does not require stopping of study intervention (does not meet liver chemistry stopping criteria as noted in Section 12.10.1 and Section 12.10.2), the following guidance for monitoring of the increase in ALT, bilirubin, and/or INR should be followed as noted below.

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

12.10.4. Liver Safety Drug Restart or Rechallenge Guidelines

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

Following drug-induced liver injury, **drug rechallenge is associated with a 13% mortality across all drugs in prospective studies** [Andrade, 2009]. Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered within 1 month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include:

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

Rechallenge refers to resuming study treatment following drug induced liver injury (DILI). Because of the risks associated with rechallenge after DILI this should only be considered for a 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 (partial response or complete response) with study treatment that exceeds risk, and no effective alternative therapy is available.
- The ALT at the time of rechallenge is <3x ULN.
- The participant did not have additional risk factors for a fatal outcome following the initial injury including hypersensitivity, jaundice, bilirubin >2x ULN (direct bilirubin >35% of total bilirubin), or INR >1.5.
- Ethics Committee or Institutional Review Board approval for rechallenge with study treatment must be obtained, as required.
- If the rechallenge is approved by GSK Medical Governance in writing, the participant must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.

- The participant must also provide signed informed consent specifically for the rechallenge with study treatment. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Participants approved by GSK Medical Governance for rechallenge with study treatment must return to the clinic twice a week for liver chemistry tests until stable liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If after study treatment rechallenge, participant meets protocol-defined liver chemistry stopping criteria, study treatment should be permanently discontinued.
- Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the participant's outcome following study treatment rechallenge.
- GSK must be notified of any AEs as per Section 9.4.4.

12.10.4.2. Rechallenge Following Transient 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

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

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
- Possible study treatment-induced liver injury has been excluded by the investigator and the study team. This includes the absence of markers of hypersensitivity (otherwise unexplained fever, rash, eosinophilia). Where a study treatment has an identified genetic marker associated with liver injury (e.g. lapatinib, abacavir, and amoxicillin/clavulanate), the presence of the marker should be excluded. If study treatment-related liver injury cannot be excluded, the guidance on rechallenge in Section 12.10.4.1 will apply.
- There is no evidence of alcoholic hepatitis.
- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.
- If restart of study treatment is approved by GSK Medical Governance in writing, the participant must be provided with a clear description of the possible benefits and

risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.

- The participant must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Participants approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If after study treatment re-start, participant meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.
- Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the participant's outcome following study treatment restart.
- GSK must be notified of any AEs, as per Section 9.4

12.11. Appendix 11: Country-Specific Requirements

Korea: Section 6.1, Inclusion Criteria #2: Participants in Korea must be age 19 years or older at the time consent is obtained.

12.12. Appendix 12: Guidelines for Assessment of Disease, Disease Progression and Response Criteria

12.12.1. RECIST 1.1 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 5 mm 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

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 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected 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.

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 1 measurable lesion. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilized as the only measurable lesion.

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

Response Criteria

Evaluation of target lesions:

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

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes must be <10mm in the short axis.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (e.g. percent change from baseline).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g. percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5mm.
- Not Applicable (NA): No target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the five preceding definitions.

Note:

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

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 particular timepoint based on the assessment schedule, should be excluded from the response determination (e.g. non-target response does not have to be "Not Evaluable").

New lesions:

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

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

Evaluation of overall response:

Table 53 presents the overall response at an individual time point for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions for subjects with measurable disease at baseline.

Table 53 Evaluation of Overall Response for Subjects with Measurable Disease at Baseline

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

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

Note:

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

Evaluation of best overall response:

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

Confirmation Criteria:

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

12.12.2. iRECIST Guidelines

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used to assess tumor response and progression, and make treatment decisions. When clinically stable and upon approval from the Medical Monitor and separate written consent of the participant (See Section 8.1), participants may continue treatment until progression is confirmed according to the rules described below. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. These data will be captured in the clinical database.

Clinical stability is defined as meeting all of the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care
- Absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g., CNS metastasis, respiratory failure due to tumor compression, or spinal cord compression) requiring urgent alternative medical intervention
- No significant, unacceptable, or irreversible toxicities related to study treatment

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

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

Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

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

Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological PD by RECIST 1.1 the investigator will decide in consultation with the Medical Monitor whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management (see Table 54 and Figure 11). This decision should be based on the participant's overall clinical condition (See discussion of clinical stability in Section 12.12.1 above). The investigator must obtain approval from the Medical Monitor and separate consent from the participant prior to continuing treatment.

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

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

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

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

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

Assessment at the Confirmatory Imaging

At the confirmatory imaging visit assessment, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR). Timing of confirmatory imaging is described in Section 9.3.1.

Confirmation of Progression

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

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

Persistent iUPD

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

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

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

Resolution of iUPD

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

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

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

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset." This means that the next visit that shows radiographic

progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

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

Detection of Progression at Visits after Pseudo-Progression Resolves

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

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

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

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

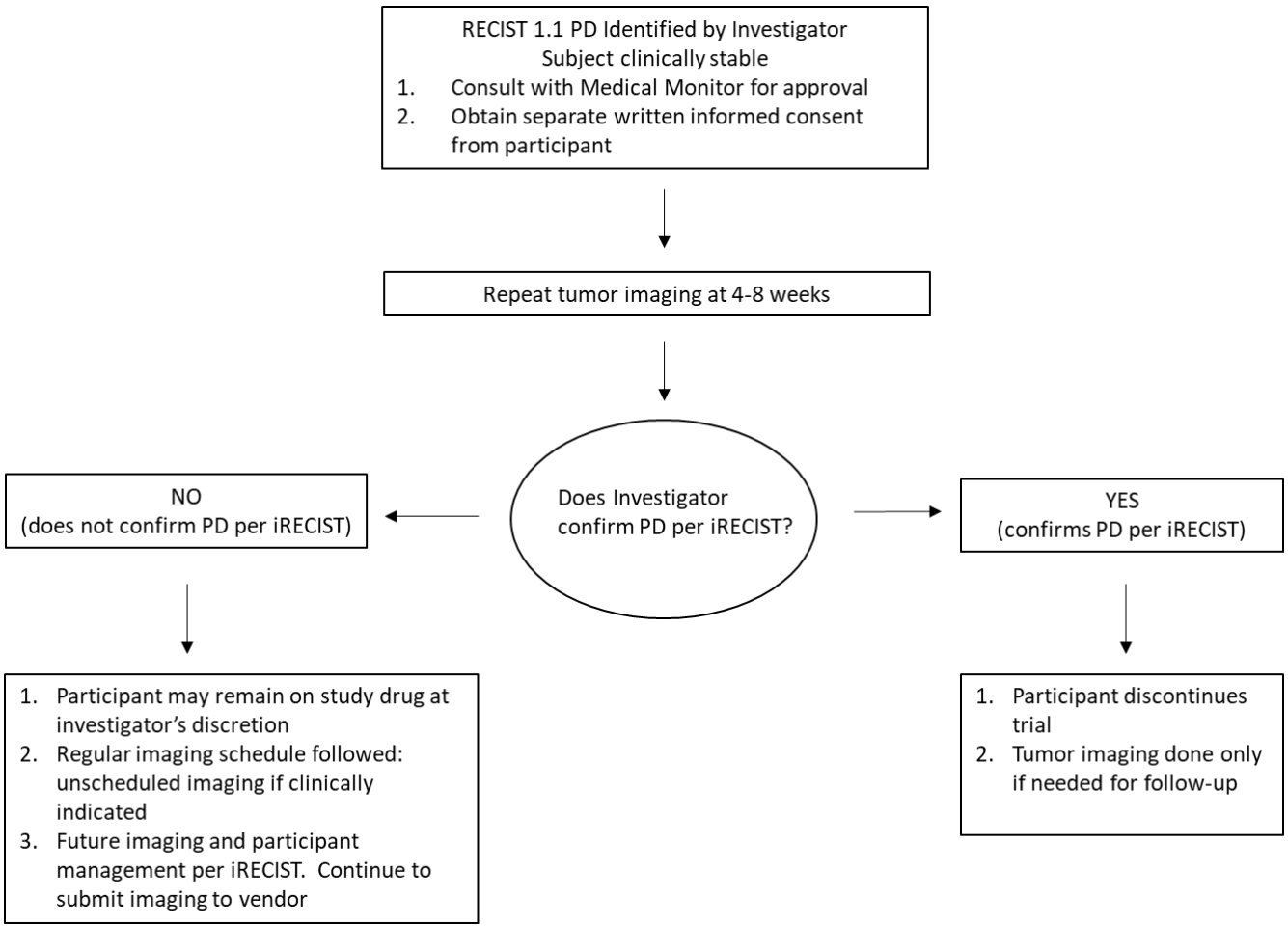
Additional details about iRECIST are provided in the iRECIST publication [Seymour, 2017].

Table 54 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the investigator's discretion, with Medical Monitor approval and participant consent, while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per investigator assessment	No additional imaging required.	Discontinue treatment	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the investigator's discretion.	Continue regularly scheduled imaging assessments.	If clinically unstable, hold treatment May consider restarting study treatment only if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.

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

Figure 11 Imaging and Treatment for Clinically Stable Participants after First Radiologic Evidence of PD Assessed by the Investigator



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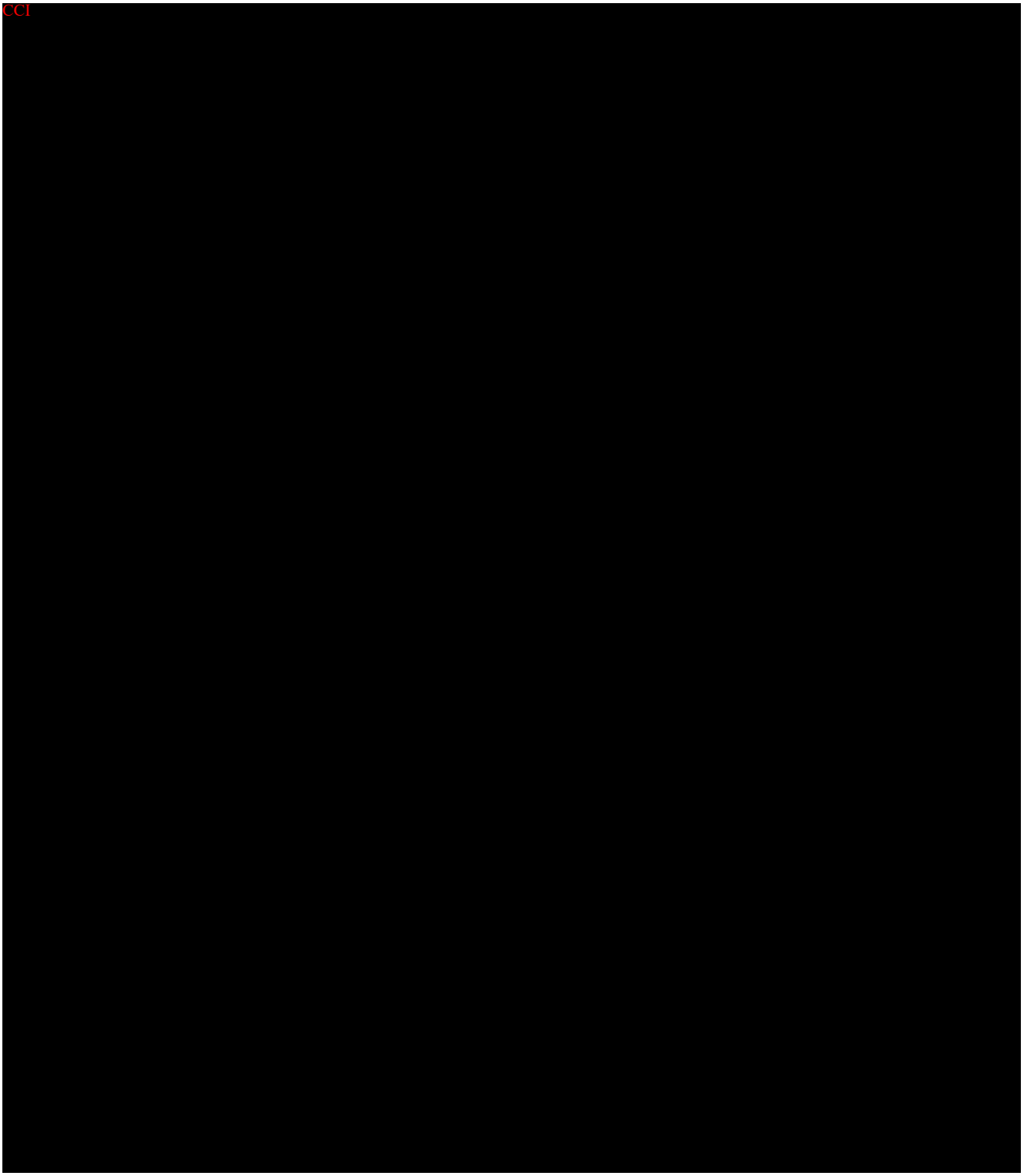

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12.14. Appendix 14: Immune-Related Diseases

Table 56 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

12.15. Appendix 15: Protocol Amendment History

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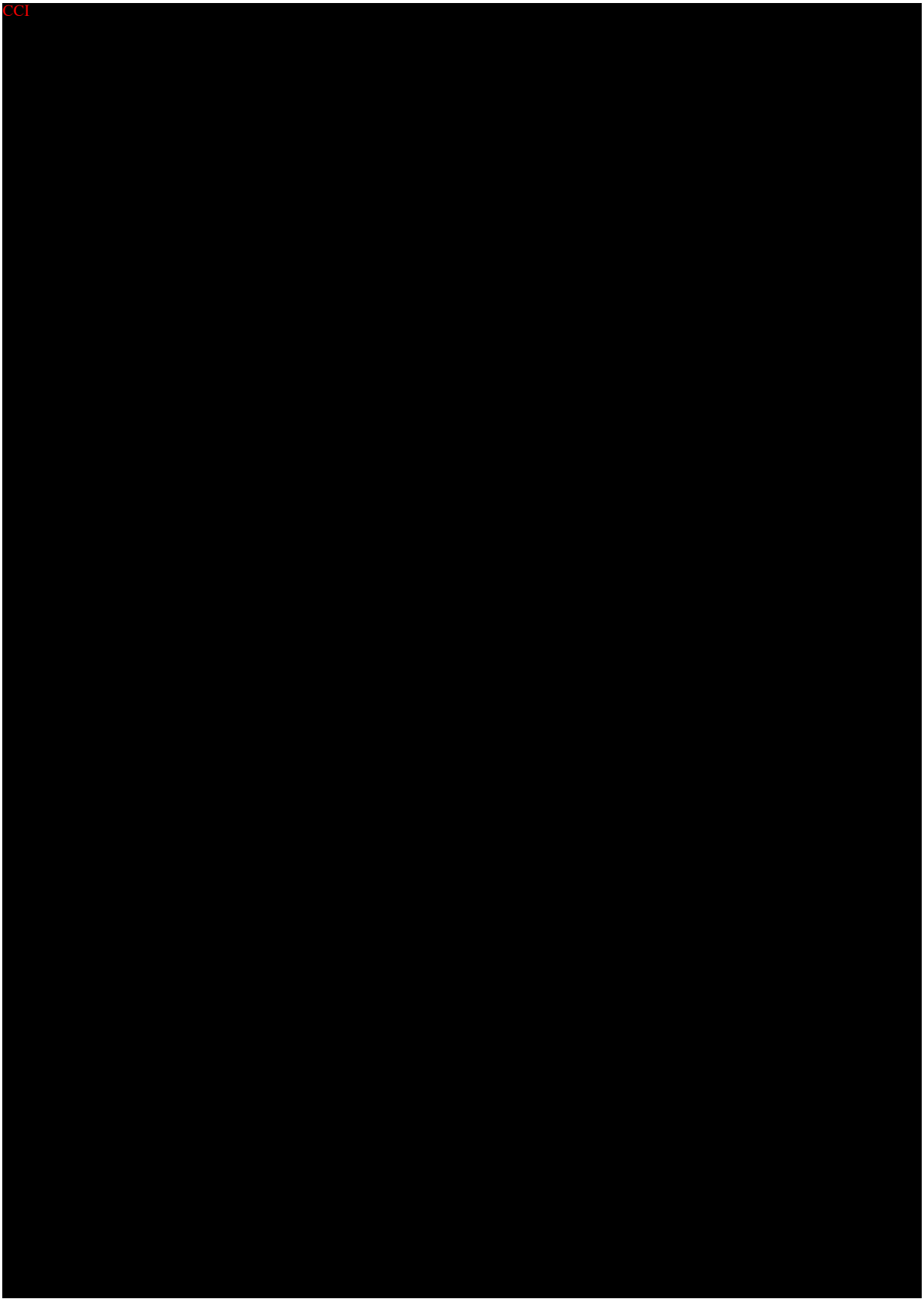

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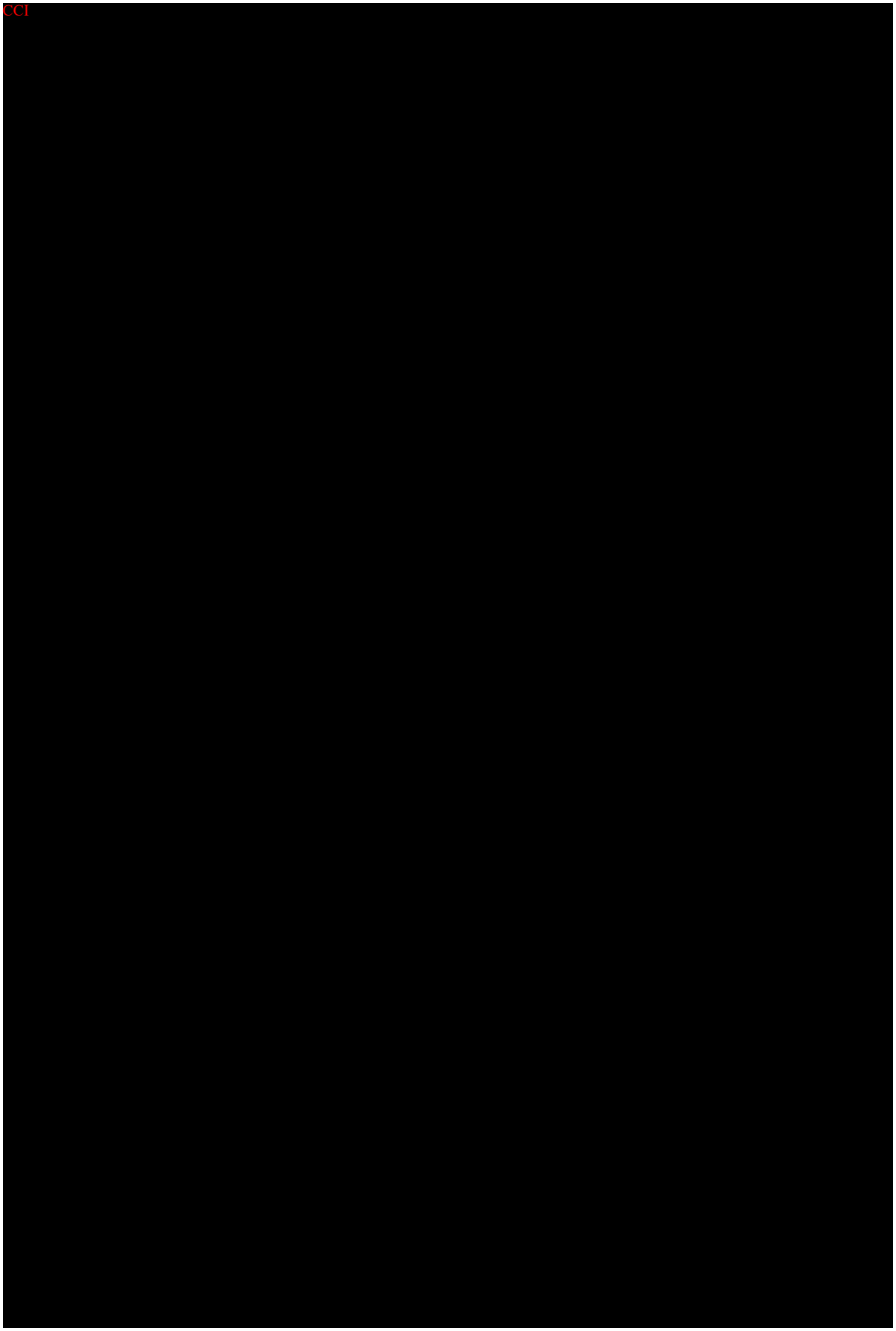

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