TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Phase I, Open-Label Study of GSK3174998 Administered Alone and in Combination with Anticancer Agents including Pembrolizumab in Subjects with Selected Advanced Solid Tumors

Compound Number: GSK3174998

Development Phase: I

Effective Date 04-FEB-2020

Protocol Amendment Number: 04

Author (s):

PPD

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Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2014N225045_00	2015-APR-29	Original
2014N225045_01	2015-AUG-17	Amendment No. 1
Amendment 1 incorporates changes to Section 4.1.4, Dose-Limiting Toxicities; 5.4 Withdrawal/Stopping Criteria; and 6.3.1.12, Dose Delay as requested by the United States Food and Drug Administration (FDA).		
2014N225045_02	2016-AUG-16	Amendment No. 2
Amendment 2 incorporates the following changes: • Addition of preliminary clinical data to support the initiation of Part 2/combination with pembrolizumab. • Addition of a new "Pharmacodynamic Cohort" in the dose escalation phase. • Removal of Soft Tissue Sarcoma (STS) from the targeted tumor types. • Extension of GSK3174998 dosing up to 2 years/35 cycles. • Addition and clarification of procedures in the Time & Events Table. • Clarification on the use of Continual Reassessment Methodology (CRM) for dose escalation decisions. • Additional details on the definitions of analyses for anticancer activity. • Administrative corrections of minor typographical and/or inconsistent language throughout the protocol.		
2014N225045_03	2018-MAR-16	Amendment No. 3
Amendment 3 incorporates the following changes: • Addition of preliminary clinical, safety, PK and PD data • Updated pembrolizumab background and dose rationale • Updated study design, with description of cohort expansion populations for Part 2B • Dose rationale for cohort expansion (Part 2B) • Updated risk assessment • Updates to Inclusion/Exclusion Criteria to define cohort expansion population • Consolidated Section 6.3 Dose and Safety Management Guidelines • Minor changes to Time & Events tables • Section 9 (Statistical Considerations and Data Analysis) – updates to hypothesis, sample size considerations, futility analysis and stopping rules		

GlaxoSmithKline Document Number	**Date**	**Version**
2014N225045_04	2020-FEB-04	Amendment No. 4

Amendment 4 documents the closure of Part 2B expansion cohorts, removes the requirement for future disease assessments and survival follow-up, and clarifies the impact of ending enrolment of expansion cohorts on the study objectives and efficacy analysis.

For expansion cohorts, enrolment of 10 subjects/cohort was initially planned, with a possibility of further enrolment if the cohorts passed planned futility analyses. However, in February 2019, a strategic decision was made not to initiate any new clinical investigations with the GSK3174998/pembrolizumab combination, including halting further expansion beyond 10 subjects/cohort. This decision was based upon the modest clinical activity observed within the study at that time, in addition to published data for other OX40 agonist antibodies combined with PD-1 or PD-L1 inhibitors reporting low/modest clinical activity for these combinations. As a consequence, the futility analyses (described in Section 4.1.5) were deemed unnecessary. Ultimately, the three expansion cohorts in Melanoma, STS and NSCLC treated a total of 9, 9, and 5 subjects, respectively. As of 5 November 2019, all subjects have completed treatment and are in post-treatment follow-up; no responses were observed in subjects enrolled in the expansion cohorts. Given the lack of responses in the expansion cohorts (Part 2B) and the modest clinical activity observed in dose escalation (Part 1A and 2A), no time-to-event summaries and analyses (TTR, DOR, PFS, OS) will be performed for efficacy data; however, TTR and DOR will be calculated and listed and considered as exploratory endpoints.

Amendment 4 incorporates the following changes:

- Removal of objectives to analyze/summarize efficacy time-to-event endpoints (PFS, OS)
- Update to make durability of response endpoints (TTR, DOR) exploratory
- Halt to enrolment of new patients and halt the occurrence of any further futility analyses
- Removal of future disease assessments or follow-up for survival
- Updated wording for treatment discontinuation
- Updated the definition of subject and study completion to be 3 months post last dose
- Updated treatment after end of study
- Updated footnotes in the T&E table to reflect the changes to further disease assessments and follow-up
- Updated Evaluation of Anti-Cancer Activity
- Updated Interim Analysis Section
- Updated Secondary Analyses Section removing the objective to analyze/ summarize efficacy time-to-event endpoints
- Updated PK analyses in section 9.4.2.2

SPONSOR SIGNATORY

PPD

04 Feb 20

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MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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

Regulatory Agency Identifying Numbers:

Investigational New Drug (IND) number: IND124839

EudraCT number: 2015-000152-14

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol 201212

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

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

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

Investigator Name:		
Investigator Signature		Date

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS FOR STUDY 201212 (ENGAGE-1)

Rationale

The stimulation of antitumor T-cell activity, through inhibition of negative T-cell regulatory pathways with immunotherapeutic checkpoint inhibitors, has been very successful in the treatment of melanoma and non-small cell lung cancer (NSCLC). Another approach that provides an attractive target for the development of immunotherapy anticancer agents is the modulation of costimulatory pathways to enhance T-cell function. OX40 is a potent costimulatory receptor expressed primarily on activated CD4+ and CD8+ T cells. OX40 agonists have been shown to increase antitumor immunity and improve tumor-free survival in non-clinical models and OX40 agonist monoclonal antibodies (mAbs) are currently being evaluated in Phase I clinical trials. GSK3174998 is a humanized wild-type immunoglobulin G1 (IgG1) anti-OX40 agonistic mAb and will be evaluated as a single-agent treatment in Part 1 of the current study.

The anticancer immune response is a multistep process and it is expected that tumors may utilize redundant mechanisms to block the antitumor response; in these instances, combination therapies will likely be required. Combining an OX40 agonist with a programmed death receptor-1 (PD-1) inhibitor targets two different steps in the cancer-immunity cycle; OX40 agonism is expected to increase priming/activation of T cells, while inhibition of PD-1 blocks its interaction with programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2), releasing the PD-1 pathway-mediated inhibition of the immune response. Based on non-clinical data, combination treatment with an OX40 agonist and a PD-1 inhibitor is anticipated to have synergistic antitumor activity, compared with single-agent treatment. The combination of GSK3174998 with the PD-1 inhibitor pembrolizumab will be evaluated in Part 2 of the current study.

Objectives/Endpoints

The primary objectives of the study are to evaluate the safety and tolerability and to identify the maximum tolerated dose (MTD) or maximum administered dose (MAD) of GSK3174998 when administered intravenously as monotherapy (Part 1) or in combination with pembrolizumab (Part 2) to subjects with selected advanced or recurrent solid tumors. Secondary objectives include: the evaluation of antitumor activity; characterization of pharmacokinetics (PK) for GSK3174998 when administered alone; characterization of PK for GSK3174998 and pembrolizumab when administered in combination; and determination of the immunogenicity of GSK3174998 when administered alone or for GSK3174998 and pembrolizumab when administered in combination. Exploratory objectives include evaluation of pharmacodynamic activity in the blood and tumor microenvironment.

- **Safety endpoints:** Adverse events (AEs), serious adverse events (SAEs), dose-limiting toxicity (DLT), withdrawals due to AEs, dose reductions or delays, and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters).

- **Antitumor activity endpoints:** Objective response rate (ORR) and Disease Control Rate (DCR) (complete response [CR]+partial response [PR]+stable disease [SD] ≥12 weeks). Unless otherwise specified, all response endpoints will be assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and by irRECIST (immune-related RECIST); the primary endpoint analysis will use irRECIST.
- **PK endpoints:** Plasma GSK3174998 and serum pembrolizumab concentrations and PK parameters including maximum observed concentration (Cmax), area under the concentration-time curve over the dosing interval (AUC(0-τ)), and minimum observed concentration (Cmin).
- **Pharmacodynamic endpoints:** Assessment of lymphocyte OX40 receptor membrane expression and occupancy by GSK3174998, along with the phenotype, quantity, and activation state of T cells in the periphery, T-cell receptor (TCR) diversity, expression of circulating soluble factors, and changes in genomic DNA and gene expression, and mutational load. Assessment of tumor biopsies via immunohistochemistry (IHC) for the numbers of tumor-infiltrating lymphocytes and other immune cells expressing key phenotypic markers. Changes in gene expression (RNA and protein), TCR diversity or mutational load (genomic DNA).
- **Immunogenicity endpoints:** Number and percentage of subjects who develop detectable antidrug antibodies (ADA).

Overall Design

This is a first time in human (FTIH), open-label, non-randomized, multicenter study designed to evaluate the safety, tolerability, PK, pharmacodynamics, and preliminary clinical activity of GSK3174998 administered intravenously to subjects with selected advanced or recurrent solid tumors. The study will be conducted in 2 parts, each part consisting of a dose-escalation phase followed by a cohort expansion phase. Part 1 will evaluate GSK3174998 monotherapy, while Part 2 will evaluate GSK3174998 in combination with pembrolizumab. GSK3174998 will first be evaluated as monotherapy in escalating doses. Once a dose of GSK3174998 has been identified that is both tolerable and demonstrates pharmacodynamic activity, enrollment of Part 2 may begin. In Part 2, escalating doses of GSK3174998 will be evaluated with fixed doses of pembrolizumab. The transition of the study from dose-escalation to cohort expansion and from monotherapy (Part 1) to combination therapy with pembrolizumab (Part 2) will be performed under the guidance of a Protocol Steering Committee. The remit, membership, roles, and responsibilities of the Steering Committee are described in a Steering Committee Charter. Pending a review of emerging data from this study and under the guidance of the Steering Committee, the protocol may be subsequently amended to include investigation of additional anticancer agent combinations with GSK3174998.

Treatment Arms and Duration

The study includes a screening period, a treatment period, and a follow-up period. Subjects will be screened for eligibility beginning approximately 4 weeks before the start

of treatment. The maximum duration of treatment with GSK3174998 ± pembrolizumab will be 2 years or 35 cycles, whichever comes first. The follow-up period for safety assessments will be a minimum of 3 months from the date of the last dose. The post-treatment follow-up period includes disease assessments every 12 weeks until confirmed disease progression (PD). Following PD, subjects will be contacted every 3 months to assess survival status.

With the implementation of Amendment 04, there will be no requirement to perform future disease assessments or survival follow-up. In Part 1, dose escalation for GSK3174998 monotherapy will begin with a starting dose of 0.003 mg/kg GSK3174998 administered once every 3 weeks (Q3W). In Part 2, dose escalation for GSK3174998 + pembrolizumab combination therapy will begin with a fixed dose of 200 mg pembrolizumab administered Q3W and a starting dose of 0.003 mg/kg GSK3174998. Dose adjustments are allowed to address tolerability and safety issues.

Type and Number of Subjects

The study will enroll up to approximately 264 subjects with tumor types that may include NSCLC, squamous cell carcinoma of the head and neck (SCCHN), renal cell carcinoma (RCC), melanoma, bladder cancer, soft tissue sarcoma (STS), triple-negative breast cancer (TNBC), and colorectal carcinoma displaying high microsatellite instability (MSI CRC).

Analysis

During the dose-escalation phases of the study, safety, PK, and pharmacodynamic marker data will be examined while the study is being conducted in order to determine subsequent dosing levels. After each dosing cohort, a continual reassessment method (CRM) analysis may be used to recommend the next dose level based on observed DLTs.

In each expansion cohort, clinical activity, safety, PK, and pharmacodynamic marker data will be examined on an on-going basis and enrollment within each cohort may be curtailed or expanded in response to unfavorable or favorable outcomes. Tumor response data will be monitored and a tumor cohort may be terminated if there is insufficient evidence of clinical activity. The futility stopping rules are based on the methodology of Lee & Liu [Lee, 2008]. CRM-recommended dose-escalation levels, futility stopping rules, and posterior probabilities are only guidelines and the totality of the data will be considered by the team in decision making.

2. INTRODUCTION

2.1. Study Rationale

The stimulation of antitumor T-cell activity, through inhibition of negative T-cell regulatory pathways with immunotherapeutic checkpoint inhibitors, has been very successful in the treatment of melanoma and NSCLC. Another approach that provides an attractive target for the development of immunotherapy anticancer agents is the modulation of costimulatory pathways to enhance T-cell function. OX40 is a potent costimulatory receptor expressed primarily on activated CD4+ and CD8+ T cells. OX40 agonists have been shown to increase antitumor immunity and improve tumor-free survival in non-clinical models and OX40 agonist mAbs are currently being evaluated in Phase I clinical trials. GSK3174998 is a humanized wild-type IgG1 anti-OX40 agonistic mAb and will be evaluated as a single-agent treatment in Part 1 of the current study.

The anticancer immune response is a multistep process and it is expected that tumors may utilize redundant mechanisms to block the antitumor response; in these instances, combination therapies will likely be required. Combining an OX40 agonist with a PD-1 inhibitor targets two different steps in the cancer-immunity cycle; OX40 agonism is expected to increase priming/activation of T cells, while inhibition of PD-1 blocks its interaction with PD-L1 and PD-L2, releasing the PD-1 pathway-mediated inhibition of the immune response. Based on non-clinical data, combination treatment with an OX40 agonist and a PD-1 inhibitor is anticipated to have synergistic antitumor activity, compared with single-agent treatment. The combination of GSK3174998 with the PD-1 inhibitor pembrolizumab will be evaluated in Part 2 of the current study.

This FTIH, open-label, dose-escalation study will assess the safety, PK, pharmacodynamics, and preliminary clinical activity of GSK3174998 in subjects with selected advanced or recurrent solid tumors as monotherapy (Part 1), in combination with pembrolizumab (Part 2), and potentially in combination with additional therapies.

2.2. Brief Background

Immunotherapy has emerged as a transformative anticancer therapeutic strategy over the past few years. In particular, the inhibition of negative T-cell regulatory pathways with the checkpoint inhibitors has been very successful, first in the treatment of melanoma and, more recently, expanding to additional indications, including NSCLC. Ipilimumab and pembrolizumab are examples of these initial checkpoint inhibitors, which are mAbs that block the activity of the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and PD-1 pathways, respectively, thereby freeing the T-cell priming and T-cell effector functions from their negative regulatory effects.

In addition to regulatory mechanisms that negatively regulate effector T-cell function, costimulatory pathways are also attractive targets to modulate for the development of anticancer agents. OX40 (CD134) is a member of the tumor necrosis factor receptor (TNFR) family of transmembrane receptors, which is induced following antigen-dependent stimulation of both CD4+ and CD8+ T cells and following interaction with its cognate ligand (OX40L, expressed on activated antigen presenting cells) generally

functions to transduce a costimulatory signal during the process of T-cell activation. In blood and peripheral tissues, OX40 expression is limited to the small subset of recently activated CD4+ and CD8+ cells; however, in tumors, infiltrating T lymphocytes are enriched for OX40 positive cells, where it functions to augment T-cell activation, proliferation, and survival through direct and indirect (e.g., cytokine release) mechanisms [Betting, 2009; Croft, 2010]. In addition to its function on effector T cells, OX40 is also expressed on tumor infiltrating regulatory T cells (Tregs), which tend to have an inhibitory effect on the immune response. Indeed, the efficacy of anti-OX40 antibodies in animal tumor models relies to some extent also on the depletion of tumor-specific Tregs residing in the tumor microenvironment [Bulliard, 2014; Marabelle, 2013]. As has been shown for anti-CTLA4 and anti-GITR (Glucocorticoid-induced TNFR family related gene) antibodies, this intratumoral Treg depletion is critical for the *in vivo* antitumor activity of immune checkpoint antibodies and is mediated by activatory FcγR positive myeloid cells residing in the tumor microenvironment [Bulliard, 2013; Selby, 2013; Simpson, 2013]. OX40 signaling has been shown to block the activity of induced Tregs, in part by blocking the release of the inhibitory cytokine interleukin-10 (IL-10), thereby further promoting effector T-cell immune responses [Ito, 2006]. Finally, OX40 can also be found on natural killer (NK) cells where it appears to stimulate NK-mediated antibody-dependent cellular cytotoxicity (ADCC) [Liu, 2008]. Together, these potential mechanisms of action make the stimulation of OX40 with agonistic agents an attractive target for a novel anti-cancer immunotherapy.

2.3. GSK3174998

2.3.1. Background

An overview of the nonclinical studies of GSK3174998 and preliminary clinical data from Protocol 201212 (ENGAGE-1) are provided below. Detailed information concerning the biology, pharmacology, PK, and safety can be found in the Investigators' Brochure (IB) [GlaxoSmithKline Document Number 2014N212091_06].

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

GSK3174998 is suitably cross-reactive to cynomolgus monkey OX40 to evaluate the pharmacology, pharmacodynamics, PK, and toxicology in this species. Single and repeat dose studies in cynomolgus monkeys demonstrated that GSK3174998 bound to OX40 positive cells. GSK3174998 is not cross-reactive with rodent OX40; however, a surrogate mAb to murine OX40 (OX86), was used to generate *in vivo* nonclinical evidence for both single agent efficacy and combination synergy with a variety of other immunotherapy agents in a range of syngeneic tumor models.

2.3.2. Nonclinical Pharmacokinetics of GSK3174998

The nonclinical PK of GSK3174998 has been investigated in mice following a single intraperitoneal (IP) administration and in cynomolgus monkeys following single and repeated intravenous (IV) administration. Details of the nonclinical PK are provided in Section 4.3 of the IB [2014N212091_06].

The PK of GSK3174998 in male mice following a single-dose IP administration had concentration profiles typical for mAbs (very slow plasma clearance and low volume of distribution at steady state) [Wang, 2008], suggesting that GSK3174998 was mainly confined to the systemic circulation. Due to lack of cross-reactivity with murine OX40 the impact on PK expression of target is not evaluable in this species.

Similar PK profiles typical for mAbs were observed in monkeys. Following a single IV administration in male cynomolgus monkeys (n=3) at 2 mg/kg, all GSK3174998-treated animals showed similar C_{max} values ranging from 31.8 to 39.9 µg/mL and similar systemic exposures ($AUC_{0\text{-}168h}$) through Day 5. There was a dramatic change in clearance observed from about 7 to 14 days in all treated animals, typical of an immunogenicity response; all animals were confirmed to be positive for ADA in an ADA bridging assay.

Following repeat dose IV administration in cynomolgus monkeys at 10 or 100 mg/kg/week for 4 weeks, the mean $AUC_{0\text{-}168h}$ and C_{max} values for GSK3174998 were similar between males and females at both doses during Weeks 1 and 4. The systemic exposure to GSK3174998 (as defined by gender-averaged $AUC_{0\text{-}168h}$ and C_{max} values) increased dose-proportionally (n=3/group). The increases in the gender-averaged $AUC_{0\text{-}168h}$ and C_{max} values of GSK3174998 from Week 1 to 4 ranged from 1.9- to 2.9 fold at both doses. Instances of decreased plasma concentrations were observed after the fourth dose in monkeys at 10 mg/kg/week due to primate ADA formation.

2.3.3. Nonclinical Safety of GSK3174998

The toxicology program was conducted in cynomolgus monkeys. These monkeys were shown to be a suitable species based on OX40 receptor expression in tissues, orthologous protein sequence homology, and similar dose-dependent binding of GSK3174998 for both human and monkey OX40 receptor on CD4+ T cells. IHC assessment of OX40 distribution in normal human tissues showed positive staining in cells or lymphoid cell aggregates, considered likely to be a subset of T cells, in a number of the tissues. These results are in general agreement with results from the evaluation of a microarray gene expression database (Gene Logic, Ocimum Biosolutions, LLC, Houston, TX, USA).

GSK3174998 was well tolerated in monkeys following weekly IV dosing for 4 weeks at doses up to 100 mg/kg/week.

ADA were observed in monkeys given ≤10 mg/kg/week; the incidence occurred inversely to dose. In a PK/pharmacodynamic study, all monkeys (n=3) or two of three monkeys given 2 or 10 mg/kg/week, respectively, demonstrated a dramatic increase in clearance as early as 7 days post-dose (2 mg/kg/week) and were confirmed to be positive for ADA. In monkeys given GSK3174998 weekly for 4 weeks followed by a 6 week off-dose period, ADA were detected in two of ten monkeys given 10 mg/kg/week, in which

one monkey (titer >10000) demonstrated a decrease in exposure following the fourth weekly dose, and the other monkey (titer = 1000), which did not have detectable ADA until the off-dose period, did not demonstrate a clear association to decreased exposure. As ADA were only noted in animals maintained throughout the off-dose period, the ability to determine toxicity in the terminal necropsy animals at this dose on this study was not compromised by ADA. The generation of ADA in animals administered humanized protein is generally not predictive of a potential for ADA formation in humans.

In an *in vivo* syngeneic efficacy study with BALB/c mice bearing 4T1 mammary carcinoma cells, mortality and clinical observations consistent with anaphylaxis were observed in the majority of mice given ≥20 μg OX86 (rat wild-type IgG1 mAb against OX40 receptor) at 3 weeks of twice-weekly dosing (5th dose). This effect appears to be unique to this specific model, as other efficacy studies using either BALB/c or C57BL/6 mice with the same batch of OX86 given at comparable doses and duration with other syngeneic cell types demonstrated no tolerability issues. Similar effects have been observed by others using 4T1 tumor-bearing mice given rat anti-PD-1 or hamster PD-L1 [Mall, 2014] or with tumor administration only [duPre, 2007]. To date, anaphylaxis has not been reported in subjects receiving OX40 agonist mAbs or approved PD-1 therapies [Curti, 2013; KEYTRUDA Prescribing Information, 2019; OPDIVO Prescribing Information, 2014]. Therefore, based upon the data and literature findings described above, it suggests that the anaphylaxis seen in 4T1 tumor-bearing mice given OX86 is model specific and that the proposed safety monitoring strategy (real time monitoring of ADA and acute hypersensitivity reactions, see Section 6.3.1) adequately addresses the potential risk of this effect.

The potential for GSK3174998 to induce cytokine release has been investigated. In a human *in vitro* assay, using whole blood or isolated peripheral blood mononuclear cells (PBMCs) (with and without prior anti-CD3 and anti-CD28 stimulation), no release of cytokines in response to soluble or immobilized GSK3174998 was observed. However, to further explore the potential for cytokine release, human PBMCs were incubated at higher (10X) cell density, incubated with immobilized GSK3174998 and stimulated instead with submaximal levels of immobilized anti-CD3 (10 and 100X lower), to provide more sensitive assay conditions. In these assays increased cytokine production (IL-2, IFNγ, TNFα) was observed compared to anti-CD3 alone. Similar cytokine increases, along with proliferation, were also observed using isolated human CD4+ T cells with immobilized GSK3174998, prior anti-CD3 and anti-CD28 stimulation to upregulate OX40 expression and longer incubation periods (48-72 hours compared with 24 hours). In repeat dose monkey studies up to 4 weeks in duration of dosing over a dose range of 0.03 to 100 mg/kg/week, there were no GSK3174998-related changes in plasma cytokine levels at either 4 or 24 hours of the first dose or 4 hours after the second weekly dose. While low levels of cytokine release in subjects given GSK3174998 is expected by activated T cells as part of the pharmacodynamics, the response may not be fully predicted by these *in vitro* assays, and close clinical monitoring is planned.

Single-dose safety pharmacology studies have not been conducted with GSK3174998. Evaluations of cardiovascular function were performed on the 3rd week of the 4-week monkey toxicology study, which evaluated heart rate, electrocardiogram (ECG)

waveform evaluation, and corrected QT interval duration (QTc) evaluation. There were no GSK3174998-related effects on these cardiovascular measurements nor were there any clinical observations of respiratory or general behavior effects of the antibody.

The no observed adverse effect level (NOAEL) was determined to be 100 mg/kg/week, the highest dose tested (Week 4 gender average mean $AUC_{0\text{-}168h:}$ 594 mg.h/mL, range 548 to 634 mg.h/mL; Cmax: 4.88 mg/mL, range 4.27 to 5.46 mg/mL).

2.3.4. Nonclinical Activity and Pharmacodynamics of GSK3174998

2.3.4.1. *In vitro* Studies

GSK3174998 demonstrated several mechanisms of action *in vitro*, including promoting effector CD4+ T-cell proliferation, inhibiting the induction of IL-10 producing CD4+ Tr1 cells and blocking the suppressive function of nTregs, and binding to FcR, which is anticipated to augment OX40 signaling via cross-linking of the antibody via the Fc domain on FcR positive cells.

GSK3174998 bound specifically to the recombinant OX40 extracellular domain from cynomolgus monkeys (Kd 408 nM) and humans (Kd 4.9 nM), but not to the related human receptors DcR3 and CD40. GSK3174998 bound to both activated cynomolgus monkey and human CD4+ T cells with similar EC_{50} values (0.35 and 0.30 μg/mL, respectively). These data suggest that affinity differences observed for binding to recombinant OX40 are not truly reflective of the binding to cell-surface OX40.

Many anti-TNFR family antibodies (including anti-OX40) appear to require the formation of high-density antibody complexes and costimulation which may occur *in vivo* during cell:cell interactions in tissues expressing various FcγRs [White, 2013]. In the case of OX40 antibodies, this can be mimicked *in vitro* by immobilizing the antibody to the surface of plastic tissue-culture plates and incubating cells on this plate-bound antibody. Importantly, it was shown that OX40 activation gives a costimulatory signal to T cells dependent on TCR engagement (e.g., CD3 ligation), suggesting that GSK3174998 is not a super agonist in the *in vitro* systems tested in absence of TCR signal. GSK3174998 (immobilized) stimulated proliferation of immobilized anti-CD3 activated cynomolgus monkey CD4+ T cells with a mean EC_{50} value of 0.72 μg/mL (4.8 nM) and anti-CD3 induced proliferation of activated human CD4+ T cells with a mean EC_{50} value of 0.19 μg/mL (1.3 nM).

OX40 agonist antibodies have been shown to reduce the suppressive function of human Tregs. Human purified CD4+ T cells were differentiated into induced Tregs using vitamin D3 and dexamethasone and cultured with human CD32a (FcγRIIA)-expressing L-cells (which could facilitate antibody crosslinking via the FcγRIIA). Addition of GSK3174998 in solution during the differentiation phase was able to prevent naïve T cells from differentiating into IL-10^{+} Tr1 cells.

As expected for an IgG1 antibody, GSK3174998 bound to cynomolgus monkey and human FcRγs (and to human complement C1q) and showed low but measurable levels of reporter FcγRIIIA engagement in a reporter assay system. In ADCC assays, some cell

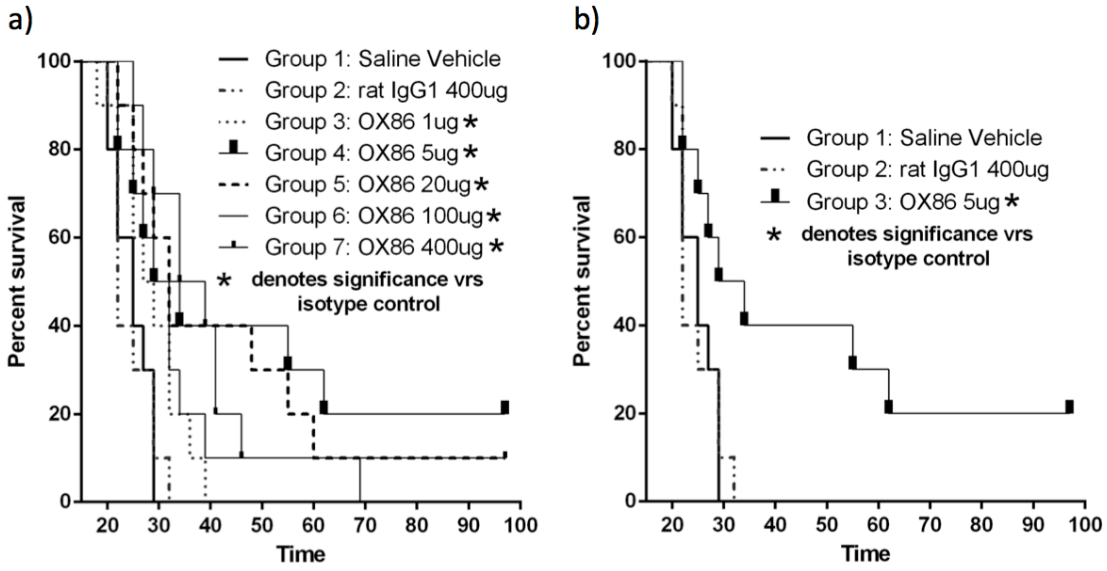
lysis of an OX40+ target cell line was observed with GSK3174998 treatment. However, in primary human PBMC assays, GSK3174998 generally did not impact the viability of CD4+ and CD8+ T cells. Statistical analysis of the PBMC ADCC data did not support a robust effect on viability with GSK3174998. In all cases the reduction in viability with GSK3174998 was less than observed for anti-CD52 or anti-CD20 positive control antibodies. Overall these *in vitro* findings suggest that GSK3174998 may have the potential to cause ADCC of OX40+ target cells *in vivo*, however effects were not consistent across donors and these *in vitro* assays may not fully reflect the immune microenvironments *in vivo*.

2.3.4.2. *In vivo* Studies

In cynomolgus monkeys given a single IV dose (2 mg/kg) of GSK3174998 there was a transient decrease in the percentage of OX40+/CD4+ T cells on Day 2, recovering by Day 7, suggesting that GSK3174998 appears to bind to OX40+ cells in peripheral blood and that these cells and may reflect margination rather than depletion of these cells. In a repeat-dose IV study, cynomolgus monkeys were given GSK3174998 (10 mg/kg/week) for 4 weeks. As observed in the single-dose study, the percentage of free OX40 on peripheral blood T cells was reduced in groups treated with GSK3174998 compared with the vehicle group, which was sustained for the duration of the study. This indirectly suggests that GSK3174998 was bound to OX40+ cells following dosing. OX40-positive cells did not appear to be depleted as they could be detected using a non-competitive anti-OX40 antibody. No clear evidence of changes in T-cell activation markers were observed in peripheral blood, spleen, or lymph nodes in treated groups compared with non-treated groups in either study. OX40 positive cells were also detected in these tissues in both treated and non-treated groups suggesting cells were not depleted in tissues by GSK3174998. There were no clinical observations considered related to treatment in either study.

A surrogate mAb to murine OX40 (OX86) was used to generate *in vivo* nonclinical evidence for monotherapy activity in syngeneic tumor models. In a series of experiments, female BALB/c mice bearing CT26 mouse colon carcinoma tumors (n=10/group), were given twice weekly IP doses of OX86 ranging from 1 to 400 μg/mouse in phosphate-buffered saline for 3 weeks. All doses showed a significant increase in survival (Figure 1) compared to control groups. Assuming similar potency between anti-OX86 and GSK3174998, exposures that have demonstrated efficacy preclinically are predicted to be achievable in human subjects.

Figure 1 OX86 monotherapy results in a statistically significant increase in survival in nonclinical mouse model; (a) all dose levels tested and (b) the 5 µg dose



Additional *in vivo* experiments were performed with BALB/c mice bearing A20 mouse lymphoma cell line tumors and showed modest tumor reduction and with C57BL/6 mice bearing B16F10 mouse melanoma cell line tumors with no significant effect on tumor reduction or survival noted. Additionally, the mouse adoptive cell transfer (ACT) model, MC38/gp100 was utilized to evaluate GSK3174998 *in vivo* since a humanized mouse model is unavailable. Overall the ACT model was not robust and produced highly variable results. Further details for all studies are available in Section 4.2.1.3 of the IB [2014N212091_06].

In vivo studies in syngeneic tumor models were also performed with GSK3174998 in combination with anti-PD-1 antibodies and anti-CTLA-4 antibodies; the anti-PD-1 combination studies are briefly described in Section 2.5 of the protocol; further details for combination studies are available in Section 4.2.1.3 of the IB [2014N212091_06].

2.3.5. Preliminary Clinical Data for GSK3174998

Data are summarized for the ongoing first time in human study with a clinical data cut-off of 13 August 2019 in the Investigator's Brochure [2014N212091_06]. Data are reported for 138 subjects; 45 subjects received doses up to 10 mg/kg of GSK3174998 monotherapy and 96 subjects received doses up to 10 mg/kg of GSK3174998 + 200 mg of pembrolizumab. Three subjects crossed over from monotherapy to combination therapy.

2.4. Pembrolizumab

Refer to the pembrolizumab IB/approved labeling for detailed background information on pembrolizumab [KEYTRUDA Prescribing Information, 2019; Merck Sharp & Dohme Corp 2019]

2.4.1. Pembrolizumab Background and Clinical Trials

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical *in vitro* data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator brochure. [Merck Sharp & Dohme Co, 2019].

2.4.2. Rationale for Pembrolizumab Dose Selection

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of

pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

2.5. Rationale for OX40 agonist and PD-1 inhibitor Combination

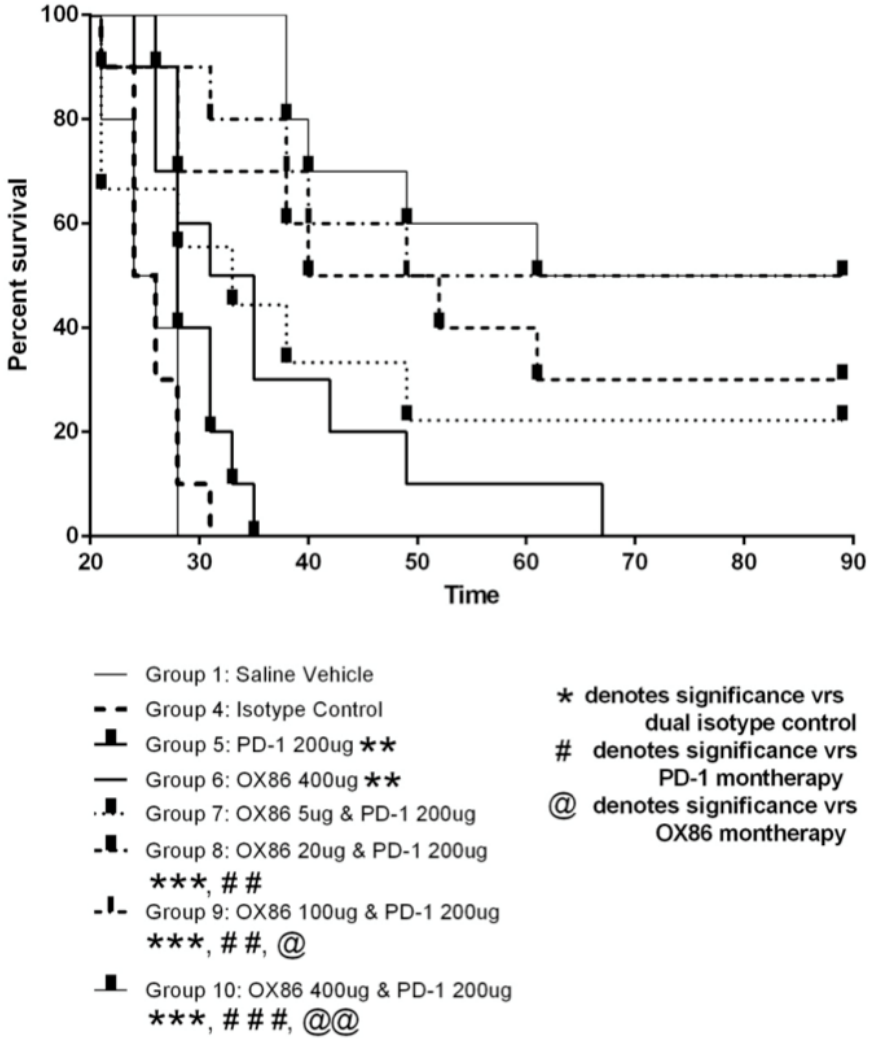
The anticancer immune response is a multistep process that includes antigen processing and presentation, T-cell priming and activation, tumor infiltration, and subsequent destruction by activated effector T cells [Chen, 2013]. Each of these steps can be negatively regulated, which provides the malignant tumor with redundant mechanisms by which to block an anticancer immune response. In some cases, tumors will be highly dependent on a single mechanism, and in these cases, there is the potential to achieve significant clinical activity with a single immunomodulatory therapy. However, it is expected that tumors will often utilize redundant mechanisms to block the antitumor immune response. In these instances, combination therapies will likely be required. One example of the benefit of combination immunotherapy is the very impressive clinical data generated by the combination of ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) in subjects with metastatic melanoma [Wolchok, 2013].

The rationale for combining an OX40 agonist with an anti-PD-1 agent is based on the fact that these two agents target different steps in the cancer-immunity cycle. Similar to the ipilimumab/nivolumab combination, GSK3174998 is expected to increase the priming/activation of antitumor T cells while the anti-PD-1 agent pembrolizumab prevents the inhibitory effect of the PD-1/PD-L1 pathway on effector T cells in the tumor. Guo et al reported synergistic antitumor activity for the combination of PD-1 blockade and OX40 agonism in a murine ID8 ovarian cancer model. The activity of the combination treatment was associated with increased CD4+ and CD8+ cells and decreased CD4+FoxP3+ Tregs and CD11b+Gr-1+ myeloid suppressor cells [Guo, 2014].

A surrogate mAb to murine OX40 (OX86) was used to generate *in vivo* nonclinical evidence for combination synergy with a PD-1 inhibitor in syngeneic tumor models. In a series of experiments, female BALB/c mice bearing CT26 mouse colon carcinoma cell line tumors (n=10/group) were given twice weekly IP dosing with OX86 at 1 to 400 μg/mouse and in combination with anti-PD-1 mAb at 20 or 200 μg/mouse for 4 weeks. Both OX86 and anti-PD-1 mAb monotherapy decreased tumor volume and increased survival compared with saline and isotype controls; however, the combination

of OX86/anti-PD-1 significantly increased survival (Figure 2) compared with monotherapy and was well tolerated. Similar combination efficacy and survival outcomes were reported for female BALB/c mice bearing A20 mouse lymphoma cell line tumors; however, no synergy or additive effects were reported in female C57BL/6 mice bearing B16F10 mouse melanoma cell line tumors. Further details for all studies are available in Section 4.2.1.3 of the IB [2014N212091_06].

Figure 2 OX86 and anti-PD1 in CT26 Syngeneic Mouse Tumor Model: Combination Therapy vs. Monotherapy



The internal and published nonclinical data described, provide empirical support for the potential of the combination of PD-1 blockade and OX40 agonism. This concept is currently being tested in the clinic with a murine OX40 antibody and a PD-L1 inhibitor (MEDI6469 and MEDI4736; Study NCT02205333). In the current study, the attractive safety profile of pembrolizumab is expected to make it a good combination partner with GSK3174998.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Part 1: GSK3174998 Monotherapy	
Primary	
• To evaluate the safety and tolerability and identify the MTD[a] or the MAD of GSK3174998 administered intravenously to subjects with selected advanced or recurrent solid tumors.	• AEs, SAEs, DLT, withdrawals due to AEs, dose reductions or delays, and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters).
Secondary	
• To evaluate the antitumor activity of GSK3174998 in subjects with selected advanced or recurrent solid tumors. • To characterize the PK of GSK3174998 monotherapy. • To determine the immunogenicity of GSK3174998.	• ORR and DCR (CR+ PR+ SD ≥12 weeks).[b] • GSK3174998 concentrations in plasma and PK parameters including Cmax, AUC(0-τ), and Cmin. • Number and percentage of subjects who develop detectable ADA.
Exploratory	
• To explore the relationship between antitumor activity, PK parameters, pharmacodynamic activity and other patient characteristics. • To explore onset and durability of response • To evaluate the pharmacodynamic activity of GSK3174998 in the peripheral blood and to explore the utility of these measures to enrich for clinical efficacy and development of a diagnostic test.	• Evaluation of antitumor activity (CR, PR, SD, PD), tumor kinetic parameters, PK parameters, pharmacodynamic activity, and other patient characteristics. • TTR and DOR • Assessment of lymphocyte OX40 receptor membrane expression and occupancy by GSK3174998. Measures of immune function in blood (e.g. phenotype, quantity, and activation state of T cells in the periphery, TCR diversity, expression of circulating soluble factors such as cytokines and stress-related proteins). Assessment of changes in genomic DNA, gene expression (RNA and protein), (e.g. using cfDNA, exosomes or circulating tumor cells [CTCs]), and mutational load.

Objectives	Endpoints
Part 1: GSK3174998 Monotherapy	
Exploratory	

• To evaluate the pharmacodynamic activity of GSK3174998 in the tumor microenvironment and to explore the utility of these measures to enrich for clinical efficacy and development of a diagnostic test.
 	
• Pharmacogenetics (PGx): To evaluate the association of genetic variations in the host DNA and response to therapy or disease characterization.
	• Assessment of tumor biopsies via IHC for the numbers of tumor-infiltrating lymphocytes and other immune cells expressing key phenotypic markers. Changes in gene expression (RNA and protein), TCR diversity, or mutational load (genomic DNA).
	
	• Germline genetic evaluations may be conducted for:
	  • Medicine response, including GSK3174998 or any concomitant medicines.
	  • Disease susceptibility, severity, and progression and related conditions.

Hypothesis	
For the primary objective, no formal statistical hypothesis will be tested; analysis will be descriptive and exploratory	

a. In the final determination of the MTD, all available safety and tolerability data will be considered
b. Unless otherwise specified, all response endpoints will be assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and by irRECIST (immune-related RECIST); irRECIST will be used to determine treatment decisions.

RNA = Ribonucleic acid; DNA = Deoxyribonucleic acid

Objectives	Endpoints
PART 2: Combination GSK3174998 plus pembrolizumab	
Primary	
• To evaluate the safety and tolerability and identify the MTD[a] or the MAD of GSK3174998 administered intravenously in combination with IV pembrolizumab to subjects with selected advanced or recurrent solid tumors.	• AEs, SAEs, DLTs, withdrawals due to AEs, dose reductions or delays, and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters).
Secondary	
• To evaluate the antitumor activity of GSK3174998 in combination with pembrolizumab in subjects with selected advanced or recurrent solid tumors.	• ORR and DCR (CR+PR+SD ≥12 weeks).[b]
• To characterize the PK of GSK3174998 and pembrolizumab when administered in combination.	• Plasma GSK3174998 and serum pembrolizumab concentrations and PK parameters including Cmax, AUC(0-τ), and Cmin.
• To determine the immunogenicity of GSK3174998 and pembrolizumab when administered in combination.	• Number and percentage of subjects who develop detectable ADA.
Exploratory	
• To explore the relationship between antitumor activity, PK parameters, pharmacodynamic activity and other patient characteristics.	• Evaluation of antitumor activity (CR, PR, SD, PD), tumor kinetic parameters, PK parameters, pharmacodynamic activity, and other patient characteristics.
• To explore onset and durability of response	• TTR and DOR
• To evaluate the pharmacodynamic activity of GSK3174998 in combination with pembrolizumab in the peripheral blood and to explore the utility of these measures to enrich for clinical efficacy and development of a diagnostic test.	• Assessment of lymphocyte OX40 receptor membrane expression and occupancy by GSK3174998. Measures of immune function in blood (e.g. phenotype, quantity, and activation state of T cells in the periphery, TCR diversity, expression of circulating soluble factors such as cytokines and stress related proteins). Assessment of changes in genomic DNA, gene expression (RNA and protein), (e.g. using cfDNA, exosomes or CTCs), and mutational load.

Objectives	Endpoints
PART 2: Combination GSK3174998 plus pembrolizumab	
Exploratory	
• To evaluate the pharmacodynamic activity of GSK3174998 in combination with pembrolizumab in the tumor microenvironment and to explore the utility of these measures to enrich for clinical efficacy and development of a diagnostic test.	• Assessment of tumor biopsies via IHC for the numbers of tumor-infiltrating lymphocytes and other immune cells expressing key phenotypic markers. Changes in gene expression (RNA and protein), TCR diversity, or mutational load (genomic DNA).
• PGx: To evaluate the association of genetic variations in the host DNA and response to therapy or disease characterization.	• Germline genetic evaluations may be conducted for: • Medicine response, including GSK3174998 and pembrolizumab or any concomitant medicines. • Disease susceptibility, severity, and progression and related conditions.
Hypothesis	
For the primary objective, no formal statistical hypothesis will be tested; analysis will be descriptive and exploratory	

a. In the final determination of the MTD, all available safety and tolerability data will be considered
b. Unless otherwise specified, all response endpoints will be assessed by RECIST v1.1 and by irRECIST; irRECIST will be used to determine treatment decisions.

RNA = Ribonucleic acid; DNA = Deoxyribonucleic acid

4. STUDY DESIGN

4.1. Overall Design

This is a FTIH, open-label, non-randomized, multicenter study designed to evaluate the safety, tolerability, PK, pharmacodynamics, and preliminary clinical activity of GSK3174998 administered intravenously to subjects with selected advanced or recurrent solid tumors.

The study will be conducted in 2 parts, each part consisting of starting with a dose-escalation phase followed by a cohort expansion phase (see Figure 3). Part 1 will evaluate GSK3174998 monotherapy, while Part 2 will evaluate GSK3174998 in combination with pembrolizumab. As shown in Figure 3, GSK3174998 will first be evaluated as monotherapy in escalating doses. Once a dose of GSK3174998 has been identified that is both tolerable and demonstrates pharmacodynamic activity, enrollment of Part 2 may begin. In Part 2, escalating doses of GSK3174998 will first be evaluated with fixed doses of pembrolizumab. Part 1A and 2A will also include a Pharmacodynamic Cohort, which requires mandatory fresh pre- and on-treatment biopsies and an additional disease assessment at week 6. Part 2 will also include expansion cohorts for specified tumor types.

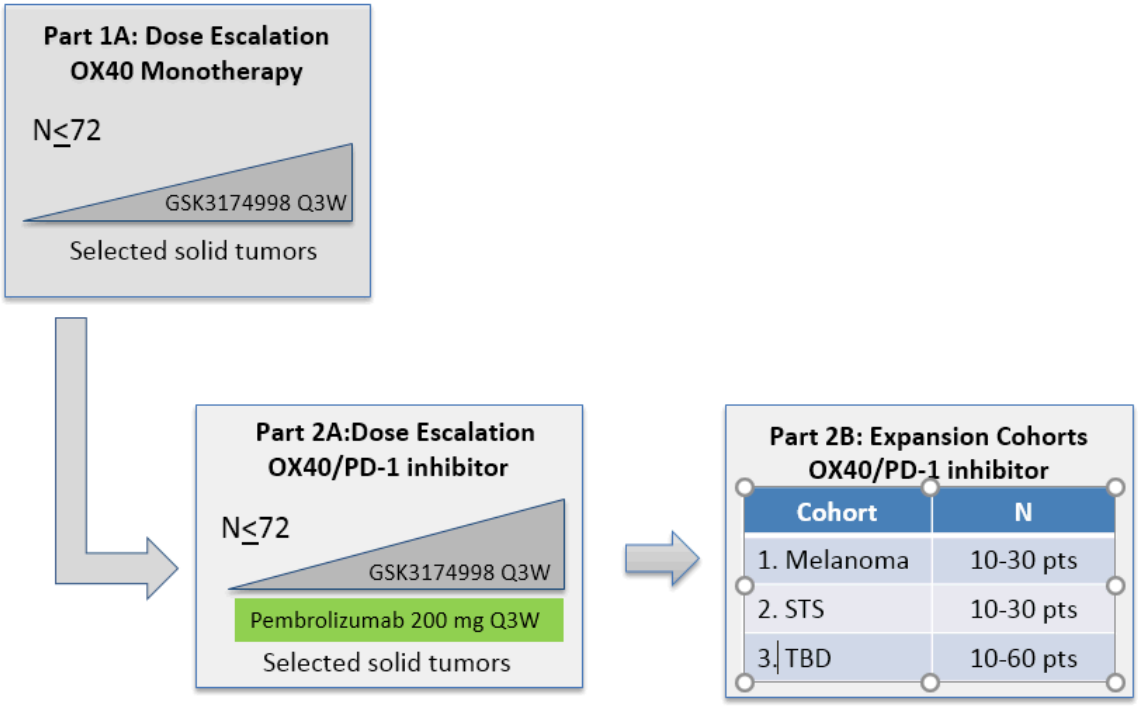
The study will enroll up to approximately 264 subjects with tumor types that may include NSCLC, SCCHN, RCC, melanoma, bladder cancer, STS, TNBC, and MSI CRC. In the dose-escalation phase of the study, subjects with any of the aforementioned tumor types may be included; whereas in the cohort expansion phase of the study, each expansion cohort will enroll subjects with one specific tumor type selected from the aforementioned list.

A subject's disease status and determination of disease progression at postbaseline visits will be evaluated by the local investigators' assessments of radiology by RECIST v1.1 and irRECIST; a decision to discontinue treatment due to disease progression will be based upon irRECIST and the primary endpoint analysis will use irRECIST. Scans will be collected centrally and stored to allow for the option of central radiologic audit or review.

A Steering Committee will be established to review safety, PK, and other clinical data during the course of the study, to provide objective interpretation of study results, and guidance for key decisions. The remit of the Steering Committee will include guidance for the transition of the study from dose-escalation to cohort expansion and from Part 1 to Part 2, the selection of specific tumor types to include in the expansion cohorts, and the selection of the recommended Phase 2 dose (RP2D); the study team will also seek endorsement from GSK Medical Governance for the transition of the study from one part to another. In the final determination of the MTD and RP2D, all available safety and tolerability data will be considered. Pending a review of emerging data from this study and under the guidance of the Steering Committee, the protocol may be subsequently amended to include investigation of additional anticancer agent combinations with GSK3174998. The remit, membership, roles and responsibilities of the Steering Committee are described in a Steering Committee Charter. Key decisions of the Steering Committee will be documented and reported to all participating principal investigators (PIs) and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs).

Figure 3 ENGAGE-1 Study Design

a) Part 1 and Part 2 Design



b) Part 1A and Part 2A Dose Escalation

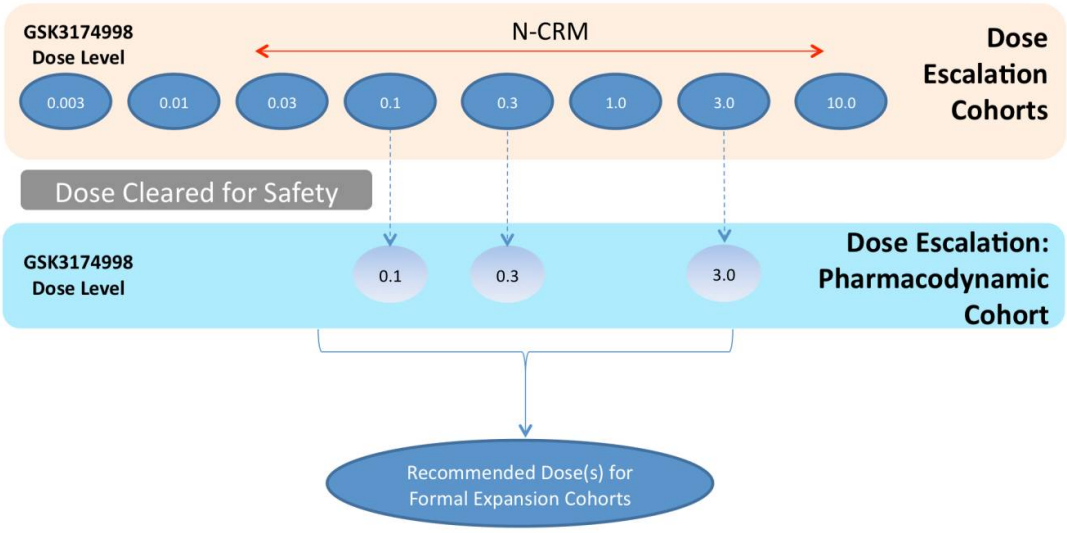


Figure 3a shows the overall study design: Part 1A GSK3174998 monotherapy dose escalation, Part 2A GSK3174998 + pembrolizumab dose escalation, Part 2B GSK3174998 + pembrolizumab cohort expansion. Figure 3b shows dose escalation (Parts 1A and 2A) including the "pharmacodynamic cohort". Note: An example of 3 dose levels being expanded in the pharmacodynamic cohort is provided to illustrate it is possible not all dose levels will be explored in the pharmacodynamic cohort, which mandates pre- and on-treatment tumor biopsies in order to further explore dose-response with biomarkers in the tumor microenvironment.

4.1.1. Dose Escalation

For the first two dose levels (see Table 2), an accelerated titration design is planned with one subject enrolled at each of these dose levels. Each subject must complete the 4 week DLT evaluation period and the available safety data must be reviewed before a decision is made on whether to proceed to the next dose level. If a subject experiences a DLT, then this will trigger the implementation of the modified 3+3 design as shown in Table 1. If a subject withdraws from the study before the completion of the 4 week DLT evaluation period for reasons other than DLT, the subject will be replaced.

For subsequent dose levels, a modified 3+3 design will be used for dose escalation as shown in Table 1. The first three subjects treated at the third dose level will begin treatment 1 week apart to allow assessment of initial safety data in each subject before beginning the next subject's treatment. Evaluation of the available safety data over the first 4 weeks of treatment is required from at least 3 subjects before a decision is made whether to enroll additional subjects at the same, or the next higher dose level. Subjects who withdraw from the study before the completion of 4 weeks treatment and 2 doses for reasons other than DLT may be replaced. After the third dose level cohort is completed, subsequent dose levels may initially enroll up to 4 subjects and subjects will begin treatment at least one calendar day apart.

If 1 of 3 (or 1 of 4) subjects experiences a DLT at a particular dose level, additional subjects will be enrolled at that dose level so that a total of 6 subjects are treated at that dose level. If at least 2 of 6 subjects experience a DLT at a particular dose level, a lower (or intermediate) dose level may be explored to better define the MTD. The Steering Committee may propose that a given dose-escalation cohort be expanded up to a total of 12 subjects if (i) further evaluation of the frequency of a given toxicity is warranted, based upon the observed safety profile in the 6 subjects already recruited in the cohort or (ii) further evaluation of pharmacodynamic markers to aid dose selection is warranted; in either case, the incidence of confirmed DLT must not exceed 33%. Dose-escalation decisions will be documented in writing with copies maintained at each site and the study files.

Table 1 3 + 3 Dose-Escalation Guidelines

Number of Subjects with DLT at a Given Dose Level	Action[a]
0 out of 3 subjects	Escalate to next dose level and enter 3 subjects
1 out of 3 subjects	Accrue 3 additional evaluable subjects at current dose level for a total of 6 evaluable subjects
1 out of 6 subjects	Escalate to next dose level
2 or more subjects in a dosing cohort (up to 6 subjects)	Dose escalation will be stopped. At this dose level, the MTD has been exceeded (highest dose administered).

a. The Steering Committee may propose that a given dose-escalation cohort be expanded up to a total of 12 subjects if (i) further evaluation of the frequency of a given toxicity is warranted, based upon the observed safety profile in the 6 subjects already recruited in the cohort or (ii) further evaluation of pharmacodynamic markers to aid dose selection is warranted; in either case, the incidence of confirmed DLT must not equal or exceed 33%.

DLT = Dose-limiting toxicity; MTD = Maximum tolerated dose

In alignment with the guidance prospectively established in the Protocol (see above), the Steering Committee proposed that dose-escalation cohorts be expanded up to a total of 12 subjects in order to further evaluate pharmacodynamic markers to aid dose selection. This proposal was agreed and implemented at the time of opening Cohort 4 (0.1 mg/kg) and documented in writing. Since the incidence of confirmed DLT must not exceed 33% in this study, the recommended dose from a Continuous Reassessment Method (N-CRM) analysis [Neuenschwander, 2008] will be calculated (as prospectively described in Section 9.3). The N-CRM is a type of Bayesian adaptive dose-escalation scheme. The method is fully adaptive and makes use of all the DLT information available at the time of each dose assignment.

From Part 1 Cohort 4 (0.1mg/kg) onwards and for all Part 2 dose levels, each dose level may initially enroll up to 4 subjects. Once at least 3 of these subjects have completed the DLT evaluation period (4 weeks), a decision may be made to initiate the next higher dose level, pending the evaluation of safety data using the N-CRM methodology. Subjects identified as eligible for enrollment after the enrollment of 4 subjects in current dose level and before next higher dose level is open may be assigned to a lower dose level.

A maximum of 12 subjects will be enrolled at any given dose level in Part 1A and Part 2A; up to 6 of these subjects at any given dose level may be part of a "Pharmacodynamic Cohort" (Figure 3). Subjects entering the "Pharmacodynamic Cohort" will have the following additional eligibility requirements (as described in Section 5.1):

- Mandatory fresh biopsy collection at baseline, on treatment (at 6 weeks), and if feasible at the time of disease progression

- Additional 6-week disease assessment and availability of a pre-baseline scan (within 24 weeks before the baseline scan), if feasible, to support exploratory investigation of tumor growth kinetics

Exploration of lower dose levels than recommended by N-CRM (or expansion of a previously-tested dose level) is allowed if agreed upon by the Medical Monitor and treating investigators. The final dose escalation decision will be made by study team on all available data, including biomarker and PK data and the safety profile of prior cohorts. Dose-escalation decisions will be documented in writing with copies maintained at each site and the study files.

4.1.2. Part 1A: Monotherapy Dose Escalation

Dose escalation for GSK3174998 monotherapy will begin with a starting dose of 0.003 mg/kg GSK3174998 administered Q3W (see Section 4.5). Table 2 illustrates the maximum dose that may be selected for each dose level increase. The maximum increase in dose is 3.33-fold or less. Dose levels intermediate to those in Table 2, or schedules other than once every three weeks may be explored if exposure is significantly higher than predicted, if there is excessive toxicity, or if further evaluation of pharmacodynamic markers to aid dose selection is warranted.

Table 2 Part 1A Dose Levels

Dose Level	GSK3174998 (mg/kg)[a]	Dose Escalation Cohort (n)	Pharmacodynamic Cohort (n)
1	0.003	1	≤6
2	0.01	1	≤6
3	0.03	3-6	≤6
4	0.1	3-6	≤6
5	0.3	3-6	≤6
6	1.0	3-6	≤6
7	3.0	3-6	≤6
8	10.0	3-6	≤6

a. Lower dose intensities may be explored if exposure is significantly higher than predicted, if there is excessive toxicity, or if further evaluation of pharmacodynamic markers to aid dose selection is warranted. This may be achieved by reducing the dose or by alternate dosing schedules.

4.1.3. Part 2A: Combination Dose Escalation (GSK3174998 + Pembrolizumab)

Dose escalation for GSK3174998 + pembrolizumab combination therapy will begin with a fixed dose of 200 mg pembrolizumab administered Q3W and a starting dose of 0.003 mg/kg GSK3174998.

GSK3174998 dose levels that may be administered in combination with pembrolizumab are described in Table 3.

Table 3 Part 2A Dose Levels

Dose Level	GSK3174998 (mg/kg)	Pembrolizumab (mg)	Dose Escalation Cohort (n)	Pharmacodynamic Cohort (n)
1	0.003	200	3-6	≤6
2	0.01	200	3-6	≤6
3	0.03	200	3-6	≤6
4	0.1	200	3-6	≤6
5	0.3	200	3-6	≤6
6	1.0	200	3-6	≤6
7	3.0	200	3-6	≤6
8	10.0	200	3-6	≤6

If the combination doses in the starting dose cohort of Part 2A are not tolerable, lower dose intensities of GSK3174998 may be evaluated in combination with 200 mg pembrolizumab. This may be achieved by reducing the dose or alternate dosing schedules. The dose of pembrolizumab will remain fixed at 200 mg throughout the study.

Dose escalation will proceed until the MTD or MAD of the combination regimen is identified, as described in Section 4.1.1. Dose-escalation decisions will take into account all available data, including the safety profile of prior cohorts throughout the time subjects are on study, which will be reviewed by the investigator(s), GSK Medical Monitor, pharmacokineticist, and statistician. The dose-escalation decision for the

subsequent cohort and rationale will be documented in writing with copies maintained at each site and the study files.

Any cohort may be expanded beyond the 3 to 6 subjects enrolled during dose escalation, to a maximum of 12 to facilitate collection of additional safety, PK, and pharmacodynamic data (Figure 3). A total of up to 12 subjects may be treated at the dose of GSK3174998 selected for Parts 1B and 2B to better characterize the safety, PK, and pharmacodynamic data at that dose, before opening the Dose-Expansion phase.

4.1.4. Dose-Limiting Toxicity

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

An AE is considered to be a DLT if it is considered by the investigator to be clinically relevant and attributed (definitely, probably, or possibly) to the study treatment during the first 4 weeks (i.e., 28 days) of treatment and meets at least one of the criteria listed in Table 4. If an AE is considered related to the underlying disease it is not a DLT. For Part 2, ≥Grade 3 toxicities that are known to occur with pembrolizumab and are controlled within 2 weeks using the recommended supportive measures (see Section 6.3.1) may not be considered dose-limiting.

Table 4 Dose-Limiting Toxicity Criteria

Toxicity	DLT Definition
Hematologic	• Febrile neutropenia • Grade 4 neutropenia of >7 days' 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 toxicity that does not downgrade to Grade 1 or baseline within 3 days despite optimal supportive care.[a] • Any Grade 2 ocular toxicity requiring systemic steroids, or any ≥ Grade 3 ocular toxicity
Other	• Toxicity that results in permanent discontinuation of GSK3174998 or GSK3174998 and pembrolizumab during the first 4 weeks of treatment • Any other toxicity considered to be dose-limiting that occurs beyond 4 weeks will be considered in the selection of the dose 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 management guidelines described in Section 6.3.1 for toxicity and may include systemic corticosteroids for immune-related toxicities; if use of systemic corticosteroids delays administration of the second dose of study treatment but the event does not otherwise meet the DLT criteria for non-hematologic toxicity, the dose delay will not be considered a DLT.

DLT = Dose-limiting toxicity; G-CSF = Granulocyte colony-stimulating factor; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; ULN = Upper limit of normal; GSK = GlaxoSmithKline

If a subject experiences a DLT in the first 4 weeks of treatment, the subject will be discontinued from study therapy unless the investigator considers it in the best interest of the subject to continue on study (e.g., in case of tumor regression, symptomatic disease improvement, and/or if the type of DLT is viewed as preventable in subsequent cycles, e.g., by pre-medication). Such cases will require approval by the Sponsor before continuation on study treatment at the same or lower dose.

Guidance for the management of toxicity, including dose modification algorithms, is provided in Section 6.3.1 and is based on the experience of management of immune-related adverse events (irAEs) since the development of ipilimumab and PD-1 inhibitors such as pembrolizumab.

4.1.5. Cohort Expansion

In accordance with the Steering Committee Charter and based upon a review of pertinent data with input from the study team and investigators, the Steering Committee recommended initiation of Part 2B expansion cohorts, including the selection of tumor types and the dose of GSK3174998 to be administered to subjects who enter the expansion cohorts as described below. Criteria considered in the determination of which dose level(s) to expand and which tumor types to select for cohort expansion included:

- **Target engagement and PK:** Observed OX40 receptor occupancy and GSK3174998 exposure.
- **Safety and tolerability:** The frequency of DLT, and frequency and severity of treatment-related AEs.
- **Clinical activity:** Evidence of clinical response, including SD of at least 12 weeks and/or minor responses.

The preliminary clinical data supporting initiation of the expansion cohorts are summarized in Section 2.3.5.

The initial expansion cohorts in Part 2B will evaluate one dose level of 0.3 mg/kg GSK3174998 (see Section 4.5.3) in tumor types where confirmed response or prolonged SD (≥12 weeks) was observed in Part 1A or 2A of this study. Tumor types selected for initial evaluation in expansion cohorts are melanoma and dedifferentiated liposarcoma (see Table 5). Additional tumor types may be included in Part 2B in accordance with existing inclusion/exclusion criteria. A maximum of approximately 120 subjects will be included in Part 2B.

Table 5 Part 2B Expansion Cohorts

	Population	Prior PD-(L)1 Treatment	GSK3174998 Dose	N
Study Part 2B	Melanoma	Yes	0.3 mg/kg	10-30
	Dedifferentiated liposarcoma[a]	No	0.3 mg/kg	10-30
	Additional tumor types [b]	TBD	TBD	10-60

a. Dedifferentiated liposarcoma will be the initial target; however, additional sarcoma sub-types may be included
b. Any of the tumor types studied in Part A (may be enriched for selected biomarkers if validated biomarker selection assays are available)

Subsequent expansion cohorts are anticipated to receive 0.3 mg/kg GSK3174998, unless emerging data from Parts A or B of the study support further exploration of an alternative tested dose. These cohorts may include any of the tumor types studied in Part A, including additional subtypes of STS, and may be enriched for selected biomarkers if validated biomarker selection assays are available (e.g., PD-(L)1 expression, OX40 expression on selected T cell populations, high mutational load, etc). The selection of any additional dose level(s) or dosing schedules and tumor types for cohort expansion will be communicated to the sites in writing.

A minimum of 10 subjects will be enrolled in each cohort. Until implementation of Amendment 4, the first futility analysis of each expansion cohort was planned to occur after approximately 10 subjects are enrolled for whom overall response data at approximately week 12 was available. After implementation of Amendment 4, no further subjects were enroled in the study, and no futility analyses were performed.

Until implementation of Amendment 4, for any of the expansion cohorts tested, if the observed clinical benefit appeared to be associated with specific patient characteristics and/or biomarkers, a new cohort may have been opened for further investigation with subjects enriched with these specific patient characteristics and/or biomarkers. After implementation of Amendment 4, no further subjects were enroled in the study.

Expansion cohorts will require mandatory fresh pre- and on-treatment biopsies (see Section 7.6.2) and an additional disease assessment at Week 6. This disease assessment is timed to coincide with the on-treatment (Week 6) tumor biopsy. If feasible, the disease assessment should be performed after the tumor biopsy.

4.1.6. Intra-Subject Dose Escalation

There will be no intra-subject dose escalation.

4.2. Treatment Arms and Duration

The study includes a screening period, a treatment period, and a follow-up period. Subjects will be screened for eligibility beginning approximately 4 weeks before the start of treatment. The maximum duration of treatment with GSK3174998 and pembrolizumab will be 2 years (Table 6) or 35 cycles whichever comes first. The follow-up period for safety assessments will be a minimum of 3 months from the date of the last dose. The post-treatment follow-up period includes disease assessments every 12 weeks until documented PD. Following PD, subjects will be contacted every 3 months to assess survival status.

With the implementation of Amendment 04, there will be no requirement to perform future disease assessments or survival follow-up.

Table 6 Study Treatments

Study Part	Study Treatment
Part 1: GSK3174998 Monotherapy	
1A – Dose escalation	GSK3174998 IV[a] Q3W for up to 2 years or 35 cycles, whichever comes first
Part 2: GSK3174998 in combination with pembrolizumab	
2A – Dose escalation	GSK3174998 IV[b] Q3W for up to 2 years or 35 cycles, whichever comes first Pembrolizumab 200mg IV Q3W for up to 2 years or 35 cycles, whichever comes first
2B – Cohort expansion	GSK3174998 IV[b] Q3W for up to 2 years or 35 cycles, whichever comes first Pembrolizumab 200 mg IV Q3W for up to 2 years or 35 cycles, whichever comes first

a. For dose levels see Table 2.
b. For dose levels see Table 3.
Alternative dosing schedules may be explored if the data warrants. This will be communicated to the sites in writing prior to implementation.
IV = Intravenous; Q3W = Every 3 weeks

4.3. Type and Number of Subjects

The number of dose levels and the level at which the MTD is reached cannot be determined in advance. An adequate number of subjects will be enrolled into the study to establish the recommended dose(s) for further study. It is estimated that a total of up to approximately 264 subjects will be enrolled in this two-part study (approximately 144 subjects in Parts 1A and 2A [dose escalation]; approximately 120 subjects in Part 2B [cohort expansion]).

In Parts 1A and 2A, if a subject prematurely discontinues before the completion of 4 weeks treatment, for reasons other than DLT, a replacement subject may be enrolled at the discretion of the Sponsor in consultation with the investigator. Subjects will not be replaced in Parts 1B and 2B of the study.

4.4. Design Justification

This study evaluates the safety, tolerability, pharmacodynamic effects, and preliminary clinical activity of GSK3174998 as a monotherapy (Part 1) and in combination with anti-PD-1, pembrolizumab (Part 2). The safety, tolerability, and pharmacodynamics of monotherapy GSK3174998 will be evaluated in a modified CRM dose escalation that includes an accelerated titration design for the first two dose levels. The dose escalation will be followed by expansion cohorts in defined subject populations. Dose escalation of GSK3174998 in combination with a 200 mg fixed dose of pembrolizumab will begin at a dose of 0.003 mg/kg GSK3174998 as described in Section 4.5.2.

In order to ensure sufficient safety and pharmacodynamic data were available before beginning enrollment to Part 2 of the study, available clinical data (clinical data cut-off: 17 May 2016; (see Section 2.3.5) from Part 1 of the study, including safety, PK, pharmacodynamics and efficacy, were reviewed by the Steering Committee. The Steering Committee also considered available data for other OX40 agonist antibodies as relevant background information [Hamid, 2016; Hansen, 2016; Infante, 2016]. GSK Medical Governance reviewed the same data as the Steering Committee and endorsed initiation of Part 2 of the study. The decision to initiate Part 2 was documented and reported to all participating PIs and IRBs/ IECs.

In the dose escalation phase, subjects will be enrolled with selected solid tumors that are likely to respond to anti-OX40 therapy (e.g., indications previously reported to have a response to immunotherapies, predicted immunogenicity, and/or expression of OX40). The tumor types to be evaluated in dose escalation are as follows: NSCLC, SCCHN, RCC, melanoma, bladder cancer, STS, TNBC, and MSI CRC.

Almost all of these histologies have demonstrated prior response to anti-CTLA-4 and/or anti-PD-1/PD-L1 therapies [Zamarin, 2015]. In addition, gene expression data [TCGA, 2014] suggest that all of these tumor types have at least moderate expression of OX40.

The inclusion of the combination with pembrolizumab is based on the preference to identify potential transformational activity early in development. Although GSK3174998 is expected to have meaningful clinical activity as a monotherapy, the full potential of the molecule is likely to be discovered in combination with other agents, particularly immunotherapies. Pembrolizumab is an ideal combination partner for GSK3174998 because it targets a different aspect of the cancer-immunity cycle, has a toxicity profile of mainly Grade 1 or 2 events, and preclinical data strongly supports the potential for synergy.

Recently reported data with OX40 agonists and other TNFR agonists [Hamid, 2016; Hansen, 2016; Infante, 2016] has highlighted the importance of understanding the impact of treatment with these agents on the tumor microenvironment. To date TNFR agonist antibodies appear to saturate receptors in the periphery at low doses, be well-tolerated,

have demonstrated biological effects in the tumor microenvironment in some but not all tumors where serial fresh biopsies were available (e.g., increased CD8 infiltration, decreased Tregs), and have demonstrated modest clinical activity. In order to better understand dose-response and variables that may influence clinical response to treatment with GSK3174998 alone or in combination with pembrolizumab, it is critical that immune biomarkers in the tumor microenvironment are assessed in this study across a range of doses and, if feasible, correlated with clinical response. In alignment with the guidance prospectively established in the Protocol, the Steering Committee proposed that dose-escalation cohorts be expanded up to a total of 12 subjects in order to further evaluate pharmacodynamic markers to aid dose selection. In order to address the need to explore the potential relationships between dose, biological effects in the tumor microenvironment, and tumor response, a "pharmacodynamic cohort" is included in each of the dose-escalation parts of the study (Part 1A and Part 2A). In order to be eligible to be enrolled in the pharmacodynamic cohorts, subjects must consent to mandatory fresh biopsy collection at baseline, on treatment (at 6 weeks), and if feasible at the time of disease progression. An additional disease assessment (at 6 weeks) and availability of a pre-baseline scan (within 24 weeks before the baseline scan), if feasible, will support exploratory investigation of tumor growth kinetics in this cohort.

4.5. Dose Justification

4.5.1. Part 1: Starting Dose

According to the International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)S9 guidance, calculating a starting dose based on 1/6 of the highest non-severely toxic dose (HNSTD) in the most relevant species (cynomolgus monkey) yields a starting dose of ~16 mg/kg/week. By determining the minimum anticipated biological effect level (MABEL), a more conservative starting dose of 0.003 mg/kg GSK3174998 Q3W was selected as a safe starting dose for this FTIH study. The projected human GSK3174998 exposure predicted by cynomolgus monkey PK, GSK3174998 binding characteristics, and OX86 efficacy data in mouse, as well as consideration of prior clinical experience with agonizing the OX40 pathway also factored into the selection of the starting dose.

Predicted exposure: The PK of GSK3174998 was assessed in several cynomolgus monkey studies, with single and repeat doses ranging from 0.03 mg/kg to 100 mg/kg; GSK3174998 exposure was approximately dose-proportional. Across the dose levels tested, PK profiles did not demonstrate any evidence of target-mediated disposition. These results suggest that allometric methods are appropriate to predict human PK; furthermore, human PK of GSK3174998 is expected to be similar to PK of mAbs of the same isotype. Assuming a plasma volume of 3L for a 70 kg subject, a Cmax of 0.07 μg/mL is predicted for a dose of 0.003 mg/kg.

Nonclinical safety: In repeat-dose toxicology studies, GSK3174998 was well tolerated in cynomolgus monkeys following weekly IV dosing for up to 4 weeks at doses ranging from 0.03 to 100 mg/kg/week. In these studies, there were no test article related changes, including those associated with T-cell modulation. The NOAEL was determined to be

100 mg/kg/week, the highest dose tested, which is well above the proposed clinical starting dose regardless of the method for computing the human equivalent dose (HED).

Potential for severe cytokine release: Several lines of investigation were followed to assess the potential of GSK3174998 to induce an excessive cytokine response as observed for super agonist TGN1412. *In vitro* and ex vivo data show that OX40 is expressed on only a small proportion of T cells, i.e., recently activated effector and regulatory T cells in blood and tissues such as lymph node and spleen. Moreover, stimulation through the TCR and CD28 pathways is required for optimal T-cell activation with OX40 agonism. A range of conditions were explored *in vitro* to assess the potential of GSK3174998 to induce cytokine release. In some assays, no evidence of cytokine release was observed; however, under the most sensitive assay conditions using immobilized GSK3174998 in pre-activated CD4+ T cells, increased cytokine production (IL-2, IFNγ, and tumor necrosis factor alpha [TNF-α]) was observed. *In vivo* cytokine monitoring in repeat dose monkey toxicology studies (doses of 0.03-100 mg/kg) and the CT26 mouse tumor model did not demonstrate excessive cytokine release. These data suggest that GSK3174998 is not a super agonist and has a low potential for severe cytokine release syndrome (sCRS).

MABEL determination: The MABEL assessment is based on receptor occupancy as characterized by *in vitro* binding experiments with primary human target cells. Using receptor occupancy as a surrogate for biological activity is appropriate as receptor occupancy provides a general characterization of GSK3174998 signaling in target cells and since individual biological effects of GSK3174998 are not yet prioritized in terms of their impact on subject safety. The binding of GSK3174998 to its ligand and target cells was characterized in several experiments yielding different binding coefficients depending on the degree of cellular activation and OX40 expression.

OX40 expression in blood is limited to the small subset of recently activated CD4+ and CD8+ cells [Croft, 2010]. In ex vivo studies, the frequency of OX40+ T-cells in human blood or PBMC cultures from healthy volunteers ranged from <1% [GlaxoSmithKline Document Number 2014N222697_00] to 25% [GlaxoSmithKline Document Number 2014N219733_00]. Also in cancer patients, lower OX40 expression was observed in peripheral blood compared to tumor sites and draining lymph nodes [Vetto, 1997]. Based on these findings, the unstimulated human whole-blood binding assay, which exhibited a low but quantifiable level of OX40 binding, was considered most representative for the OX40 response in peripheral blood and was selected to determine the MABEL. GSK3174998 was shown to bind to lymphocytes in whole blood in a concentration-dependent manner with an EC50 value of 1.45 µg/mL (pooled data derived from 4 donors) [2014N219733_00]. Using the Cmax of 0.07 µg/mL predicted for the first 0.003 mg/kg dose, a receptor occupancy of 5% is predicted based on the binding to lymphocytes in human whole blood (the MABEL dose corresponding to 10% receptor occupancy in this experiment is 0.007 mg/kg). Note, that the receptor occupancy calculations here and below assume that the difference between free and total GSK3174998 is negligible, i.e. receptor occupancy = Cmax/(EC50 + Cmax). This approach yields higher receptor occupancy and more conservative dose estimates compared to an approach which assumes a specific level of target expression.

OX40 expression in certain tissues may be higher than observed in peripheral blood; for example, in the spleen and additionally in the microenvironment of a tumor. In normal cynomolgus monkeys, where GSK3174998 was well tolerated, a frequency of 2-30% of OX40+ lymphocytes was detected in lymphoid tissue (spleen) [2014N213593_00]. In the tumor and draining lymph nodes of cancer patients the frequency of activated CD4+/OX40+ T-cells was reported to be up to 30% in tumor and draining lymph node samples compared with 0% in peripheral blood [Vetto, 1997]. Data from stimulated OX40 binding experiments, in which cells are activated and OX40 expression is highly upregulated, are therefore expected to be more representative for the OX40 response to GSK3174998 in tumor and draining lymph node tissues. For stimulated PBMC half-maximal binding was typically achieved between 0.1 µg/mL to 0.3 µg/mL and similarly, GSK3174998 bound to activated human CD4+ T cells with a mean EC50 value of 0.19 µg/mL [2014N219733_00]. Monoclonal antibody concentrations in peripheral tissues are expected to be substantially lower than time-matched concentrations in serum [Tabrizi, 2010; Shah, 2013]. Assuming an antibody biodistribution coefficient of 25% [Shah, 2013] for a given tumor tissue, the peak concentrations are expected be ≤0.018 µg/mL resulting in ≤8% receptor occupancy when using a binding EC50 of 0.2 µg/mL for the stimulated PBMC or CD4+ T cell assays. Applying the stimulated binding EC50 of 0.2 µg/mL to the Cmax of 0.07 µg/mL in peripheral blood yields predicted receptor occupancy of 26%. However, this prediction is not considered representative of the clinical OX40 response as the stimulated assays had much larger degrees of cellular activation than would be expected in patient blood.

In summary, the starting dose of 0.003 mg/kg is expected to result in less than 10% occupancy of OX40 receptors in blood (based on unstimulated binding experiments) and tumor tissues and draining lymph nodes (based on stimulated binding experiments), which is generally assumed a safe level of receptor engagement for immune agonists.

Clinical experience with OX40 agonism: Clinical experience with MEDI6469 did not show cytokine release syndrome (CRS) or other severe toxicity in subjects dosed with single cycles of 0.1 to 2 mg/kg of the antibody [Curti, 2013]. MEDI6469 did not show a significant dose-dependent difference in efficacy for single cycles of 0.1, 0.4, and 2 mg/kg dose levels. Maximal biological activity as defined by stimulation of T-cell proliferation measured by changes in Ki-67 expression in response to MEDI6469 dosing was achieved at the 0.4 mg/kg dose level. With an EC50 of 0.048 µg/mL for binding as measured by ELISA [Curti, 2013], the potency of MEDI6469 appears to be comparable to (or possibly higher than) that of GSK3174998. Using the same approach as specified above to predict Cmax and binding, the starting dose of 0.1 mg/kg MEDI6469 with a binding constant of 0.048 µg/mL [Curti, 2013] leads to a predicted receptor occupancy of 98% in the central circulation at Cmax, further supporting the starting dose of GSK3174998 of 0.003 mg/kg.

Potential for clinical benefit: Efficacy for agonizing the OX40 pathway has been assessed with an anti-OX86 antibody, a surrogate mAb to murine OX40. In the CT26 mouse colon cancer model, robust efficacy was observed at doses as low as 5 µg per mouse in the most sensitive experiments (Figure 1b). Assuming similar potency between anti-OX86 and GSK3174998, the HED is estimated to be 0.015 or 0.027 mg/kg assuming that AUC drives efficacy and using a clearance based scaling approach with allometric

scaling exponents of 0.67 (body surface area normalization) or 0.75 (quarter power scaling) for systemic clearance and mouse and human weights of 0.025 kg and 70 kg, respectively. Assuming that Cmax drives efficacy and using a volume of distribution based scaling approach the HED is estimated to be 0.2 mg/kg assuming an allometric scaling exponent of 1 for volume of distribution. The starting dose is therefore predicted to lie at the lower end of the predicted therapeutic dose range in subjects.

Dosing frequency: In a clinical study with MEDI6469 a key biomarker, Ki-67 expression on T cells exhibited maximal stimulation at about 14 days after the first dose [Curti, 2013]. The Ki-67 stimulation declined by about 28 days after the first dose (or 23 days after the last dose in the cycle). Guided by these biomarker dynamics and the expectation of standard IgG1 mAb PK (terminal elimination half-life longer than 2 weeks), a dosing frequency of Q3W for GSK3174998 was chosen. This dosing frequency also increases subject convenience for administration with the planned combination partner pembrolizumab which is also dosed Q3W per label.

In summary, the proposed 0.003 mg/kg starting dose of GSK3147998 Q3W in study 201212 is anticipated to be safe and tolerable. Subjects will undergo extended clinical observation following GSK3174998 dosing and other measures to monitor and treat all subjects for any possible excessive cytokine release.

4.5.2. Part 2: Starting Dose

No drug-drug interaction affecting the PK for the combination is expected for GSK3174998 and pembrolizumab. As a checkpoint inhibitor rather than a direct immune-stimulator pembrolizumab is not expected to substantially increase the potential for excessive cytokine release in response to GSK3174998, but specific synergies cannot be excluded a priori. In the CT26 mouse efficacy experiments, no differences with regard to indicators of excessive immune stimulation were noted in the anti-PD-1 combination versus the OX86 monotherapy groups at all the dose levels tested. Similar to monotherapy, robust efficacy was seen for OX86 doses as low as 5 µg per mouse (in combination with 200 µg anti-PD-1 mouse homolog) and combination dosing was well tolerated.

The starting dose of GSK3174998 for the Part 2/Combination Dose-Escalation phase was planned to be at least 2 dose levels below a dose that has been shown to be tolerated during the monotherapy dose escalation. This determination was based on an allowance that a 10-fold lower dose of GSK3174998 should provide a sufficient safety margin when pembrolizumab is added. Using these criteria, data from Part 1 Cohort 3 (0.03 mg/kg), with a clinical data cut-off of 17 May 2016, supported a Part 2 starting dose of 0.003 mg/kg GSK3174998. The 0.03 mg/kg dose level was tolerated and transient peripheral OX40 receptor saturation was observed in 3 of 4 subjects with the fourth subject having 100% OX40 receptor saturation throughout the first dosing period (21 days). These data were reviewed by the Steering Committee and GSK Medical Governance (as described in Section 4.4) and are briefly summarized in Section 2.3.5 of the protocol. The dose of pembrolizumab will be 200 mg IV Q3W (see Section 2.4.2).

4.5.3. Dose Rationale for Cohort Expansion (Part 2B)

GSK3174998 will be administered intravenously at a dose of 0.3 mg/kg once every 3 weeks (Q3W) on Day 1 of each 21-day cycle in combination with 200 mg pembrolizumab Q3W.

For GSK3174998 doses of 0.3 mg/kg and higher peripheral receptor occupancy saturation over the whole dose interval was observed. Peripheral OX40 receptor occupancy on circulating CD3+ T cells, provides a measure of target engagement. While the relationship between the extent of peripheral receptor occupancy and clinical response has not been established, clinical activity was observed in Part 1A at this dose level for monotherapy. In Part 2A, clinical responses were reported at GSK3174998 dose levels 0.01 to 0.3 mg/kg in combination with pembrolizumab at the time of the clinical data cut off (13 August 2019). Please refer to the GSK3174998 Investigator's Brochure for further details [2014N212091_06].

Safety data were reported for the full dose range of GSK3174998 monotherapy (0.003 to 10 mg/kg) and for GSK3174998 (0.003 to 10 mg/kg) when administered in combination with pembrolizumab 200 mg at the time of the clinical data cut-off (13 August 2019). No DLTs were reported for monotherapy. Two DLTs (pleural effusion and myocarditis) were reported in the combination setting. Out of 9 subjects dosed at GSK31748998 0.03 mg/kg + pembrolizumab, one DLT of pleural effusion was reported. Out of 4 subjects dosed at GSK3174998 10 mg/kg + pembrolizumab, one DLT of myocarditis was reported. Overall, there did not appear to be a dose-relationship for AEs and the 0.3 mg/kg dose level for the combination treatment was well tolerated. Safety data are described in more detail in the Investigator's Brochure [2014N212091_06].

In summary, the 0.3 mg/kg GSK3174998 dose level was well tolerated during dose escalation, demonstrated target engagement on circulating T cells and clinical activity was observed at this dose level for both monotherapy and in combination with pembrolizumab.

4.6. Benefit:Risk Assessment

Summaries of findings from nonclinical studies conducted with GSK3174998 can be found in the IB [2014N212091_06]. The following section outlines the risk assessment and mitigation strategy for this protocol.

In toxicology studies performed in monkeys with GSK3174998, no adverse effects were observed. Additionally, nonclinical data with GSK3174998 and a rat surrogate antibody in mouse models do not suggest CRS as a significant concern (limitations of nonclinical models are recognized).

Another agonistic anti-OX40 antibody was previously administered in subjects without evidence of severe cytokine release [Curti, 2013]. MEDI6469 (mouse IgG1 mAb currently being developed by Medimmune/AZ) was very well tolerated for doses of 0.1 to 2 mg/kg (single cycle of 3 doses per week), with transient lymphopenia and Grade 1/2

flu-like symptoms as primary toxicities. The proposed starting dose for GSK3174998 is well below those administered in the study using MEDI6469.

In addition, OX40 is expressed on a small proportion of T cells, primarily recently activated effector T cells and Tregs. This significantly limits the potential for sCRS. OX40 is not a super agonist and requires stimulation through TCR and CD28 for optimal T-cell activation.

Due to the mechanism of action of GSK3174998, toxicities commonly associated with other immune-modulating agents such as checkpoint inhibitors may also occur after administration of GSK3174998. However, these toxicities were not seen in nonclinical models. Table 7 outlines the risk assessment and mitigation strategy for this protocol.

4.6.1. Risk Assessment GSK3174998 ± Pembrolizumab

Table 7 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hypersensitivity reaction	• Risk for infusion reactions and hypersensitivity is inherent to many mAbs [Brennan, 2010]	Subjects Severe hypersensitivity to another mAb are not eligible for participation in this study See Section 6.3.1.3
Severe cytokine release syndrome (sCRS)	OX40 is a costimulatory receptor that can stimulate proliferation and activation of T cells GSK3174998 is an OX40 agonist that can costimulate T-cell activation in the context of TCR signal and CD28 cosignal. An anti-CD28 super agonist (TGN1412) induced rapid-onset catastrophic CRS in 6 healthy volunteers	See Section 6.3.1.3
Other immune-related AEs	Inflammatory AEs such as diarrhea/colitis, pneumonitis, and hepatotoxicity are well established after treatment with immune-modulating agents, and are consistent with the immune-stimulatory mechanism of action of these agents.	Subjects with the following medical history are not eligible for participation in this study Toxicity (≥Grade 3) related to prior immunotherapy leading to study treatment discontinuation Severe hypersensitivity to another mAb See Section 6.3.1.1

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Embryo-fetal toxicity	Currently there are a number of monoclonal antibodies targeting immune checkpoints approved for use in humans (e.g., ipilimumab, nivolumab, durvalumab and pembrolizumab). These agents have embryo-fetal toxicity documented in the Warnings and Precautions section of the USPI and in Section 4.6 of the EU-SPC. This risk has been identified in a variety of animal species (generally cynomolgus monkeys or experiments in mice with PD-(L)1 antagonism), and link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. Human IgG4 (immunoglobulins) are known to cross the placenta; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus. There are no available human data informing the risk of embryo-fetal toxicity.	Advise females of reproductive potential of the potential risk to a fetus. Women of child-bearing potential and their male partners are required to use highly effective contraception as described in Section 5.1
TCR = T-cell receptor; mAb = Monoclonal antibody; AEs = Adverse Events		

4.6.2. Overall Benefit:Risk Conclusion

This is an open-label, dose escalation study and the FTIH study of this agent to be conducted in subjects with relapsed/refractory solid tumors for which no standard therapies are anticipated to result in a durable remission. GSK3174998 has nonclinical activity *in vivo*, however it is unknown whether GSK3174998 will have clinical activity, thus any potential beneficial effect for an individual subject attributable to GSK3174998 is unknown. Data obtained in this study may help identify individuals more likely to benefit or have side effects from GSK3174998. Study participants may benefit from the medical tests and screening performed during the study.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

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

5.1. Inclusion Criteria

Subjects eligible for enrollment in the study must meet all of the following criteria:

1. Provide signed, written informed consent.
2. Male and female subjects, age ≥18 years (at the time consent is obtained).
3. Histological documentation of locally advanced, recurrent or metastatic solid malignancy that has progressed after standard therapy appropriate for the specific tumor type, or for which standard therapy has proven to be ineffective, intolerable, or is considered inappropriate (with the possible exception of the PD-(L)1 naive populations described in inclusion criterion 4). Subjects should not have received more than 5 prior lines of therapy for advanced disease including both standards of care and investigational therapies. Subjects whose cancers harbor molecular alterations for which targeted therapy is standard of care should have received health authority-approved appropriate targeted therapy for their tumor types before enrollment.
4. Subjects with the following solid tumors are eligible for screening: NSCLC, SCCHN, RCC, melanoma, bladder, STS, TNBC, and MSI CRC.

   In Part 2B (Cohort Expansion), specific subgroups of the above solid tumors will be studied. These subgroups may be defined by specific lines of treatment, types of prior treatment, histological subtypes, and may be enriched for selected biomarkers or patient characteristics. Populations to be studied in Amendment 3 include but are not limited to the following. Enrolment of additional populations will be communicated in writing.

   - Subjects with dedifferentiated liposarcoma who have not received prior treatment with a PD-(L)1 inhibitor
   - Subjects with melanoma who have received a prior PD-(L)1 inhibitor, had a CR, PR or SD and subsequently progressed while on PD-(L)1 therapy. Subjects who have received prior treatment with a PD-(L)1 inhibitor must have documented disease progression as defined by meeting all of the following criteria:
     - Has received at least 2 doses of an approved PD-(L)1 inhibitor
     - Has demonstrated disease progression as defined by RECIST v1.1. The initial evidence of disease progression is to be confirmed by a second assessment no less than four weeks from the date of the first documented PD, in the absence of rapid clinical progression.
     - Progressive disease has been documented within 18 weeks from the last dose of the PD-(L)1 inhibitor.
5. In Parts 1A and 2A, a biopsy of the tumor tissue obtained at anytime from the initial diagnosis to study entry. Although a fresh biopsy obtained during screening is preferred, archival tumor specimen is acceptable if it is not feasible to obtain a fresh biopsy.

   Subjects enrolled in Part 1A or Part 2A Pharmacodynamic Cohorts or in Part 2B of the study must provide a fresh biopsy of a tumor lesion not previously irradiated during the screening period and must agree to provide at least one additional on-treatment biopsy. In addition, an archived tumor tissue should be submitted for subjects in Part 2B, if

available.The criterion for collection of fresh biopsies may be waived once GSK has determined an appropriate number of viable tissue samples have been analysed.

6. Measurable disease per RECIST version 1.1 - please refer to Appendix 5. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilized as the only measurable lesion

7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1.
8. Life expectancy of at least 12 weeks.
9. Adequate organ function (see Table 8):

Table 8 Definitions for Adequate Organ Function

System	Laboratory Values
Hematologic	
ANC	≥1.5x10^9/L
Lymphocyte count	≥800/mm^3
Hemoglobin	≥9 g/dL
Platelets	≥100x10^9/L
Hepatic	
Total bilirubin *For subjects with Gilbert's Syndrome (only if direct bilirubin ≤35%)*	≤1.5xULN *≤3.0xULN*
Part 1A and 2A: ALT	≤1.5xULN
Part 2B: ALT	≤2.5xULN
Renal	
Serum Creatinine **OR** Calculated CrCl[a]	≤1.5xULN > 50 mL/min
Endocrine	
TSH[b]	WNL

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

a. Estimated CrCl should be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (see Appendix 12) or per institutional standard.
b. If TSH is not within normal limits at baseline, the subject may still be eligible if total T3 or free T3 and free T4 are within the normal limits.

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

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

11. In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.
12. Female subject: is eligible to participate if she is not pregnant (as confirmed by a negative serum beta-human chorionic gonadotrophin (β-hCG) test), not lactating, and at least one of the following conditions applies:

a. Non-reproductive potential defined as:

- Pre-menopausal females with one of the following:
  - Documented tubal ligation
  - Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
  - Hysterectomy
  - Documented Bilateral Oophorectomy
- Postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels)]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.

b. Reproductive potential and agrees to follow one of the options listed below in the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) requirements from 30 days prior to the first dose of study medication and until 120 days after the last dose of study medication and completion of the follow-up visit.

GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis.

- Contraceptive subdermal implant with a <1% rate of failure per year, as stated in the product label
- Intrauterine device or intrauterine system with a <1% rate of failure per year, as stated in the product label [Hatcher, 2007]
- Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007]
- Injectable progestogen [Hatcher, 2007]
- Contraceptive vaginal ring [Hatcher, 2007]
- Percutaneous contraceptive patches [Hatcher, 2007]
- Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2007].

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The

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

13. Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until 120 days after the last dose of study medication.
    - Vasectomy with documentation of azoospermia.
    - Male condom plus partner use of one of the contraceptive options below:
    - Contraceptive subdermal implant with a <1% rate of failure per year, as stated in the product label [Hatcher, 2007]
    - Intrauterine device or intrauterine system with a <1% rate of failure per year, as stated in the product label [Hatcher, 2007]
    - Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007] Injectable progestogen [Hatcher, 2007]
    - Contraceptive vaginal ring [Hatcher, 2007]
    - Percutaneous contraceptive patches [Hatcher, 2007]

    These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

5.2. Exclusion Criteria

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

1. Prior treatment with the following agents (from last dose of prior treatment to first dose of GSK3174998):
    - TNFR agonists, including OX40, CD27, CD137 (4-1BB), CD357 (GITR): at any time.

      NOTE: Subjects treated in Part 1/monotherapy with GSK3174998 may be enrolled into Part 2/combination with pembrolizumab upon disease progression and upon discussion and approval from the GSK Medical Monitor.
    - Checkpoint inhibitors, including PD-1, PD-L1, and CTLA-4 inhibitors: within 4 weeks. NOTE: Subjects entering the PD-(L)1 naive expansion cohort may not have received any prior PD-(L)1 anti-cancer treatment.
    - Other anticancer therapy, including chemotherapy, targeted therapy, and biological therapy: within 4 weeks or 5 half lives of the drug, whichever is shorter. Prior radiation therapy is permissible if at least one unirradiated measurable lesion is available for assessment via RECIST version 1.1. A wash out of at least two weeks before start of study drug for palliative radiation to the

extremities for osseous bone metastases and 4 weeks for radiation to the chest, brain, or visceral organs is required.

- Investigational therapy: if the subject has participated in a clinical trial and has received an investigational product: within 30 days or 5 half-lives of the investigational product (whichever is shorter). At least 14 days must have passed between the last dose of prior investigational agent and the first dose of study drug. Note: if the agent is a TNFR agonist or a checkpoint inhibitor, the above exclusions take precedence.

2. Prior allogeneic or autologous bone marrow transplantation or other solid organ transplantation.
3. Toxicity from previous treatment:
    - Subjects with ≥Grade 3 toxicity related to prior immunotherapy leading to study treatment discontinuation are not eligible.
    - Subjects whose toxicity related to prior treatment has not resolved to ≤Grade 1 (except alopecia, hearing loss, grade ≤2 neuropathy or endocrinopathy managed with replacement therapy) are not eligible.
4. Malignancy other than disease under study, except as noted below:
    - Any other malignancy from which the subject has been disease-free for more than 2 years and, in the opinion of the principal investigators and GSK Medical Monitor, will not affect the evaluation of the effects of this clinical trial treatment on currently targeted malignancy, can be included in this clinical trial.
5. Central nervous system (CNS) metastases, with the following exception:
    - Subjects who have previously-treated CNS metastases, are asymptomatic, and have had no requirement for steroids for 2 weeks prior to first dose of study drug.

    Note: Subjects with carcinomatous meningitis are excluded regardless of clinical stability.
6. Has received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF], recombinant erythropoietin) within 2 weeks before the first dose of study drug.
7. Major surgery ≤4 weeks before the first dose of study treatment. Subjects must have also fully recovered from any surgery (major or minor) and/or its complications before initiating study treatment.
8. Active autoimmune disease (see Appendix 2) that has required systemic treatment within the last 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
9. Concurrent medical condition requiring the use of systemic immunosuppressive medications within 28 days before the first dose of study treatment. Physiologic

doses of corticosteroids for treatment of endocrinopathies or steroids with minimal systemic absorption, including topical, inhaled, or intranasal corticosteroids may be continued if the subject is on a stable dose.

10. Active infection, known human immunodeficiency virus infection, or positive test for hepatitis B surface antigen or hepatitis C.
11. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver metastases, or otherwise stable chronic liver disease per investigator assessment).

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

12. Known, current drug or alcohol abuse.
13. Recent history (within the past 6 months) of acute diverticulitis, inflammatory bowel disease, intra-abdominal abscess, or gastrointestinal obstruction
14. Receipt of any live vaccine within 4 weeks.
15. Recent history of allergen desensitization therapy within 4 weeks of starting study treatment.
16. History of severe hypersensitivity to other mAbs.
17. History or evidence of cardiovascular risk including any of the following:
    - Recent (within the past 6 months) history of serious uncontrolled cardiac arrhythmia or clinically significant ECG abnormalities including second degree (Type II) or third degree atrioventricular block.
    - Documented cardiomyopathy, myocardial infarction, acute coronary syndromes (including unstable angina pectoris), coronary angioplasty, stenting, or bypass grafting within the past 6 months before enrollment.
    - Documented congestive heart failure (Class II, III, or IV) as defined by the New York Heart Association functional classification system (NYHA, 1994).
    - Recent (within the past 6 months) history of symptomatic pericarditis.
18. Current or history of idiopathic pulmonary fibrosis, interstitial lung disease, or organizing pneumonia. Note: post-radiation changes in the lung related to prior radiotherapy and/or asymptomatic radiation-induced pneumonitis not requiring treatment may be permitted if agreed by the investigator and Medical Monitor.
19. History of (non-infectious) pneumonitis that required steroids or current pneumonitis.
20. Recent history (within 6 months) of uncontrolled symptomatic ascites or pleural effusions.
21. Any serious and/or unstable pre-existing medical, psychiatric disorder, or other condition that could interfere with the subject's safety, obtaining informed consent, or compliance to the study procedures.

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

23. History of severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

5.3. Screening Failures

In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any SAE.

5.4. Withdrawal/Stopping Criteria

5.4.1. Treatment Discontinuation

Subjects will receive study treatment for the scheduled time period, unless one of the following occurs earlier: disease progression (as determined by irRECIST), death, or unacceptable toxicity, including meeting stopping criteria for liver chemistry defined in Section 5.4.2. In addition, study treatment might be permanently discontinued for any of the following reasons:

- Major deviation(s) from the protocol
- Request of the subject or proxy (withdrawal of consent by subject or proxy)
- Investigator's discretion
- Subject is lost to follow-up
- Study is closed or terminated
- Subjects 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.

Note: Subjects who require permanent discontinuation of one of the study treatments due to toxicity in a given treatment combination must permanently discontinue both treatments (unless continued treatment with the remaining agent is agreed upon by the treating investigator and Sponsor/Medical Monitor) in that combination and the reason for discontinuation must be recorded. The treatment discontinuation visit (TDV) should be conducted within 30 days (+10 days) of the decision to discontinue study drug(s).

- Intercurrent illness that prevents further administration of study treatment(s)
- Criteria for discontinuation of study drug(s) as described in Section 6.3.1 (Safety Management Guidelines) have been met
- Criteria described in Section 5.4.3 (QTcF Stopping Criteria) have been met

- Criteria described in Section 5.4.4 (Stopping Rules for Clinical Deterioration) have been met

The primary reason study treatment was permanently discontinued must be documented in the subject's medical records and electronic case report form (eCRF).

All subjects who permanently discontinue study treatment without disease progression will be followed for disease progression according to the protocol schedule until:

- New anticancer therapy is initiated
- Disease progression
- Death
- Study closure/termination (with implementation of Protocol Amendment 4).

A subject with a CR requires confirmation of response via imaging at least 4 weeks after the first imaging showed a CR. Early discontinuation of GSK3174998 and/or pembrolizumab may be considered for subjects who have attained a confirmed complete response per RECIST 1.1 that have been treated for at least 6 months and had at least two treatments beyond the date when the initial CR was declared.

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

The follow-up period for safety assessments will be a minimum of 3 months from the date of the last dose. The post treatment follow-up period includes disease assessments every 12 weeks until documented PD. Following PD, subjects will be contacted every 3 months to assess survival status.

With the implementation of Amendment 04, there will be no requirement to perform future disease assessments or survival follow-up. If the subject voluntarily discontinues from treatment due to toxicity, 'AE' will be recorded as the primary reason for permanent discontinuation on the eCRF.

All subjects who discontinue from study treatment will undergo safety assessments at the time of discontinuation and during post-study treatment follow-up as specified in the Time and Events Table (see Section 7.1, Table 13 and Table 14).

5.4.2. Liver Chemistry Stopping Criteria

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

If any of the following criteria are met, study treatment must be discontinued:

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

a. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

b. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants

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

For additional guidance on the management of hepatotoxicity, please see Section 6.3.1.1

5.4.2.1. Study Treatment Restart or Rechallenge

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

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

Refer to Appendix 3 for full guidance.

5.4.3. QTcF Stopping Criteria

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

If a subject meets either of the following criteria, they must be discontinued.

- QTcF >500 msec

OR

- Change from baseline of QTcF >60 msec

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

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

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

5.4.4. Stopping Rules for Clinical Deterioration

Accumulating clinical evidence indicates that the emergence of objective responses to agents that activate antitumor immune responses may follow delayed kinetics of weeks or months, and can be preceded by initial apparent progression with appearance of new lesions or some enlarging lesions while certain index lesions are regressing ("mixed response"). Therefore, it is reasonable to allow a subject experiencing apparent progression to continue to receive treatment until progression is confirmed at the next imaging assessment at least 4 weeks later. These considerations should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment.

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

- ECOG PS decrease of at least 2 points from baseline

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

5.5. Subject and Study Completion

Upon protocol Amendment 4 implementation, ongoing subjects will be considered withdrawn due to study closure and will be followed for up to 3 months after the last dose. Only when a subject dies is he/she considered to have completed the study; consequently "death" is not listed as a reason for withdrawal from the study. Furthermore, disease progression, discontinuation of study treatment, and AEs, are not by themselves reasons for withdrawal from the study. If a subject dies a copy of the death certificate should be available for review, if possible, and the cause of death should be evaluated and documented.

The end of the study is defined as the last subject's last visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

GSK3174998 (Table 9) will be intravenously administered to subjects at each study site under medical supervision of an investigator or designee. When administered in combination with pembrolizumab in Part 2 of the study, GSK3174998 will be administered first. The date and time of administration will be documented in the source documents and reported in the eCRF.

In Part 2 of the study, pembrolizumab (Table 9) will be intravenously administered to subjects starting at least 1 hour and no more than 2 hours following the end of the GSK3174998 infusion under medical supervision of an investigator or designee. The date and time of administration will be documented in the source documents and reported in the eCRF.

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 and study visit procedures. Infusions may be administered up to 72 hours before or after the planned date of treatment for administrative reasons only (e.g., scheduling an infusion around a holiday).

The Study Reference Manual (SRM) contains specific instructions for the calculation of GSK3174998 doses, and for the preparation of both GSK3174998 and pembrolizumab infusions, and administration of these infusions.

Table 9 Investigational Product Dosage/Administration

	Study Treatment	
Product name:	GSK3174998	Pembrolizumab
Dosage form:	Lyophilized powder for reconstitution	Solution for infusion
Unit dose strength(s)/ Dosage level(s):	40 mg lyophilized powder Dose range: 0.003 to ≤10 mg/kg	100 mg/ 4 mL solution Dose range: 200 mg
Route of Administration	IV infusion – 30 min[a, b]	IV infusion – 30 min[a]
Frequency of Administration	Q3W[b, c]	Q3W[b]
Dosing instructions:	Make every effort to target infusion timing to be as close to 30 min as possible. However, given the variability of infusion pumps from site to site, a window of -5 min and +10 min is permitted (i.e., infusion time is 30 min: -5 min/+10 min or 25 to 40 min).	Make every effort to target infusion timing to be as close to 30 min as possible. However, given the variability of infusion pumps from site to site, a window of -5 min and +10 min is permitted (i.e., infusion time is 30 min: -5 min/+10 min or 25 to 40 min).
Manufacturer/ source of procurement	GSK	Merck

a. Infusions may be prolonged in the event of an infusion reaction. If multiple subjects experience clinically significant infusion reactions, the infusion rate may be slowed for all future administrations of study drug(s) for all subjects. Should this global change in infusion rate be required, it will be communicated to the sites in writing.
b. Dose levels 1 and 2 will be administered less than 30 min, please refer to the SRM for infusion directions
c. Alternative dosing schedules may be explored if emerging data warrants. This will be communicated to the sites in writing prior to implementation.
Q3W = Every 3 weeks; GSK = GlaxoSmithKline

6.2. Treatment Assignment

Subjects will be identified by a unique subject number that will remain consistent for the duration of the study.

Upon completion of all the required screening assessments, eligible subjects will be registered into a GSK designated registration and medication ordering system, by the investigator or authorized site staff.

Subjects will be assigned to study treatment in the order in which they complete screening assessments (i.e., the study is not randomized).

6.3. Planned Dose Adjustments

6.3.1. Dose and Safety Management Guidelines

6.3.1.1. Dose Modification and Toxicity Management for Immune-Related AEs Associated with GSK3174998 ± Pembrolizumab

AEs associated with treatment with GSK3174998 ± pembrolizumab exposure may be immune-mediated. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of GSK3174998 ± pembrolizumab treatment, or anywhere in between, and may affect more than on 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 study 201212, most irAEs were reversible and could be managed with interruptions of GSK3174998 ± pembrolizumab, administration of corticosteroids and/or other supportive care. 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 GSK3174998 ± pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for ir AEs associated with GSK3174998 ± pembrolizumab are provided in Table 10.

Table 10 Dose modification and toxicity management guidelines for immune-related AEs

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where GSK3174998 ± pembrolizumab has been withheld, GSK3174998 ± pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. GSK3174998 ± pembrolizumab 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.
3. 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	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to GSK3174998 ± pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg methylprednisolone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent grade 2	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to GSK3174998 ± pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Diarrhea / colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg methylprednisolone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of enterocolitis (i.e. diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. peritoneal signs and ileus). • Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to GSK3174998 ± pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
AST / ALT elevation or increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg methylprednisolone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable • See Section 6.3.1.2 for additional details on Liver Event Follow-Up Assessments
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg methylprednisolone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of -cell failure	Withhold	• Initiate insulin replacement therapy for subjects with T1DM • Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue1		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or Permanently discontinue1		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g. levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to GSK3174998 ± pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (methylprednisolone 1-2mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes •
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Grade 3, or intolerable/ persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 4 or recurrent Grade 3	Permanently discontinue		

NOTES:

1. The decision whether to withhold or permanently discontinue GSK3174998 ± pembrolizumab is at the discretion of the investigator or treating physician.
2. For subjects with Grade 3 or 4 immune-related endocrinopathy where interruption of GSK3174998 ± pembrolizumab is required, treatment with GSK3174998 ± pembrolizumab may be resumed when the event resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or, for T1DM, metabolic control has been achieved.

6.3.1.2. Liver Event Follow-up Assessments

- **Viral hepatitis serology:** Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
- **Quantitative hepatitis B DNA and hepatitis delta antibody:** Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen). If hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction of Hepatitis D RNA virus (where needed) [Le Gal, 2005].
- **Blood sample for PK analysis,** obtained within 28 days after last dose of study drug: Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample

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

6.3.1.3. Dose Modification and Toxicity Management of Infusion-Reactions Related to GSK3174998 ± Pembrolizumab

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

Infusion reactions may affect any organ system in the body. Most are mild in severity, although severe and even fatal reactions occur. As a group, infusion reactions (including both cytokine mediated and allergic) usually occur during or within a few hours of drug infusion. Occasionally, a reaction may occur one to two days after administration. The NCI-CTCAE (version 4.0) 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 subject is having an allergic infusion reaction or a non allergic infusion reaction.

Clinically, 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.

In order 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. The serum tryptase, CRP and ferritin panels should be performed at the PI's designated local laboratory. The serum cytokine panel will be performed at a GSK designated laboratory. These results will help us better understand (albeit retrospectively) the etiology of the AE, as outlined in Table 11.

Table 11 Biomarker Panel

Biomarker	Relationship to Adverse Event
Serum tryptase[a]	IgE-related infusion reaction (Allergic/anaphylaxis) [Schwartz, 2006]
Serum CRP[a]	Elevated in CRS [Lee, 2014]
Serum ferritin[a]	Elevated in CRS [Lee, 2014]
Plasma cytokine panel[b] (IFN-γ*^, TNF-α*^, IL-2*, IL-4, IL-5*, IL-6*^, IL-8*, IL-10*, IL-12p70, IL-13, and IL-17)	* Reported to be elevated in CRS [Lee, 2014] ^consistently reported as elevated in CRS [Lee, 2014]

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

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

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

Table 12 GSK3174998 ± Pembrolizumab 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 subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of study drugs with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

6.3.1.4. Dose Delay

GSK3174998 ± pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

If there is a dose delay between 1 and 49 days (2 dosing cycles + 7 days), the procedures at the original scheduled visit (including dosing) should be performed as soon as possible. All subsequent visits will follow a Q3W calendar schedule. Subjects with infusion delays causing 2 consecutive missed doses due to toxicity should discontinue study drug(s) unless the treating investigator and Sponsor/Medical Monitor agree there is strong evidence supporting continued treatment. While no washout from study treatments is required for subjects requiring elective surgery or palliative radiation therapy while on study, investigators and site staff are encouraged to schedule these procedures to fall in between dosing days (see Section 6.10.1. for details on permitted medications and non-drug therapies).

6.4. Blinding

This will be an open-label study.

6.5. Packaging and Labeling

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

6.6. Preparation/Handling/Storage/Accountability

Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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

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

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

A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.7. Compliance with Study Treatment Administration

GSK3174998 and pembrolizumab will be intravenously administered to subjects at the site. Administration will be documented in the source documents and reported in the eCRF.

6.8. Treatment of Study Treatment Overdose

6.8.1. GSK3174998 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 should:

- Contact the Medical Monitor immediately.
- Closely monitor the subject for AEs/SAEs and laboratory abnormalities for at least 90 days.
- 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).

- 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 subject.

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

6.8.2. Pembrolizumab Overdose

An overdose of pembrolizumab will be defined as ≥1000 mg (5 times the dose) of pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, any overdose of pembrolizumab, or follow up to an overdose, whether or not related to the Sponsor's product, must be reported within 5 days to GSK as an AESI, either by electronic media or paper.

6.9. Treatment after the End of the Study

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

Refer to Section 5.4 and Section 7.1 for follow-up assessments.

6.10. Concomitant Medications and Non-Drug Therapies

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

Medications or vaccinations specifically prohibited (see Section 6.10.2) are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject

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

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

6.10.1. Permitted Medications and Non-Drug Therapies

Supportive Care: Subjects should receive full supportive care during the study, including transfusion of blood and blood products, palliative radiation to non-target lesions, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate. Seasonal flu vaccine is permitted as an injection only. Intra-nasal flu vaccine is excluded. Elective surgery or non-palliative radiation may be permitted on a case-by-case basis in agreement with the Medical Monitor.

Growth Factors and Bisphosphonates: The use of growth factors, RANK-L inhibitors, and bisphosphonates (if on a stable dose for at least 4 weeks) is permitted while participating in this study. However, the initiation of growth factors and bisphosphonates is not allowed during the first 4 weeks of study treatment, unless used in the management of toxicity and agreed upon by the investigator and Medical Monitor.

Steroids: Use of steroids is permitted for treatment of AEs (as per Table 10 ***and*** Table 12***, Dose Modification Guidelines for Immune-Related AEs or Infusion Reactions.***

All attempts should be made to rule out other causes such as metastatic disease, infection or other ocular disease (e.g. glaucoma or cataracts). However the AE should be reported regardless of etiology.

Subjects with conditions pre-existing before study enrollment requiring steroids are permitted to continue taking up to a maximum of 10 mg of prednisone or equivalent provided that the subject has been on a stable dose for at least 4 weeks before enrollment.

6.10.2. Prohibited Medications and Non-Drug Therapies

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

- Any investigational drug(s)
- Other anticancer therapy (chemotherapy, radiation therapy [unless administered palliatively] – see Section 6.10.1), immunotherapy, biologic therapy, or hormone therapy other than for replacement). The use of pembrolizumab during Part 2 is permitted.
- Live vaccines such as intra-nasal flu vaccine.

7. STUDY ASSESSMENTS AND PROCEDURES

If assessments are scheduled for the same nominal time, it is recommended that the assessments should occur in the following order: 12-lead ECG, vital signs, and blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time.

The timing and number of planned study assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring for the following assessments: safety, PK, pharmacodynamic/biomarker, or other assessments.

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

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

No more than 500 mL of blood for the purposes of this study, will be collected over the first 6 doses of study treatment, plus the post-treatment follow-up period. No more than 30 mL of blood will be collected at each dosing visit following dose number 6. The total volume will depend on how long the subject remains on treatment. There may be additional blood collection performed for non-study reasons.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (Section 7.1, Table 13 and Table 14), are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1 (Table 13 and Table 14).

7.1. Time and Events Table

Table 13 Time and Events Table – Monotherapy and Combination Therapy

	Scrn[a/b]			Treatment[a]										Follow-up	
Week[a]	**≤4**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**9**	**12**	**> 12 - 48[c]**	**≥49 -105[c]**	**TDV[d]**	**DFS FU[e]**	**SFU[f]**
Day	**≤28**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**64**	**85**	**106-337**	**≥344-736**	**30d after last dose**	**Q12W**	**Q12W**
Dose		**1**			**2**			**3**	**4**	**5**	**6-17**	**18-36**			
Informed Consent	X														
Inclusion/Exclusion	X	X													
Demographics, Medical History, Prior Medications	X														
Concomitant Medications		Assess at each visit from first dose until the TDV visit													
Subject Registration		X													
Anti-Cancer Treatment[f]													X	X	X
Part I Study Treatment Monotherapy															
Administer GSK3174998 (± 3 days)[g]		X			X			X	X	X	X	X			
Part 2 Study Treatment Combination Therapy (note: administer pembrolizumab 1 hour after the end of the GSK3174998 infusion)															
Administer GSK3174998[g]		X			X			X	X	X	X	X			
Administer Pembrolizumab[g]		X			X			X	X	X	X	X			
Safety															
AE/SAE Assessment		Assess at each visit from first dose until the TDV visit for AEs and until 90 days after last dose for AESI and SAEs[d]													
ECOG PS	X	X	X	X	X	X	X	X	X	X	Q6w	Q6w	X		
Physical Examination	X	X			X			X	X	X	Q6w	Q6w	X		
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X	X	X		
12-lead ECG[l]	X	X[l]			X[l]			X	X	X[l]	Q12w	Q12w	X		

	Scrn[a/b]			Treatment[a]										Follow-up	
Week[a]	**≤4**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**9**	**12**	**> 12 - 48[c]**	**≥49 -105[c]**	**TDV[d]**	**DFS FU[e]**	**SFU[f]**
Day	**≤28**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**64**	**85**	**106-337**	**≥344-736**	**30d after last dose**	**Q12W**	**Q12W**
Dose		**1**			**2**			**3**	**4**	**5**	**6-17**	**18-36**			
Laboratory Assessments (Safety) – perform assessments pre-dose on each dosing day															
Hepatitis B and C	X														
Pregnancy Test: Serum β-hCG	≤3d	Monthly (urine or serum)													
Clinical Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X		
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X		
Thyroid function tests	X							X		X	Q6W	Q6W	X		
Calculated CrCl	X				X			X	X	X	X	X	X		
Urinalysis	X		X	X	X	X	X	X	X	X	X	X	X		
Disease Assessments															
Tumor imaging [h]	X							X[j]		X	Q12W				
Telephone call for survival status[f]															X
Tumor Biopsies															
Archived tumor [i]	X														
Fresh tissue sample[i, m]	X							X							
PD tissue sample[k]				X[k]											

Visit Abbreviations: Scrn = Screen; TDV = Treatment Discontinuation Visit; DFSFU = Disease-Free Survival Follow-up; SFU = Survival Follow-up; PD = Progressive Disease; AE = Adverse Event; SAE = Serious Adverse Event; AESI = Adverse Events of Special Interest; ECOG PS = Eastern Cooperative Oncology Group performance status; ECG = Electrocardiogram; β-hCG = Beta-human chorionic gonadotropin; CrCl = Creatinine clearance

a. Visit Windows: With the exception of Screening/baseline and Day 1 visits and unless otherwise specified, assessments performed at ≤3-week intervals will have a ±3 day window and assessments performed at >3 week intervals will have a ±1 week window. For Screening/Baseline and Day 1 visits, all procedures must be completed before first dose.
b. Screening assessments or procedures to be performed within 4 weeks (28 days) of the first dose (unless otherwise specified, with the exception of the serum pregnancy test which must be performed within 3 days of the first dose of study treatment).
c. The frequency of safety assessments from week 12 onwards will be as follows (unless stated otherwise in the table):
   Every GSK3174998 or pembrolizumab dosing day (pre-dose): Clinical chemistry, hematology, urinalysis, vital signs and weight
   Every 6 weeks: Thyroid function tests, ECOG PS assessments, physical examination
   Every 12 weeks: 12-lead ECG,
d. The treatment discontinuation visit should be completed 30 days from the last dose of study treatment. The window for this visit is +10 days. All AEs and concurrent medications will be collected until at least 30 days after the last dose of study treatment. All AESIs and SAEs and any concurrent medications relevant to the reported AESIs and SAEs will be collected until at least 90 days after the last dose of study treatment. If another anti-cancer agent is started during the 90 day reporting period, only AESI and SAEs that occur within 30 days from the last dose of study drug(s) should be recorded. (see Section 7.4.1.1)
e. If study treatment has been permanently discontinued in the absence of PD, the subject will return for disease assessments every 12 weeks until PD is documented (by irRECIST), another anticancer treatment is initiated, or death, whichever occurs first. These visits are described as Disease Free Survival Follow-up (DFS FU) visits. Upon implementation of Protocol Amendment 4, no future disease assessments are required.
f. The Survival FU visit should be completed every 12 weeks after documented disease progression (or after initiation of another anticancer treatment). Subjects should be contacted every 12 weeks (±2 weeks) until death occurs. Upon implementation of Protocol Amendment 4, no future survival follow-up is required.
g. Dosing of GSK3174998 and pembrolizumab at every 3-week intervals is shown in the Time and Events Table; however, dosing of GSK3174998 may be delayed due to toxicity. During the combination phase, GSK3174998 should be administered first, and pembrolizumab should be administered at least 1 hour and no more than 2 hours following the end of the GSK3174998 infusion. GSK3174998 and pembrolizumab will be dosed for a maximum of 2 years or 35 cycles, whichever comes first. Alternative dosing schedules of GSK3174998 and pembrolizumab may be explored if the data warrants. This will be communicated in writing to sites prior to implementation.
h. Screening tumor imaging must be obtained within 28 days of the first dose. Tumor imaging will be performed every 12 weeks (±1 week) until disease progression has been confirmed by irRECIST; Subjects whose disease progresses must have a confirmatory scan performed at least 4 weeks after the date of assessment during which the first indication of PD was demonstrated. Immune-related RECIST will be used to determine treatment decisions for PD and the primary endpoint analysis will use irRECIST. If a subject has achieved a CR or PR in the previous radiologic assessment, a repeat scan should be performed as a part of the confirmation of response, within at least 4 weeks to confirm the response. At the TDV, tumor imaging is only required if the last disease assessment did not show PD and was performed ≥6 weeks before TDV. During the DFS FU visits (performed when a subject has permanently discontinued study treatment before disease progression has been documented), tumor imaging will be obtained every 12 weeks (±1 week) until PD, initiation of a new anticancer treatment, or death, whichever comes first. Pre-baseline scans (within 24 weeks before the baseline scan) may be collected to assess tumor growth rate in selected subjects to support exploratory investigation of tumor growth kinetics. Upon implementation of Protocol Amendment 4, no future disease assessments are required..
i. A fresh tumor biopsy should be attempted at screening (before first dose) and at Week 6 (after the 3rd dose of study treatment +1 week). Fresh biopsies are mandatory for all patients in the Pharmacodynamic Cohort and the Dose Expansion phase. Tumor lesions planned for biopsy must not be used as indicator lesions for assessment of disease, unless discussed and agreed with the GSK Medical Monitor. For subjects in the initial dose escalation cohorts, where biopsy is not mandatory, a recent archival tumor specimen is acceptable if it is not feasible to obtain a fresh biopsy.

j. The 6-week disease assessment will be performed for subjects enrolled in Part A in the Pharmacodynamic Cohort and in all Part B expansion cohorts. This disease assessment is timed to coincide with the on-treatment (6 week) tumor biopsy. If feasible, the disease assessment should be performed **after** the tumor biopsy.
k. Progressive Disease Tissue Sample: An optional fresh tumor biopsy should be attempted at the time of disease progression.
l. For Part 1A only: On Day 1 ECG measurements will be performed in triplicate predose and at the following times after the infusion: EOI+30m, EOI + 4h, EOI +24h, on Day 22 ECG measurements will be performed in triplicate predose and on Day 85 ECG measurements will be performed in triplicate predose and at the following times after the infusion: EOI+30m.
m. With subject consent and agreement by the PI and GSK Medical Monitor, additional, optional fresh biopsies may be obtained during the study. One example of when this may be considered is when a mixed response occurs and tumor biomarker data are anticipated to inform why some lesions are, and some are not, responding to the treatment.

Table 14 Time and Events Table – Pharmacokinetics, Antidrug Antibodies, and Pharmacodynamics (Parts 1 and 2)

		Treatment													
Day	**1**	**2**	**8**	**15**	**22**	**23**	**29**	**36**	**43**	**64**	**85**	**106**	**≥148**	**30 D after Last Dose**	**12 Wks Post-Treatment ±1 week**
Dose	**1**				**2**				**3**	**4**	**5**	**6**	**≥8**		
Pharmacogenetics (6 mL)[a]	X														
Receptor occupancy and phenotyping panels(10 mL)[i]	Pre EOI+4h[g]	EOI+24h	X	X	Pre EOI+4h[g]				Pre EOI + 4h[g]					X	X
Plasma + PBMC prep (20 mL)[b]	Pre		X		Pre				Pre		Pre			X	X
Cytokines (5 mL)	Pre EOI+4h	EOI+24h	X		Pre EOI+4h				Pre EOI+4h		Pre EOI+4h				
Plasma for cfDNA + exosomes (20 mL)[h]	Pre								At time of biopsy if done						
Serum (5 mL)	Pre														
GSK3174998 Pharmacokinetics (1 mL)	Pre EOI+30m EOI+4h	EOI+24h[d]	X	X	Pre EOI+30m EOI+4h	EOI+24[d]	X	X	Pre EOI+30m	Pre EOI+30m	Pre EOI+30m	Pre EOI+30m	Pre[e]	X	X
Part 2 only: Pembrolizumab Pharmacokinetics (3 mL)	Pre EOPI+30m	EOI+24h	X	X	Pre					Pre		Pre	Pre[e]	X	X
Anti- GSK3174998 antibodies[c,f] (4 mL)	Pre				Pre				Pre	Pre	Pre	Pre	Pre[e]	X	X[f]
Part 2 only: Anti-Pembrolizumab antibodies[c,f] (6 mL)	Pre				Pre					Pre		Pre	Pre[e]	X	X[f]

Timepoint Definitions:
X = Anytime during visit
Pre = within 60 min before the start of the GSK3174998 infusion
EOI+30m = within 30 minutes of the end of the GSK 3174998 infusion
EOPI+30m = within 30 minutes of the end of the pembrolizumab infusion
EOI +4h = within 4 hours ±10 minutes of the end of the GSK3174998 infusion
EOI+24h = 24 hours ± 4 hours after the end of the GSK3174998 infusion

a. Informed consent for optional pharmacogenetics research must be obtained before collecting a sample. It is recommended that the blood sample be taken at the first opportunity after a subject has met all eligibility requirements, and can be done up to 28 days before Day 1.
b. If the baseline/pre-dose sample is not viable, samples for PBMCs are not needed at subsequent visits.
c. In addition to these scheduled immunogenicity assessments, "event-driven" testing will also be employed for those subjects that experience anaphylaxis, serious hypersensitivity, or AEs related to study drug administration that led to withdrawal from the study. See Section 9.4.2.4 for full details.
d. Day 2 PK samples are only required during the dose-escalation phases of the study.
e. Dose 8 and every 4 dosing cycles
f. In the event of a hypersensitivity reaction that is either 1) clinically-significant in the opinion of the investigator, or 2) leads to the subject withdrawing from the study, blood samples should be taken from the subject for immunogenicity testing at the time of the event and again 30 days, 12 weeks, and 24 weeks after.
g. If the EOI+4h RO sample is scheduled to be collected after the last lab courier pick-up time of the day, the sample should be collected as late as possible to enable processing and shipping on the same day as collection.
h. If a tumor biopsy is taken at the time of PD, then a plasma sample should also be collected for cfDNA + exosomes,
i. Receptor Occupancy and phenotyping panels will only be collected in Parts 1A and 2A of the study

D = Days; PBMC = Peripheral blood mononuclear cell; EOI = End of infusion
Procedures for blood sample collection, processing, storage, and shipping are described in the SRM.

7.2. Screening and Critical Baseline Assessments

7.2.1. Demographic and Baseline Assessments

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

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

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

7.2.1.1. Critical Baseline Assessments

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

7.2.2. Baseline Documentation of Target and Non-Target Lesions

- All baseline lesion assessments must be performed within 28 days before the first dose.
- Lymph nodes that have a short axis of <10 mm are considered non-pathological and should not be recorded or followed.
- Pathological lymph nodes with <15 mm, but ≥10 mm short axis are considered non-measurable.
- Pathological lymph nodes with ≥15 mm short axis are considered measurable and can be selected as target lesions; however, lymph nodes should not be selected as target lesions when other suitable target lesions are available.
- Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

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

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

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by computed tomography (CT) or magnetic resonance imaging (MRI) can be considered measurable. Bone scans, fluorodeoxyglucose-positron-emission tomography (FDG-PET) scans or X-rays are not considered adequate imaging techniques to measure bone lesions.

- All other lesions (or sites of disease) should be identified as non-target and should also be recorded at baseline. Non-target lesions will be grouped by organ. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

The following are required at baseline: A CT scan with contrast of the chest, abdomen, and pelvis, other areas as indicated by the subject's underlying disease, and clinical disease assessment for palpable lesions. For subjects with head and neck cancer, a CT or MRI of the head and neck area is required. At each post-baseline assessment, evaluations of the sites of disease identified by these scans are required.

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

Confirmation of CR and PR are required per protocol. Confirmation assessments must be performed at least 4 weeks after the criteria for response have initially been met and may be performed at the next protocol scheduled assessment. If a confirmation assessment is performed prior to the next protocol schedule assessment, the next protocol scheduled evaluation is still required (e.g., evaluations must occur at each protocol scheduled time point regardless of unscheduled assessments).

7.3. Efficacy

7.3.1. Evaluation of Anticancer Activity

- Lesion assessment method and timing, evaluation of disease, disease progression and response criteria will be conducted according to RECIST (version 1.1) [Eisenhauer, 2009] and irRECIST as outlined below and in Appendix 5 of this protocol. irRECIST will be used to determine treatment decisions and will be used for the primary analysis of anticancer activity.
- Disease assessment modalities may include imaging (e.g., CT scan, MRI, bone scan, plain radiography) and physical examination (as indicated for palpable/superficial lesions).
- The baseline disease assessment will be completed within 4 weeks prior to the first dose of GSK3174998, then every 12 weeks thereafter, and at the final study visit. For subjects enrolled in the Part A "Pharmacodynamic Cohort" and in all Part B expansion cohorts an additional disease assessment will be performed at Week 6. See the Time and Events Table (Section 7.1, Table 13) for the schedule of assessments of anticancer activity.
- Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays.
- For post-baseline assessments, a window of ±7 days is permitted to allow for flexible scheduling. If the last radiographic assessment was more than 12 weeks prior to the subject's withdrawal from study and PD has not been documented, a

disease assessment should be obtained at the time of withdrawal from the study. Upon implementation of Protocol Amendment 4, no future disease assessments are required.

- Subjects whose disease responds (either CR or PR) should have a confirmatory disease assessment performed at least 4 weeks after the date of assessment during which the response was demonstrated.
- Subjects whose disease progresses (PD) must have a confirmatory scan performed at least 4 weeks after the date of assessment during which the first indication of PD was demonstrated.
- To ensure comparability between the baseline and subsequent assessments, the same method of assessment and the same technique will be used when assessing response.
- Pre-baseline scans (within 24 weeks before the baseline scan) may be collected to assess tumor growth rate in selected subjects to support exploratory investigation of tumor growth kinetics.

7.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1, Table 13 and Table 14).

7.4.1. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 8.

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

7.4.1.1. Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information

- AEs and SAEs will be collected from the start of study treatment until the follow-up contact (see Section 7.4.1.3) at the time points specified in the Time and Events Table (Section 7.1, Table 13).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- Any AESI and SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to 90 days after the last dose of study drug(s). If another anti-cancer agent is started during the 90 day reporting period, only AESI and SAEs that occur within 30 days from the last dose of study drug(s) should be recorded. SAEs must be reported within 24 hours to the Sponsor either by electronic media or paper

- All AESI and SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 8.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating, and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 8.

7.4.1.2. Method of Detecting Adverse Events and Serious Adverse Events

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

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

7.4.1.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and non-serious AESI (as defined in Appendix 8) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 8.

7.4.1.4. Cardiovascular and Death Events

For any cardiovascular (CV) events (as defined in Section 7.4.1.4.1) and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the eCRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV death.

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

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

7.4.1.4.1. Definition of Cardiovascular Events

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

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

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

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

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

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

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

7.4.1.6. Regulatory Reporting Requirements for SAEs

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

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

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

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

7.4.2. Pregnancy

- Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of dosing until 120 days after the last dose of study medication.
- If a pregnancy is reported, then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 9.

7.4.3. Physical Exams

- A complete physical examination will be done at screening and will include assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- A brief, targeted physical examination will be done at all other timepoints, unless physician's judgement requires a full exam.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- For melanoma subjects, a full body dermatological examination will be performed by a dermatologist (or suitably qualified physician) to identify abnormal skin lesions within the 28 day screening period. All findings will be photographed and identified during screening. Subsequently, brief skin examinations will be included in the PE exams as per the Time and Events Table (Section 7.1, Table 13) or more frequently as necessitated. Wherever possible, the same physician should perform these examinations. Follow-up skin examinations by a referral dermatologist should be conducted if clinically indicated ECOG PS.

The PS will be assessed using the ECOG scale (Appendix 6) as specified in the Time and Events Table (Section 7.1, Table 13).

7.4.4. Vital Signs

- Vital sign measurements to be measured in semi-supine position after 5 minutes rest will include temperature, systolic and diastolic blood pressure, and pulse rate.
- Vital signs will be measured more frequently if warranted by clinical condition of the subject. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.
- If a subject develops a fever, refer to Section 6.3.1 for fever management guidelines.

7.4.5. Electrocardiogram (ECG)

12-lead ECGs will be obtained at each planned ECG assessment during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 5.4.3 for QTcF stopping criteria and additional QTcF readings that may be necessary.

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

For Part 1A of the study, ECG measurements will be performed in triplicate at specified times (see Table 13, including footnotes). All other measurements may be performed as single ECG measurements.

7.4.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 15, must be conducted in accordance with the laboratory manual, and Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labeled with the subject number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the SRM. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

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

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

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

- Hematology
- Clinical Chemistry
- Hepatitis B and C

- Pregnancy Test
- Urinalysis, calculated creatinine clearance (CrCl)
- Thyroid Function Tests
- The results of each test must be entered into the eCRF.

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 15.

Table 15 Clinical Laboratory Assessments

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

a. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 5.4.2 and Section 6.3.1.3

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

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 should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.

7.5. Pharmacokinetics

7.5.1. Blood Sample Collection

Blood samples for PK analysis of GSK3174998 and pembrolizumab will be collected at the time points described in Section 7.1, Time and Events Table (Table 14). The actual date and time of each blood sample collection will be recorded in the eCRF. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring. Details on PK blood sample collection, processing, storage, and shipping procedures are provided in the SRM.

Blood samples (1 mL) for analysis of plasma GSK3174998 concentrations and blood samples (3 mL) for analysis of serum pembrolizumab concentrations will be collected from all subjects at the times indicated in Table 14.

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

7.5.2. Blood Sample Analysis

Plasma or serum analysis for GSK3174998 and pembrolizumab will be performed under the control of Department of Bioanalysis, Immunogenicity and Biomarkers (BIB), IVIVT, PTS, GSK or Merck Sharp & Dohme Corp the details of which will be included in the SRM. Concentrations of GSK3174998 and pembrolizumab will be determined in plasma and serum samples, respectively, using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM). Once the plasma or serum has been analyzed for GSK3174998 and pembrolizumab any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate BIB, PTS, GSK or Merck Sharp & Dohme protocol.

7.6. Biomarkers/Pharmacodynamic Markers

7.6.1. Blood Biomarkers

Blood samples will be collected and analyzed by flow cytometry to evaluate the binding of GSK3174998 to the OX40 receptor, and its pharmacodynamic effect on lymphocytes. OX40 receptor occupancy will be determined prior to dosing of GSK3174998, after treatment, and at selected treatment intervals. The numbers of T cells, B cells, and NK cells as well as subsets of T cells will be simultaneously evaluated in whole blood by flow cytometry. The activation and proliferation status of T cells will also be simultaneously assessed in the same sample.

Blood samples will also be collected for isolation of PBMC, plasma, and serum. Plasma and serum samples will be used for an analysis of circulating soluble factors in relation to T-cell activation, cfDNA, exosomes circulating proteins, and may be analyzed for soluble OX40 and soluble OX40-drug complex depending on the availability of the assays. Factors to be analyzed may include but are not limited to: the presence of IFN-γ, TNF-α, IL-2, IL-4, IL-5, IL-6, IL 10, IL-8, IL-12p70, IL-13, and IL-17 as well as antibodies against tumor, self tumor mutations, i.e., tumor mutational load, gene expression (RNA or protein) or viral antigens.

PBMCs isolated from whole blood will be preserved and stored for flow cytometry of additional cell types such as immune regulatory populations which may include but are not limited to myeloid derived suppressor cells, subsequent functional analysis or assessment of the diversity of the T-cell repertoire, its relationship to clinical responses, and changes in response to treatment with GSK3174998. The functional state of PBMCs may be analyzed for expression of cytokines which may include but not limited to IFN-γ, IL-2, TNFα, IL-17, Granzyme B, and CD107a. PBMCs may also be evaluated for genomic (DNA) and gene expression (RNA or protein) alterations to determine treatment-related changes in immune-related signatures.

7.6.2. Tumor Tissue

Archival tumor tissue, as well as fresh pre- and on-treatment biopsies in subjects in the pharmacodynamic cohorts, dose-expansion cohorts, and if possible in the dose escalation cohorts will be evaluated by IHC for expression of phenotypic and functional immune cell markers on tumor infiltrating lymphocytes (TILs) and other immune cells and as well as immune signaling markers on the surface of tumor cells (e.g. including, but not limited to PD-L1), to understand antitumor immune responses. In addition, when possible, similar analyses will be performed on tumor tissue samples obtained upon progression. Additionally, tumor tissue may be sequenced to assess TCR diversity as well as evaluated for any DNA/RNA/protein changes correlating with response, such as but not limited to tumor mutational burden.

In the pharmacodynamic cohort and expansion cohorts, mandatory fresh pre- and on-treatment biopsies are required (see Table 13 for timing). These mandatory biopsy samples will be evaluated as previously described for the archival, pre- and on-treatment and progression biopsies.

If feasible, for all of the fresh pre-and on-treatment biopsies, both samples should be obtained from the same tumor lesion. If not possible, the on-treatment biopsy should be obtained from the same organ as the pre-treatment biopsy. The tumor site chosen for biopsy must not be the used as an indicator lesion for assessment of disease unless otherwise discussed and agreed upon with the GSK medical monitor.

With subject consent and agreement by the PI and GSK Medical Monitor, additional, optional fresh biopsies may be obtained during the study. One example of when this may be considered is when a mixed response occurs and tumor biomarker data are anticipated to inform why some lesions are, and some are not, responding to the treatment. In this case, the additional biopsies are not required to be obtained from the same lesion or organ as the pre-treatment biopsy. .

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

Blood and tumor samples may be used for purposes related to the quality assurance of the laboratory tests described in this protocol, or for the development of a diagnostic assay.

7.7. Anti-Drug Antibodies

7.7.1. Blood Sample Collection

Serum samples will be collected and tested for the presence of antibodies that bind to GSK3174998 and pembrolizumab. Serum samples for testing anti-GSK3174998 and anti-pembrolizumab antibodies will be collected as described in the Time and Events schedule (Section 7.1). The actual date and time of each blood sample collection will be recorded. Details of blood sample collection (including volume to be collected), processing, storage, and shipping procedures are provided in the SRM.

The timing and number of planned immunogenicity samples may be altered during the course of the study, based on newly-available data to ensure appropriate safety monitoring. In the event of a hypersensitivity reaction that is either 1) clinically-significant in the opinion of the investigator, or 2) leads to the subject withdrawing from the study, blood samples should be taken from the subject for immunogenicity testing at the time of the event and again 30 days, 12 weeks, and 24 weeks after. For subjects who prematurely withdraw from the study, immunogenicity testing will occur at withdrawal and at follow-up 30 days, 12 weeks, and 24 weeks after the last dose.

7.8. Genetics

Information regarding genetic research is included in Appendix 7.

8. DATA MANAGEMENT

For this study, subject data will be entered into GSK defined eCRFs, transmitted electronically to GSK or designee, and combined with data provided from other sources in a validated data system.

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

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

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

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

9.1.1. Part 1: Monotherapy Dose Escalation (GSK3174998)

With respect to the primary objectives and endpoints, no specific statistical hypotheses are being tested. The primary focus will be on determining the recommended dose for further exploration, the safety profile, and antitumor activity of GSK3174998.

9.1.2. Part 2: Combination Dose Escalation (GSK3174998 + Pembrolizumab)

No formal statistical hypotheses are being tested. Analysis of the data obtained from this study will be focused on comparison between dose cohorts and only descriptive methods will be used in analysis of the data obtained from this study.

9.1.3. Part 2: Combination Dose Expansion (GSK3174998 + Pembrolizumab)

The expansion cohorts of GSK3174998 + pembrolizumab are designed to evaluate preliminary clinical activity. Futility assessments will be conducted to evaluate accumulating data including safety, responses, PK and pharmacodynamics. The methodology is based on the predictive probability of success if enrollment continues until all planned subjects are recruited [Lee, 2008].

There are mutiple dose expansion cohorts being planned for STS, melanoma and other cancers types in the dose-expansion phase. For each cohort the objective is to test the null hypothesis that the overall response rate for the combination of GSK3174998 + pembrolizumab is equal to the historical response rate of monotherapy pembrolizumab.

The observed monotherapy pembrolizumab overall response rate was approximately 18% for STS [Burgess, 2017]. The observed monotherapy pembrolizumab overall response rate was assumed to be approximately 10% for melanoma in the pretreated population [Robert, 2014].

The sample size is chosen based on an improvement of 20% in the overall response rate on the combination therapy over the null hypothesis, with power of at least 80% and no more than a 10% type 1 error rate. In the population previously treated with pembrolizumab, the goal would be to observe a response rate of 30% after treatment with the combination of GSK3174998 and pembrolizumab.

Therefore, the hypotheses for both **PD-(L)1** naïve and **PD-(L)1** pretreated cohorts are shown as below:

For **PD-(L)1** naïve dose expansion cohorts (e.g., STS),

the *null hypothesis* for ORR is:

H_0: p=18%

and the *alternative hypothesis* is:

H_A:p=38%

For **PD-(L)1** pretreated dose expansion cohorts (e.g., melanoma),

the *null hypothesis* for ORR is:

H_0: p=10%

and the *alternative hypothesis* is:

H_A:p=30%

9.2. Sample Size Considerations

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

The study will enroll up to approximately 264 subjects with tumor types that may include NSCLC, SCCHN, RCC, melanoma, STS, bladder cancer, TNBC, and MSI CRC.

Up to 72 subjects will be enrolled in each of the two dose escalation parts of the study (Parts 1A and 2A); up to 30 subjects will be enrolled in each of dose expansion cohorts. The sample size of each expansion cohort at a given dose level will be minimum of 10 subjects and maximum of 30 subjects based on the overall response assessments.

The trial is not designed to stop early for efficacy but is designed to continuously assess futility if the predictive probability of success is 10% or less. The type I error rate, power, and predictive probability for assessing futility were determined from stating the minimum and maximum sample size, futility stopping rate, and the optimizing criterion as minimizing the sample size under null hypothesis. A weak informative prior distribution with a mean response rate equal to the target response rate is assumed. Thus, the predictive probability for the response rate will be primarily driven by the data. The detailed decision criteria for all cohorts are documented in Section 9.3.2.

Table 16 Expansion Cohorts Power and Type I Error

	Power	Type I error
STS PD-(L)1 naïve population: p0=18% and p1=38%	0.802	0.062
Melanoma pretreated PD1/PDL1 population: p0=10% and p1=30%	0.831	0.051

For the PD-(L)1 naïve combination expansion cohorts in STS, starting with 10 subjects in each cohort and allowing for a maximum sample size of 30 for each cohort, this design will have approximately 80.2% power with an overall type I error rate (α) of 6.2%. Under null hypotheses with an 18% ORR, the probability of early termination (PET) is 43% after data from 10 subjects evaluable for response are available and 77% after data from 20 evaluable subjects are available. Under the alternative hypothesis, if the true response rate is 38%, PET is 6% after data from 10 evaluable subjects are available and 13% after data from 20 evaluable subjects are available.

For the expansion cohorts in PD-(L)1 pretreated melanoma, starting with 10 subjects in each cohort and allowing for a maximum sample size of 30 for each cohort, this design will have approximately 83.1% power with an overall type I error rate (α) of 5.1%. Under null hypotheses with a 10% ORR, PET is 35% and 80% when data for 10 and 20 evaluable subjects are available. Under the alternative hypothesis, if the true response rate is 30%, PET is 3% by 10 subjects evaluated and 13% by 20 subjects evaluated.

9.2.1. Sample Size Re-estimation or Adjustment

Up to 30 subjects/cohort are expected to be enrolled in each dose-expansion phase of Part 2. There is no other sample size re-estimation or adjustment planned.

9.3. Data Analysis Considerations

In the dose escalation cohorts, the dose will be escalated based on all available data, including biomarker and PK data and the safety profile of prior cohorts. In addition, the recommended dose from a Continuous Reassessment Method (N-CRM) analysis [Neuenschwander, 2008] will be calculated. The N-CRM is a type of Bayesian adaptive dose-escalation scheme. The method is fully adaptive and makes use of all the DLT information available at the time of each dose assignment. The Fixed and Adaptive Clinical Trial Simulator (FACTS) will be used to conduct the N-CRM analysis. The DLT information on all subjects enrolled in the trial are used to update the estimated dose-toxicity relationship and provide supportive information in addition to the 3+3 design in the next escalation/de-escalation decision.

The expansion phases are designed to evaluate preliminary efficacy. A futility assessment will be conducted and enrollment may be paused in order to evaluate accumulating data including safety, responses and pharmacodynamic data. The

methodology is based on the predictive probability of success if enrollment continues until all planned subjects are recruited [Lee, 2008].

In addition, a Bayesian hierarchical model may be used to share information across cohorts if PK and biomarker data suggest a strong similarity in clinical activity among cohorts.

9.3.1. Analysis Populations

The **All Treated Population** is defined as all subjects who receive at least one dose of GSK3174998. Safety and anticancer activity will be evaluated based on this analysis population.

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

9.3.2. Interim Analysis

No formal interim analyses will be performed using the data generated from dose escalation cohorts. Preliminary safety and available PK/PD data will be performed and reviewed by study team (to include at minimum, the GSK medical monitor and investigator) after completion of each dose cohort. This review will support the decision on the dose level in the next dose cohort. Dose escalation decisions making will be based on the rules as described in Section 4.1.1 and Section 9.3. The Steering Committee will guide the transition of the study from dose escalation to cohort expansion for both monotherapy and combination therapies

For dose expansion cohorts, continuous assessment of efficacy and safety was planned to be performed after first interim analysis based upon a minimum of 10 subjects in at least one of the disease-specific cohorts with available unconfirmed overall response data for at least 12 weeks. However, after implementation of Amendment 4, no further subjects were enroled in the study; therefore, no futility analyses were performed.

Planned futility interim analysis decision rules for the 10^{th} to 30^{th} evaluable subjects are presented in Table 17 and Table 18, which specify the number of subjects with an unconfirmed response required for continuing enrolment when total sample size is up to 30. Additional futility looks may have been performed, if necessary. These rules were intended as a guideline only. If applicable, appropriated data from dose escalation may have been integrated into dose expansion decisions.

Actual decisions will depend on the totality of the data. Any additional decision rules will be documented in the RAP before the interim analysis. Should the recommendation to stop for futility be disregarded in favor of a decision to continue the trial based on the totality of the data, the overall type I error rate of the expansion phase will be inflated. The Steering Committee will monitor safety and efficacy over the course of the study following the randomization and futility rules for expansion cohorts.

Table 17 Futility Boundary for PD(L)-1 naive Pembrolizumab Combination Therapy Expansion Cohorts in STS.

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

a. Shaded regions indicate enrollment pause based on meeting futility

Table 18 Futility Boundary for PD(L)-1 Experienced Pembrolizumab Combination Therapy Expansion Cohorts in Melanoma

Number of Subjects[a]	Number of Responders					
	0	1	2	3	4	5
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						
29						
30						

a. Shaded regions indicate enrollment pause based on meeting futility.

9.4. Key Elements of Analysis Plan

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

9.4.1. Primary Analyses

9.4.1.1. Safety Analyses

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

9.4.1.2. Extent of Exposure

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

9.4.1.3. Adverse Events

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

Events will be summarized by frequency and proportion of total subjects, by system organ class and preferred term. Separate summaries will be given for all AEs, treatment-related AEs, SAEs and AEs leading to discontinuation of study treatment. AEs, if listed in the NCI-CTCAE (version 4.0) will be summarized by the maximum grade. Otherwise, the AEs will be summarized by maximum intensity.

Characteristics (e.g., number of occurrences, action taken, grade, etc) of AESI (see Section 6.3.1.3 and Appendix 11) will be summarized separately.

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

9.4.1.4. Clinical Laboratory Evaluations

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

9.4.1.5. Other Safety Measures

Data for vital signs and ECGs will be summarized based on pre-determined criteria identified to be of potential clinical concern. Further details will be provided in the RAP.

9.4.2. Secondary Analyses

9.4.2.1. Anticancer Activity Analyses

The All Treated Population will be used for anticancer activity analyses. Since this is a Phase I study, anticancer activity will be evaluated based on clinical evidence and response criteria. If data warrant, the response data will be summarized by dose level. irRECIST is the primary measure of clinical activity for response endpoints; RECIST v1.1 guidelines are used for disease measurements.

If the data warrant, ORR, DCR, TTR, and DOR will be calculated and listed for each subject.

ORR is defined as the percentage of subjects with a best overall confirmed CR or PR at any time as per disease-specific criteria (refer to Appendix 5). DCR is defined as the percentage of subjects with a confirmed CR + PR at any time, plus SD ≥12 weeks.

DOR will be calculated and listed for subjects with a confirmed CR or PR and is defined as the first documented evidence of CR or PR until disease progression or death due to any cause among subjects who achieve an overall response (i.e., unconfirmed or confirmed CR or PR). TTR is defined as the interval from the first dose of study treatment to the date of the first documented CR or PR. DOR and TTR are considered as exploratory endpoints. No summary tables for DOR and TTR will be provided.

Further details will be provided in the RAP.

9.4.2.2. Pharmacokinetic Analyses

9.4.2.2.1. Pharmacokinetic Parameters

PK analysis of GSK3174998 and pembrolizumab will be the responsibility of the Clinical Pharmacology Modeling and Simulation (CPMS) Department, GSK or Merck Sharp and Dohme Corp.

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

- Cmax
- time to Cmax (tmax)
- Cmin
- area under the plasma concentration-time curve, AUC(0-τ) (repeat dosing)
- apparent terminal phase half-life (t½) (single dose)
- systemic clearance of parent drug (CL)
- steady-state volume of distribution (Vss)

9.4.2.2.2. Statistical Analysis of Pharmacokinetic Data

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

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

The data from this study may be combined with the data from other studies for a population PK analysis, which will be reported separately.

9.4.2.3. Pharmacokinetic/Pharmacodynamic Analyses

Data obtained from the pharmacodynamic samples will be descriptively and/or graphically summarized, and if warranted, exploratory PK/Pharmacodynamic analyses will be conducted to inform dose selection decisions.

9.4.2.4. Immunogenicity Analyses

Serum samples will be tested for the presence of anti-GSK3174998 antibodies using the currently approved analytical methodology using a tiered testing schema: screening, confirmation and titration steps. The presence of treatment emergent ADA will be determined using a GSK3174998 bridging style ADA assay with a bio-analytically determined cut-point determined during assay validation. Samples taken after dosing with GSK3174998 that have a value at or above the cut-point will be considered treatment-emergent ADA-positive. These ADA positive samples will be further evaluated in a confirmatory assay, and confirmed positive samples will be further characterized by assessment of titer. Results of anti-GSK3174998 antibody testing will be reported at the end of the study and will include incidence and titer. The presence or absence of antibodies to GSK3174998 in dosed subjects will be analyzed, then summarized descriptively and/or graphically presented.

9.4.3. Other Analyses

9.4.3.1. Translational Research Analyses

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

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

9.4.3.2. Novel Biomarker(s) Analyses

The results of these biomarker investigations may be reported separately from the main clinical study report. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Additional exploratory analyses may be performed to further characterize the novel biomarker.

9.4.3.3. Longitudinal tumor size modeling

Longitudinal tumor size data may be analyzed using a non-linear mixed effects model to determine tumor kinetic constants. These parameters may be related to other patient characteristics, such as dose group, GSK3174998 exposure, or biomarkers.

9.4.3.4. Pharmacogenetic Analyses

Further details on PGx analyses will be addressed in Appendix 7 and the PGx RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

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

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

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

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

review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.

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

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

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

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

10.3. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

In the event of an assessment, audit, or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s), and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues, and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.4. Study and Site Closure

Upon completion or premature discontinuation of the study, the GSK designated monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.

If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.

If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant

regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.

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

10.5. Records Retention

Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.

The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including regenerating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.

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

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

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

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

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

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ACT	Adoptive cell transfer
ADA	Antidrug antibody
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event(s)
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC(0-t)	Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration)
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
BAL	Bronchoalveolar lavage
β-hCG	Beta-human chorionic gonadotropin
BUN	Blood urea nitrogen
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	Systemic clearance of parent drug
CrCl	Calculated creatinine clearance
Cmax	Maximum observed concentration
Cmin	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
CRM	Continual reassessment method
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSR	Clinical Study Report
CT	Computed tomography
CTC	Circulating Tumor Cell
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
CV	Cardiovascular
DCR	Disease Control Rate
DFS	Disease-free survival
DFSFU	Disease-free survival follow-up
DILI	Drug-induced liver injury
dL	Deciliter
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid

DOR	Duration of Response
DRE	Disease-related event
ECG	Electrocardiogram(s)
ECOG	Eastern Cooperative Oncology Group
EOI	End of infusion
EOPI	End of pembrolizumab infusion
eCRF	Electronic case report form
FACTS	Fixed and Adaptive Clinical Trial Simulator
FcγR	Antibody receptor crystalizable fragments gamma
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose-positron-emission tomography
FRP	Females of reproductive potential
FSH	Follicle stimulating hormone
FTIH	First time in human
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GITR	Glucocorticoid-induced TNFR family related gene
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GSK	GlaxoSmithKline
HED	Human equivalent dose
HNSTD	Highest non-severely toxic dose
HPLC	High-performance liquid chromatography
h	Hour(s)
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IL-10	Interleukin 10
INR	International normalized ratio
IP	Intraperitoneal
irAE	Immune-related adverse event(s)
IRB	Institutional Review Board(s)
irRECIST	Immune-related RECIST
ITIM	Immunoreceptor tyrosine-based inhibition motif
ITSM	Immunoreceptor tyrosine-based switch motif
IV	Intravenous
Kd	Equilibrium dissociation constant
kg	Kilogram(s)
L	Liter
LDH	Lactate dehydrogenase
LFT	Liver function Tests

mg	Microgram
mAb	Monoclonal antibody
MABEL	Minimum anticipated biological effect level
MAD	Maximum administered dose
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
min	Minute(s)
mL	Milliliter(s)
mmHg	Millimeters of mercury
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
MSI CRC	Colorectal carcinoma displaying high microsatellite instability
MTD	Maximum tolerated dose
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NK	Natural killer
NOAEL	No observed adverse effect level
NSCLC	Non-small cell lung cancer
nTregs	Natural Tregs
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD-1	Programmed death receptor-1
PD	Progressive disease
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PFS	Progression-free survival
PGx	Pharmacogenetics
PI	Principal investigator
PK	Pharmacokinetic(s)
PR	Partial response
PS	Performance status
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QTc	Corrected QT interval duration
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
RANKL	Receptor activator of nuclear factor-kappaB ligand
RBC	Red blood cells
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid

RP2D	Recommended Phase 2 dose
SAE	Serious adverse event(s)
SCCHN	Squamous cell carcinoma of the head and neck
sCRS	Severe cytokine release syndrome
SD	Stable disease
SFU	Survival follow-up
SLD	Sum of the longest diameters
SRM	Study Reference Manual
STS	Soft Tissue Sarcoma
TCR	T-cell receptor
TDV	Treatment discontinuation visit
TILs	Tumor infiltrating lymphocytes
TNBC	Triple-negative breast cancer
TNF	Tumor necrosis factor
TNFR	Tumor necrosis factor receptor
Tregs	Regulatory T cells
Tr1	Type 1 regulatory
TSH	Thyroid stimulating hormone
TTR	Time to Response
ULN	Upper limit of normal
WBC	White blood cells
WNL	Within normal limits

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
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Opdivo
Yervoy

12.2. Appendix 2: Immune-related Diseases

Table 19 List of 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

12.3. Appendix 3: Liver Safety – Study Treatment Restart or Rechallenge Guidelines

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

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

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

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

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

Risk factors for a fatal drug rechallenge outcome include:

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

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

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

- Investigator requests consideration of rechallenge with study treatment for a subject who is receiving compelling benefit with study treatment that exceeds risk, and no effective alternative therapy is available.

- Ethics Committee or IRB approval for rechallenge with study treatment must be obtained, as required.
- If the rechallenge is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the rechallenge with study treatment. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for rechallenge with study treatment must return to the clinic twice a week for liver chemistry tests until stable liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If after study treatment rechallenge, subject meets protocol-defined liver chemistry stopping criteria, study treatment should be permanently discontinued.
- GSK Medical Monitor, and the Ethics Committee or IRB as required, must be informed of the subject's outcome following study treatment rechallenge.
- GSK to be notified of any AEs, as per Section 7.4.1.

AND/OR

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

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

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

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
- Restart risk factors (e.g., fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis, possible study treatment-induced liver injury or study treatment has a human leukocyte antigen (HLA) genetic marker associated with liver injury (e.g., lapatinib, abacavir, amoxicillin/clavulanate) are reviewed and excluded.
- Ethics Committee or IRB approval of study treatment restart must be obtained, as required.

- If restart of study treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.
- GSK Medical Monitor, and the Ethics Committee or IRB as required, must be informed of the subject's outcome following study treatment restart.
- GSK to be notified of any AEs, as per Section 7.4.1.

12.4. Appendix 4: NYHA Functional Classification System for Heart Failure

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

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

12.5. Appendix 5: Guidelines for Assessment of Disease, Disease Progression and Response Criteria – adapted from RECIST version 1.1

12.5.1. Assessment Guidelines

Please note the following:

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

Clinical Examination: Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler/calipers to measure the size of the lesion, is required.

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

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.

12.5.2. Guidelines for Evaluation of Disease

12.5.2.1. Measurable and Non-measurable Definitions

12.5.2.1.1. 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.

12.5.2.1.2. Non-measurable lesion:

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

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

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

12.5.2.2. Immune-Related RECIST Response Criteria

12.5.2.2.1. Evaluation of target lesions

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

a. Measureable according to RECIST v1.1.
b. Treatment decisions will be based upon the immune-related RECIST criteria.

12.5.2.2.2. Antitumor response based on total measurable tumor burden

For the Modified RECIST criteria based on RECIST v1.1 and Immune-Related RECIST Criteria [Wolchok, 2009], the initial index and measurable new lesions are taken into account. At the baseline tumor assessment, the sum of the longest diameters (SLD) in the plane of measurement of all index lesions (maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved) is calculated. Note: If lymph nodes are included in the SLD, only the short axis of the lymph node(s) is added into the sum. The short axis is the longest perpendicular diameter to the longest diameter of a lymph node or nodal mass. At each subsequent tumor assessment, the SLD of the baseline index lesions and of new, measurable lesions (≥10 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total tumor burden:

$$\text{Tumor Burden} = SLD_{\text{index lesions}} + SLD_{\text{new, measurable lesions}}$$

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

Percentage changes in tumor burden per assessment time point describe the size and growth kinetics of both conventional and new, measurable lesions as they appear. At each tumor assessment, the response in index and new, measurable lesions is defined based on the change in tumor burden (after ruling out irPD). Decreases in tumor burden must be

assessed relative to baseline measurements (i.e., the SLD of all index lesions at screening).

12.5.2.2.4. 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 time point based on the assessment schedule, should be excluded from the response determination (e.g. non-target response does not have to be "Not Evaluable").

12.5.2.2.5. 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.

12.5.3. Evaluation of overall response

Table 20 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 20 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

12.5.3.1. Evaluation of best overall response

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

- To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after the first dose at a minimum interval of 77 days.
- If the minimum time for SD is not met, best response will depend on the subsequent assessments. For example if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement the best response will be PD. Alternatively, subjects lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

12.5.3.2. 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.

12.6. Appendix 6: ECOG Performance Status[a]

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

a. Oken, 1982.

12.7. Appendix 7: Genetic Research

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including GSK3174998 or pembrolizumab or any concomitant medicines;
- NSCLC, SCCHN, RCC, melanoma, bladder, STS, TNBC or MSI CRC, susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

12.7.1. Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

12.7.2. Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 mL blood sample will be taken for deoxyribonucleic acid (DNA) extraction. A blood sample is collected at the baseline visit, after the subject has met all eligibility requirements and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labeled (or "coded") with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or the study closure/termination. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

12.7.3. Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood sample for genetic research being taken.

12.7.4. Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

12.7.5. Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should

instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

12.7.6. Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

12.8. Appendix 8: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.8.1. Definition of Adverse Events

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

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). See Section 6.8.2 for details on an overdose with pembrolizumab • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

Events NOT meeting definition of an AE include:
• Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. • Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.8.2. Definition of Serious Adverse Events

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

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires hospitalization or prolongation of existing hospitalization NOTE: • In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in disability/incapacity NOTE: • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse
g. Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT 3xULN and total bilirubin 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.
• Refer to Section 6.3.1.3 for the required liver chemistry follow-up instructions

12.8.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the eCRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack

Cardiovascular Events (CV) Definition:
• Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

12.8.4. Recording of AEs and SAEs

AEs and SAE Recording:
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. • The investigator will then record all relevant information regarding an AE/SAE in the eCRF • It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE eCRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.8.5. Evaluating AEs and SAEs

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

Assessment of Causality
• The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE. • A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated. • The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment. • For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.** • The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE. • The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator may be asked to provide GSK with a copy of any post-mortem findings, including histopathology. • New or updated information will be recorded in the originally completed eCRF. • The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.8.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and email to PPD or fax to PPD PPD .Site will enter the SAE data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information to the Medical Monitor by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.9. Appendix 9: Collection of Pregnancy Information

12.9.1. Action to be taken if pregnancy occurs

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator will be reported to GSK. 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.

12.9.2. Action to be taken if pregnancy occurs in a female partner of a male study subject

- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who are randomized to receive study medication.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks 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.

Any female subject who becomes pregnant while participating

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

12.10. Appendix 10: Country Specific Requirements

No country-specific requirements exist.

12.11. Appendix 11: Adverse Events of Special Interest

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

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

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

Pembrolizumab-specific events of clinical interest for this trial include:

- An overdose of pembrolizumab, as defined in Section 6.8.2 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
- An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

12.12. Appendix 12: 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.

12.13. Appendix 13: Protocol Amendment Changes

12.13.1. Amendment 1

12.13.1.1. Where the Amendment Applies

This amendment applies to all sites and countries.

12.13.1.2. Summary of Amendment Changes with Rationale

Amendment 1 incorporates changes to Section 4.1.4, Dose-Limiting Toxicities; 5.4 Withdrawal/Stopping Criteria; and 6.3.1.12, Dose Delay as requested by the United States FDA.

Additionally, the SAE contact information was updated due to internal departmental changes.

12.13.1.3. List of Specific Changes

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

REVISED TEXT:

Medical Monitor/Serious Adverse Event (SAE) Contact Information:

Role	Name	Office Phone Email Address	Mobile	Fax
Primary Medical Monitor	PPD , MD	PPD	PPD	
Secondary Medical Monitor	PPD , MD, PhD	PPD	PPD	
SAE contact information		PPD		PPD

Section 4.1.4 Dose-Limiting Toxicity

REVISED TEXT:

Table 4 Dose-Limiting Toxicity Criteria

Toxicity	DLT Definition
Hematologic	• Febrile neutropenia • Grade 4 neutropenia of >7 days' 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 toxicity that does not downgrade to Grade 1 ~~≤Grade 2~~ or baseline within 3 days despite optimal supportive care[a]~~, with the following exceptions:~~ ~~• Laboratory abnormality that is not clinically significant according to the investigators (for example, isolated Grade 3 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis)~~ ~~• Grade 3 endocrinopathy that is adequately controlled by hormonal replacement~~ • Any Grade 2 ocular toxicity requiring systemic steroids, or any ≥ Grade 3 ocular toxicity
Other	• Toxicity that results in permanent discontinuation of GSK3174998 or GSK3174998 and pembrolizumab during the first 4 weeks of treatment • Any other toxicity considered to be dose-limiting that occurs beyond 4 weeks will be considered in the selection of the dose 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 management guidelines described in Section 6.3.1 for toxicity and may include systemic corticosteroids for immune-related toxicities; if use of systemic corticosteroids delays administration of the second dose of study treatment but the event does not otherwise meet the DLT criteria for non-hematologic toxicity, the dose delay will not be considered a DLT.

b. DLT = Dose-limiting toxicity; G-CSF = Granulocyte colony-stimulating factor; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; ULN = Upper limit of normal; GSK = GlaxoSmithKline

Section 5.4 Withdrawal/Stopping Criteria

REVISED TEXT:

Subjects will receive study treatment for the scheduled time period, unless one of the following occurs earlier: disease progression (as determined by irRECIST), death, or unacceptable toxicity, including meeting stopping criteria for liver chemistry defined in Section 5.4.1. In addition, study treatment might be permanently discontinued for any of the following reasons:

- Deviation(s) from the protocol
- Request of the subject or proxy (withdrawal of consent by subject or proxy)
- Investigator's discretion

- Subject is lost to follow-up
- Study is closed or terminated
- Subjects with infusion delays greater than 3 weeks due to toxicity ~~>49 days (i.e., 2 missed doses + 7 days)~~ should discontinue study drug(s) unless the treating investigator and Sponsor/Medical Monitor agree there is strong evidence supporting continued treatment.

  Note: Subjects who require permanent discontinuation of one of the study treatments due to toxicity in a given treatment combination must permanently discontinue both treatments (unless continued treatment with the remaining agent is agreed upon by the treating investigator and Sponsor/Medical Monitor) in that combination and the reason for discontinuation must be recorded. The treatment discontinuation visit (TDV) should be conducted within 30 days of the decision to discontinue study drug(s).
- Intercurrent illness that prevents further administration of study treatment(s)
- Criteria for discontinuation of study drug(s) as described in Section 6.3.1 (Safety Management Guidelines) have been met
- Criteria described in Section 5.4.2 (QTcF Stopping Criteria) have been met
- Criteria described in Section 5.4.3 (Stopping Rules for Clinical Deterioration) have been met

Section 6.3.1.12 Dose Delay

REVISED TEXT:

If there is a dose delay between 1 and 7 days, the procedures at the original scheduled visit (including dosing) should be performed as soon as possible. If the delay is ≥8 days, the visit and dose(s) will be considered missed. The procedures at the next scheduled visit should be performed, and subsequent visits will follow Q3W. Subjects with infusion delays greater than 3 weeks due to toxicity ~~>49 days (i.e., 2 missed doses + 7 days)~~ should discontinue study drug(s) unless the treating investigator and Sponsor/Medical Monitor agree there is strong evidence supporting continued treatment. For subjects requiring elective surgery or radiation therapy, every effort should be made to wait 1 to 2 weeks after the last dose of study drug(s) before performing surgery or starting radiation. Study drug(s) should not be administered again until 1 to 2 weeks after recovery from surgery or radiation (see Section 6.10.1. for details on permitted medications and non-drug therapies).

12.13.2. Amendment 2 Protocol Changes for Amendment 2 (16-AUG-2016) from the Protocol Amendment 1 (17-AUG-2015)

Where the Amendment Applies

This amendment applies to all sites and countries.

Summary of Amendment Changes with Rationale

Amendment 2 includes the addition of preliminary clinical data to support the initiation of Part 2/combination with pembrolizumab, the addition of a new Pharmacodynamic Cohort to allow collection of additional tumor biopsies, removal of Soft Tissue Sarcoma from the targeted tumor types, extension of GSK3174998 dosing up to 2 years or 35 cycles, definitions of analyses for anticancer activity, addition and clarifications of procedures in the T&E table, clarification on the use of CRM for dose escalation, as well as minor typographical and/or inconsistent language throughout the protocol.

List of Specific Changes

Section 1 PROTOCOL SYNOPSIS FOR STUDY 201212 (ENGAGE-1)

REVISED TEXT:

Objectives/Endpoints:

The primary objectives of the study are to evaluate the safety and tolerability and to identify the maximum tolerated dose (MTD) or maximum administered dose (MAD) of GSK3174998 when administered intravenously as monotherapy (Part 1) or in combination with pembrolizumab (Part 2) to subjects with selected advanced or recurrent solid tumors. Secondary objectives include: the evaluation of antitumor activity; characterization of pharmacokinetics (PK) for GSK3174998 when administered alone; characterization of PK for GSK3174998 and pembrolizumab when administered in combination; ~~evaluation of pharmacodynamic activity in the blood and tumor microenvironment;~~ and determination of the immunogenicity of GSK3174998 when administered alone or for GSK3174998 and pembrolizumab when administered in combination. Exploratory objectives include evaluation of pharmacodynamic activity in the blood and tumor microenvironment.

2 nd point:

Antitumor activity endpoints: Objective response rate (ORR) and Disease Control Rate (DCR) (complete response [CR]+partial response [PR]+stable disease [SD] ≥12 weeks), time to response (TTR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS). Unless otherwise specified, all response endpoints will be assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and by irRECIST (immune-related RECIST); the primary endpoint analysis will use irRECIST.

3rd point:

Pharmacodynamic endpoints: Assessment of lymphocyte OX40 receptor membrane expression and occupancy by GSK3174998, along with the phenotype, quantity, and activation state of T cells in the periphery, expression of circulating soluble factors, and changes in genomic DNA and gene expression. Assessment of tumor biopsies via immunohistochemistry (IHC) for the numbers of tumor-infiltrating lymphocytes and other immune cells expressing key phenotypic markers.

Treatment Arms and Duration:

The study includes a screening period, a treatment period, and a follow-up period. Subjects will be screened for eligibility beginning approximately 4 weeks before the start of treatment. The maximum duration of treatment with GSK3174998 ~~will be 48 weeks; the maximum duration of treatment with~~ ± pembrolizumab will be 2 years or 35 cycles, whichever comes first. The follow-up period for safety assessments will be a minimum of 3 months from the date of the last dose. The post-treatment follow-up period includes disease assessments every 12 weeks until confirmed disease progression (PD). Following PD, subjects will be contacted every 3 months to assess survival status.

In Part 1, dose escalation for GSK3174998 monotherapy will begin with a starting dose of 0.003 mg/kg GSK3174998 administered once every 3 weeks (Q3W). In Part 2, dose escalation for GSK3174998 + pembrolizumab combination therapy will begin with a fixed dose of 200 mg pembrolizumab administered Q3W and a starting dose of 0.003 mg/kg GSK3174998 ~~that is two dose levels below a tolerated dose of GSK3174998 monotherapy that has also demonstrated pharmacodynamic activity in Part 1A of the study~~. Dose adjustments are allowed to address tolerability and safety issues.

Type and Number of Subjects:

The study will enroll up to approximately 264 ~~180~~ subjects with tumor types that may include NSCLC, squamous cell carcinoma of the head and neck (SCCHN), renal cell carcinoma (RCC), melanoma, bladder cancer, ~~soft tissue sarcoma (STS)~~, triple-negative breast cancer (TNBC), and colorectal carcinoma displaying microsatellite instability (MSI CRC).

Section 2.3.1 Background

REVISED TEXT:

An overview of the nonclinical studies of GSK3174998 and preliminary clinical data from Protocol 201212 (ENGAGE-1) are ~~is~~ provided below. Detailed information concerning the biology, pharmacology, PK, and safety can be found in the Investigators' Brochure (IB) [GlaxoSmithKline Document Number 2014N212091_00.

ADDED SECTIONS:

Section 2.3.5 Preliminary Clinical Data for GSK3174998

Data are summarized for the ongoing first time in human study with a clinical data cut-off of 17 May 2016. Data are reported for six subjects enrolled at the following GSK3174998 dose levels: 0.003 mg/kg (Cohort 1, n=1), 0.01 mg/kg (Cohort 2, n=1), and 0.03 mg/kg (Cohort 3, n=4). At the time of reporting, three subjects had discontinued treatment due to disease progression (one at each dose level).

Section 2.3.5.1 Preliminary Safety Data (ENGAGE-1: Part 1)

No dose-limiting toxicities, no treatment-related Grade 3 or 4 toxicities, and no treatment discontinuations due to AEs were reported. One SAE was reported (Grade 3 urinary tract infection and Grade 4 hydronephrosis) in a subject with bladder cancer treated at the 0.003 mg/kg dose level; the SAE was attributed to disease progression. The subject discontinued study treatment due to disease progression and at that time had received 2 doses of GSK3174998. All other AEs were Grade 1 or 2 in severity. One AE (fatigue) was reported in two subjects; all other events were reported once each: Actinic keratosis, anemia, arthralgia, asthenia, blood creatinine increased, cough, diarrhea, dizziness, dry mouth, fall, headache, hernia, hyperkalemia, hypoesthesia, myalgia, nausea, pain in extremity, vomiting. Two events (Grade 1 dry mouth, Grade 1 nausea) were considered treatment-related.

For further details on the safety of GSK3174998, please refer to the IB [GlaxoSmithKline Document Number GlaxoSmithKline Document Number 2014N212091.

Section 2.3.5.2 Preliminary Pharmacokinetic Data (ENGAGE-1: Part 1)

Maximum observed concentrations (Cmax) of GSK3174998 in plasma were in the predicted range anticipated for each dose level (44 ng/mL for 0.003 mg/kg, 267 ng/mL for 0.01 mg/kg, 458 – 1624 ng/mL for 0.03 mg/kg). Clearance was greater than anticipated at the lower dose levels; this was considered to be due to target mediated clearance. Subject 4, dosed at 0.03 mg/kg was the heaviest subject treated (119 kg), thus received the largest dose and had the highest GSK3174998 exposure (1624 ng/mL).

Section 2.3.5.3 Preliminary Receptor Occupancy Data (ENGAGE-1: Part 1)

Receptor occupancy (RO) was assessed for CD3+ cells from peripheral blood. Preliminary receptor occupancy (RO) data after the first dose was higher than predicted; approximately 85% RO was seen in Subject 1 who received the lowest dose of GSK3174998 (0.003 mg/kg). Subject 4, who had the largest GSK3174998 exposure, had >90% RO throughout the first dosing period (21 days); while Subjects 6, 7, and 502, treated with the same dose level (0.03 mg/kg) had >90% RO for approximately 8 days during the first dosing period.

Section 2.3.5.4 Preliminary Clinical Activity Data (ENGAGE-1: Part 1)

Due to the frequency of disease assessments (every 12 weeks), few subjects had their first post-baseline disease assessments performed at the time of clinical data cut-off (17 May 2016) and no objective responses were observed. Subject 1 (0.003 mg/kg), 3 (0.01 mg/kg) and 4 (0.03 mg/kg) discontinued treatment due to disease progression after 2, 4, and 3 doses of GSK3174998, respectively.

Section 2.4 Pembrolizumab

DELETED SECTION:

Section 2.4.1 PD-1 as a Therapeutic Target:

~~The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control [Pedoeem, 2014]. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4, which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structures of murine PD-1 alone [Zhang, 2004] and in complex with its ligands were first resolved [Lazar-Molnar, 2008;Lin, 2008], and more recently the NMR-based structure of the human PD-1 extracellular region and analyses of its interactions with its ligands were also reported [Cheng, 2013]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules, such as CD3ζ, PKCθ and ZAP70, which are involved in the CD3 T-cell signaling cascade [Sheppard, 2004]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from that of CTLA-4 [Ott, 2013]. PD-1 was shown to be expressed on activated lymphocytes, including peripheral CD4+ and CD8+ T cells, B cells, Tregs and NK cells [Yao, 2014]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T cells [Nishimura, 1996], as well as subsets of macrophages [Huang, 2009] and dendritic cells [Pea-Cruz, 2010]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types [Keir, 2008]. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments [Keir, 2008]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell~~

~~function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor [Karim, 2009, Taube, 2012], which, via its interaction with the PD-1 receptor on tumor-specific T cells, plays a critical role in immune evasion by tumors [Sanmamed, 2014]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in cancer [Topalian, 2012].~~

REVISED TEXT:

~~2.4.2~~ 2.4.1 Pembrolizumab Background and Clinical Trials:

~~Pembrolizumab [KEYTRUDA (US); previously known as lambrolizumab, MK-3475 and SCH-9000475] is a potent and highly selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab was recently approved in the US and is indicated for the treatment of subjects with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor [KEYTRUDA Prescribing Information, 2014,Poole, 2014]. It is the first anti-PD-1 therapy to receive regulatory approval in the US, and is currently under regulatory review in the EU.~~

Pembrolizumab, a humanized monoclonal antibody against the PD-1 protein, has been developed by Merck & Co for the treatment of patients with cancer. Pembrolizumab is approved for treatment of patients with melanoma in several countries; in the US and EU it is approved for the treatment of patients with advanced (unresectable or metastatic) melanoma in adults. Pembrolizumab has also been approved for treatment of patients with NSCLC in several countries; in the US it is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with NSCLC and EGFR or ALK genomic tumor aberrations should also have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab. In the US, pembrolizumab is also approved for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after platinum-containing chemotherapy.

Pembrolizumab has demonstrated initial clinical efficacy in single arm monotherapy trials in subjects with non-small cell lung cancer, head and neck squamous cell carcinoma, urothelial cancer, gastric cancer, triple negative breast cancer and Hodgkin's Lymphoma as determined by response rate. Ongoing clinical trials are being conducted in advanced melanoma, NSCLC, head and neck cancer, urothelial cancer, gastric cancer, TNBC, Hodgkin's lymphoma and a number of other advanced solid tumor indications and hematologic malignancies. For study details please refer to the IB [Merck Sharp & Dohme Corp, 2015]

2.4.2 Rationale for Pembrolizumab Dose Selection

DELETED TEXT:

~~An open-label Phase I trial (KEYNOTE-001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified.~~

~~PK data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life [Merck Sharp & Dohme Corp, 2014]. Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q3W dosing schedule. Because Q3W dosing is more convenient for subjects, Q3W dosing will be furthered studied.~~

ADDED TEXT:

The dose of pembrolizumab planned to be studied in this trial is 200 mg Q3W. The dose recently approved in the United States and several other countries for treatment of melanoma subjects is 2 mg/kg Q3W. Information on the rationale for selecting 200 mg Q3W is summarized below.

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

An integrated body of evidence suggests that 200 mg every 3 weeks (Q3W) is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in subjects with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with 2 mg/kg Q3W dose.

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

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

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

Section 3. Objectives and Endpoints

REVISED TEXT:

Objectives	Endpoints
Part 1: GSK3174998 Monotherapy	
Primary	
• To evaluate the safety and tolerability and identify the MTD[a] or the MAD of GSK3174998 administered intravenously to subjects with selected advanced or recurrent solid tumors.	• AEs, SAEs, DLT, withdrawals due to AEs, dose reductions or delays, and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters).
Secondary	
• To evaluate the antitumor activity of GSK3174998 in subjects with selected advanced or recurrent solid tumors. • To characterize the PK of GSK3174998 monotherapy. • ~~To evaluate the pharmacodynamic activity~~	• ORR and DCR (CR+ PR+ SD ≥12 weeks), ~~time to response~~TTR, ~~duration of response~~ DOR, PFS, and OS.[b] • GSK3174998 concentrations in plasma and PK parameters including Cmax, AUC(0-τ), and Cmin. • ~~Assessment of lymphocyte OX40 receptor~~

Objectives	Endpoints
Part 1: GSK3174998 Monotherapy	
~~of GSK3174998 in the periphery, i.e., blood and in the tumor microenvironment~~	~~membrane expression and occupancy by GSK3174998, along with the phenotype, quantity, and activation state of T cells in the periphery.~~ • ~~Assessment of tumor biopsies via IHC for the numbers of tumor-infiltrating lymphocytes and other immune cells expressing key phenotypic markers~~
• To determine the immunogenicity of GSK3174998.	• Number and percentage of subjects who develop detectable ADA.

Objectives	Endpoints
Part 1: GSK3174998 Monotherapy	
Exploratory	
• To explore the relationship between antitumor activity, PK parameters, ~~and~~ pharmacodynamic activity and other patient characteristics. ~~response after treatment with GSK3174998.~~	• Evaluation of antitumor activity (CR, PR, SD, PD), tumor kinetic parameters, PK parameters, ~~and~~ pharmacodynamic activity, and other patient characteristics.
• To evaluate the pharmacodynamic activity of GSK3174998 in the peripheral blood and to explore the utility of these measures to enrich for clinical efficacy and development of a diagnostic test. • ~~To explore the association between treatment with GSK3174998 and changes in genomic DNA, gene expression (RNA and protein), measures of immune function in tissue and blood and antitumor activity~~	• Assessment of lymphocyte OX40 receptor membrane expression and occupancy by GSK3174998. Measures of immune function in blood (e.g. phenotype, quantity, and activation state of T cells in the periphery, expression of circulating soluble factors such as cytokines and stress-related proteins). Changes in genomic DNA, gene expression (RNA and protein), (e.g, using cfDNA, exosomes or circulating tumor cells [CTCs]). • ~~Correlation between antitumor activity and expression of immune related genes, e.g., but not limited to TCR sequences and gene signatures, along with the expression of circulating soluble factors such as cytokines and stress-related proteins in both tissues and blood.~~
• To evaluate the pharmacodynamic activity of GSK3174998 in the tumor	• Assessment of tumor biopsies via IHC for the numbers of tumor-infiltrating

microenvironment and to explore the utility of these measures to enrich for clinical efficacy and development of a diagnostic test. • ~~To explore the immune response biomarkers in tumor tissue and their association with the antitumor activity with GSK3714998.~~	lymphocytes and other immune cells expressing key phenotypic markers. Changes in gene expression (RNA and protein),TCR diversity or mutational load (genomic DNA). • ~~Determination of the correlation between the immune response in tumor samples and antitumor activity of GSK3174998 to identify potential selection biomarkers for subject enrichment.~~
• Pharmacogenetics (PGx): To evaluate the association of genetic variations in the host DNA and response to therapy.	• Germline genetic evaluations may be conducted for: • Medicine response, including GSK3174998 or any concomitant medicines. • Disease susceptibility, severity, and progression and related conditions.
Hypothesis	
For the primary objective, no formal statistical hypothesis will be tested; analysis will be descriptive and exploratory	

In the final determination of the MTD, all available safety and tolerability data will be considered

Unless otherwise specified, all response endpoints will be assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and by irRECIST (immune-related RECIST); irRECIST will be used to determine treatment decisions.

RNA = Ribonucleic acid; DNA = Deoxyribonucleic acid

Objectives	Endpoints
Part 2: Combination GSK3174998 plus pembrolizumab	
Primary	
• To evaluate the safety and tolerability and identify the MTD[a] or the MAD of GSK3174998 administered intravenously in combination with IV pembrolizumab to subjects with selected advanced or recurrent solid tumors.	• AEs, SAEs, DLTs, withdrawals due to AEs, dose reductions or delays, and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters).
Secondary	
• To evaluate the antitumor activity of GSK3174998 in combination with pembrolizumab in subjects with selected advanced or recurrent solid tumors. • To characterize the PK of GSK3174998 monotherapy when administered in combination.	• ORR and DCR (CR+ PR+ SD ≥12 weeks), ~~time to response~~TTR, ~~duration of response~~ DOR, PFS, and OS.[b] • Plasma GSK3174998 and serum pembrolizumab concentrations and PK parameters including Cmax, AUC(0-τ), and Cmin.

Objectives	Endpoints
Part 2: Combination GSK3174998 plus pembrolizumab	
~~• To evaluate the pharmacodynamic activity of GSK3174998 in combination with pembrolizumab in the periphery, i.e., blood and in the tumor microenvironment~~	~~• Assessment of lymphocyte OX40 receptor membrane expression and occupancy by GSK3174998, along with the phenotype, quantity, and activation state of T cells in the periphery.~~ ~~• Assessment of tumor biopsies via IHC for the numbers of tumor-infiltrating lymphocytes and other immune cells expressing key phenotypic markers~~
• To determine the immunogenicity of GSK3174998 and pembrolizumab when administered in combination.	• Number and percentage of subjects who develop detectable ADA.

Objectives	Endpoints
Part 2: Combination GSK3174998 plus pembrolizumab	
Exploratory	
• To explore the relationship between antitumor activity, PK parameters, ~~and~~ pharmacodynamic activity and other patient characteristics. ~~response after treatment with GSK3174998 in combination with pembrolizumab~~ • To evaluate the pharmacodynamic activity of GSK3174998 in combination with pembrolizumab in the peripheral blood and to explore the utility of these measures to enrich for clinical efficacy and development of a diagnostic test. • ~~To explore the association between treatment with GSK3174998 and changes in genomic DNA, gene expression (RNA and protein), measures of immune function in tissue and blood and antitumor activity~~	• Evaluation of antitumor activity (CR, PR, SD, PD), tumor kinetic parameters, PK parameters, ~~and~~ pharmacodynamic activity, and other patient characteristics. • Assessment of lymphocyte OX40 receptor membrane expression and occupancy by GSK3174998. Measures of immune function in blood (e.g. phenotype, quantity, and activation state of T cells in the periphery, expression of circulating soluble factors such as cytokines and stress-related proteins). Changes in genomic DNA, gene expression (RNA and protein), (e.g, using cfDNA, exosomes or circulating tumor cells [CTCs]). • ~~Correlation between antitumor activity and expression of immune related genes, e.g., but not limited to TCR sequences and gene signatures, along with the expression of circulating soluble factors such as cytokines and stress-related proteins in both tissues and blood.~~
• To evaluate the pharmacodynamic activity of GSK3174998 in combination with pembrolizumab in the tumor microenvironment and to explore the utility of these measures to enrich for clinical efficacy and development of a diagnostic test. • ~~To explore the immune response biomarkers in tumor tissue and their association with the antitumor activity with GSK3714998.~~ • (PGx): To evaluate the association of genetic variations in the host DNA and response to therapy.	• Assessment of tumor biopsies via IHC for the numbers of tumor-infiltrating lymphocytes and other immune cells expressing key phenotypic markers. Changes in gene expression (RNA and protein), TCR diversity or mutational load (genomic DNA). • ~~Determination of the correlation between the immune response in tumor samples and antitumor activity of GSK3174998 to identify potential selection biomarkers for subject enrichment.~~ • Germline genetic evaluations may be conducted for: • Medicine response, including GSK3174998 and pembrolizumab or any concomitant medicines. • Disease susceptibility, severity, and progression and related conditions.

Objectives	Endpoints
Part 2: Combination GSK3174998 plus pembrolizumab	
Hypothesis	
For the primary objective, no formal statistical hypothesis will be tested; analysis will be descriptive and exploratory	

a. In the final determination of the MTD, all available safety and tolerability data will be considered
b. Unless otherwise specified, all response endpoints will be assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and by irRECIST (immune-related RECIST); irRECIST will be used to determine treatment decisions.

RNA = Ribonucleic acid; DNA = Deoxyribonucleic acid

Section 4.1 Overall Design

REVISED TEXT:

2nd, 3 rd , 4 th Paragraph and figure 3:

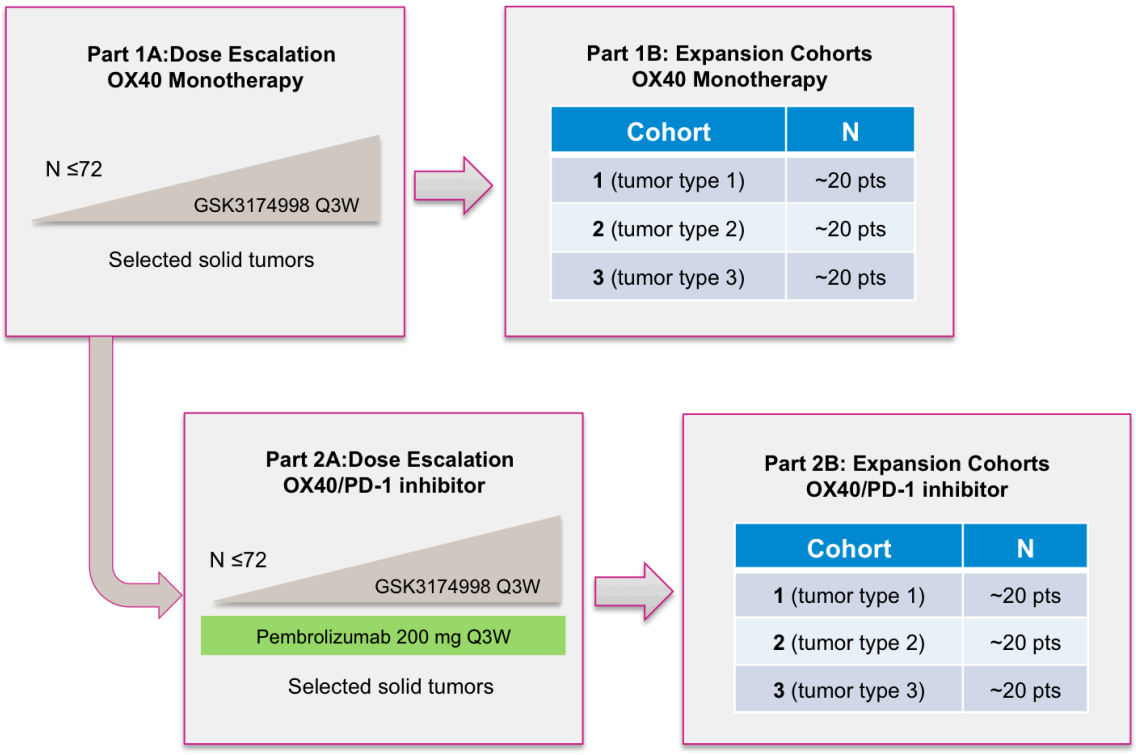
The study will be conducted in 2 parts, each part consisting of a dose-escalation phase followed by a cohort expansion phase (see Figure 3). Part 1 will evaluate GSK3174998 monotherapy, while Part 2 will evaluate GSK3174998 in combination with pembrolizumab. As shown in Figure 3, GSK3174998 will first be evaluated as monotherapy in escalating doses. Once a dose of GSK3174998 has been identified that is both tolerable and demonstrates pharmacodynamic activity, enrollment of Part 2 may begin. In Part 2, escalating doses of GSK3174998 will first be evaluated with fixed doses of pembrolizumab. Part 1A and 2A will also include a Pharmacodynamic Cohort, which requires mandatory fresh pre- and on-treatment biopsies and an additional disease assessment at week 6. Each part will also include expansion cohorts for up to three different tumor types.

The study will enroll up to approximately ~~180~~ 264 subjects with tumor types that may include NSCLC, SCCHN, RCC, melanoma, bladder cancer, ~~STS,~~ TNBC, and MSI CRC. In the dose-escalation phase of the study, subjects with any of the aforementioned tumor types may be included; whereas in the cohort expansion phase of the study, each expansion cohort will enroll subjects with one specific tumor type selected from the aforementioned list. Up to three expansion cohorts may be included for each part of the study.

A subject's disease status and determination of disease progression at postbaseline visits will be evaluated by the local investigators' assessments of radiology by RECIST v1.1 and irRECIST; a decision to discontinue treatment due to disease progression will be based upon irRECIST~~; however,~~ and the primary endpoint analysis will use irRECIST~~v1.1~~. Scans will be collected centrally and stored to allow for the option of central radiologic audit or review.

Figure 4 ENGAGE-1 Study Design

a) Part 1A and Part 2A Design



b) Part 1A and Part 2A Dose Escalation

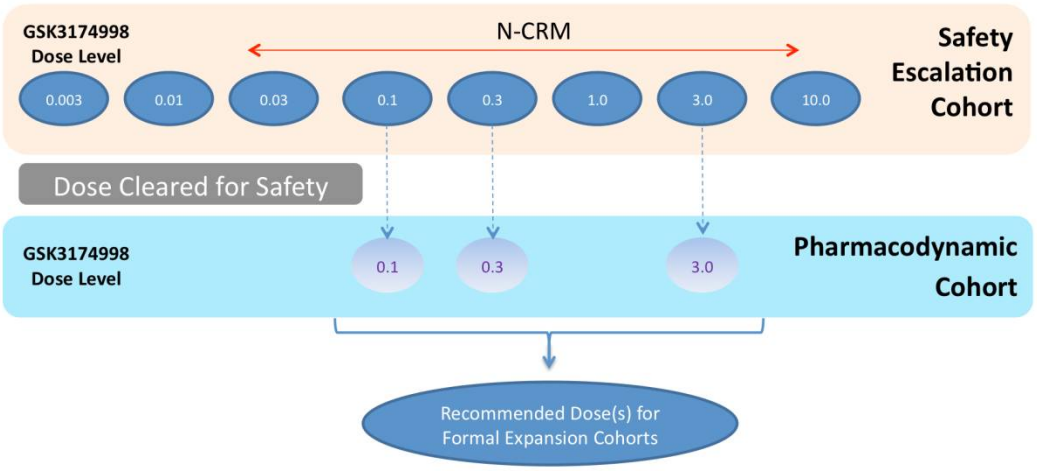


Figure 3a shows the overall study design: Part 1A GSK3174998 monotherapy dose escalation, Part 1B GSK3174998 monotherapy cohort expansion, Part 2A GSK3174998 + pembrolizumab dose escalation, Part 2B GSK3174998 + pembrolizumab cohort expansion. Figure 3b shows dose escalation (Parts 1A and 2A) including the "pharmacodynamic cohort". Note: An example of 3 dose levels being expanded in the pharmacodynamic cohort is provided to illustrate it is possible not all dose levels will be explored in the pharmacodynamic cohort, which mandates pre- and on-treatment tumor biopsies in order to further explore dose-response with biomarkers in the tumor microenvironment.

Section 4.1.1 Dose Escalation

REVISED TEXT:

2 nd paragraph:

For subsequent dose levels, a modified 3+3 design will be used for dose escalation as shown in Table 1. The first three subjects treated at the third dose level will begin treatment 1 week apart to allow assessment of initial safety data in each subject before beginning the next subject's treatment. Evaluation of the available safety data over the first 4 weeks of treatment is required from at least 3 subjects before a decision is made whether to enroll additional subjects at the same, or the next higher dose level. Subjects who withdraw from the study before the completion of 4 weeks treatment and 2 doses for reasons other than DLT may be replaced. After the third dose level cohort is completed, subsequent dose levels may initially enroll up to 4 subjects and subjects will begin treatment at least ~~24 hours~~ one calendar day apart.

Table 1 3 + 3 Dose-Escalation Guidelines

REVISED TEXT:

Number of Subjects with DLT at a Given Dose Level	**Action[a]**
0 out of 3 subjects	Escalate to next dose level and enter 3 subjects
1 out of 3 subjects	Accrue 3 additional evaluable subjects at current dose level for a total of 6 evaluable subjects. ~~If 0 of the 3 additional subjects experience a DLT, proceed to next dose level.~~ ~~If 1 or more of the additional subjects experience a DLT, the dose escalation is stopped and this dose is declared the MTD.~~
1 out of 6 subjects	Escalate to next dose level
2 or more subjects in a dosing cohort (up to 6 subjects)	Dose escalation will be stopped. At this dose level, the MTD has been exceeded (highest dose administered).

a.The Steering Committee may propose that a given dose-escalation cohort be expanded up to a total of 12 subjects if (i) further evaluation of the frequency of a given toxicity is warranted, based upon the observed safety profile in the 6 subjects already recruited in the cohort or (ii) further evaluation of pharmacodynamic markers to aid dose selection is warranted; in either case, the incidence of confirmed DLT must not equal or exceed 33%.
DLT = Dose-limiting toxicity; MTD = Maximum tolerated dose

In alignment with the guidance prospectively established in the Protocol (see above), the Steering Committee proposed that dose-escalation cohorts be expanded up to a total of 12 subjects in order to further evaluate pharmacodynamic markers to aid dose selection. This proposal was agreed and implemented at the time of opening Cohort 4 (0.1 mg/kg) and documented in writing. Since the incidence of confirmed DLT must not exceed 33% in this study, the recommended dose from a Continuous Reassessment Method (N-CRM) analysis [Neuenschwander, 2008] will be calculated (as prospectively described in Section 9.3). The N-CRM is a type of Bayesian adaptive dose-escalation scheme. The method is fully adaptive and makes use of all the DLT information available at the time of each dose assignment.

From Part 1 Cohort 4 (0.1mg/kg) onwards and for all Part 2 dose levels, each dose level may initially enroll up to 4 subjects. Once at least 3 of these subjects have completed the DLT evaluation period (4 weeks), a decision may be made to initiate the next higher dose level, pending the evaluation of safety data using the N-CRM methodology. Subjects identified as eligible for enrollment after the enrollment of 4 subjects in current dose level and before next higher dose level is open may be assigned to a lower dose level.

A maximum of 12 subjects will be enrolled at any given dose level in Part 1A and Part 2A; up to 6 of these subjects at any given dose level maybe part of a "Pharmacodynamic Cohort" (Figure 3). Subjects entering the "Pharmacodynamic Cohort" will have the following additional eligibility requirements (as described in Section 5.1):

- Mandatory fresh biopsy collection at baseline, on treatment (at 6 weeks), and if feasible at the time of disease progression

- Additional 6-week disease assessment and availability of a pre-baseline scan (within 24 weeks before the baseline scan), if feasible, to support exploratory investigation of tumor growth kinetics

Exploration of lower dose levels than recommended by N-CRM (or expansion of a previously-tested dose level) is allowed if agreed upon by the Medical Monitor and treating investigators. The final dose escalation decision will be made by study team on all available data, including biomarker and PK data and the safety profile of prior cohorts. Dose-escalation decisions will be documented in writing with copies maintained at each site and the study files.

Section 4.1.2 Part 1A: Monotherapy Dose Escalation

REVISED TEXT:

Table 2 Part 1A Dose Levels

Dose Level	GSK3174998 (mg/kg)[a]	Dose Escalation Cohort (n)	Pharmacodynamic Cohort (n)
1	0.003	1	≤6
2	0.01	1	≤6
3	0.03	3-6	≤6
4	0.1	3-6	≤6
5	0.3	3-6	≤6
6	1.0	3-6	≤6
7	3.0	3-6	≤6
8	10.0	3-6	≤6

a. Lower dose intensities may be explored if exposure is significantly higher than predicted, if there is excessive toxicity, or if further evaluation of pharmacodynamic markers to aid dose selection is warranted. This may be achieved by reducing the dose or by alternate dosing schedules.

Section 4.1.3 Part 2A: Combination Dose Escalation (GSK3174998 + Pembrolizumab)

REVISED TEXT:

Dose escalation for GSK3174998 + pembrolizumab combination therapy will begin with a fixed dose of 200 mg pembrolizumab administered Q3W and a starting dose of 0.003 mg/kg GSK3174998. ~~that is at least 2 dose levels below a tolerated dose of GSK3174998 monotherapy that has also demonstrated pharmacodynamic activity in Part 1A of the study.~~

GSK3174998 dose levels that may be administered in combination with pembrolizumab are ~~An example of potential combinations of GSK3174998 and pembrolizumab is~~ described in Table 3~~. In this example, a dose of 1 mg/kg GSK3174998 alone was tolerated in at least 3 subjects in Part 1A of the study.~~

Table 25 ~~Example of~~ Part 2A Dose Levels

Dose Level	GSK3174998 (mg/kg)	Pembrolizumab (mg)	Dose Escalation Cohort (n)	Pharmacodynamic Cohort (n)
1	0.003	200	3-6	≤6
2	0.01	200	3-6	≤6
3	0.03	200	3-6	≤6
4 ~~1~~	0.1	200	3-6	≤6
~~2~~5	0.3	200	3-6	≤6
~~3~~6	1.0	200	3-6	≤6
47	3.0	200	3-6	≤6
~~5~~8	10.0	200	3-6	≤6

If the combination doses in the starting dose cohort of Part 2A are not tolerable, lower dose intensities of GSK3174998 may be evaluated in combination with 200 mg pembrolizumab. This may be achieved by reducing the dose or alternate dosing schedules. The dose of pembrolizumab will remain fixed at 200 mg throughout the study.

Dose escalation will proceed until the MTD or MAD of the combination regimen is identified, as described in Section 4.1.1. Dose-escalation decisions will take into account all available data, including the safety profile of prior cohorts throughout the time subjects are on study, which will be reviewed by the investigator(s), GSK Medical Monitor, pharmacokineticist, and statistician. The dose-escalation decision for the subsequent cohort and rationale will be documented in writing with copies maintained at each site and the study files.

Any cohort may be expanded beyond the 3 to 6 subjects enrolled during dose escalation, to a maximum of 12 to facilitate collection of additional safety, PK, and pharmacodynamic data (Figure 3). A total of up to 12 subjects may be treated at the dose of GSK3174998 selected for Parts 1B and 2B to better characterize the safety, PK, and pharmacodynamic data at that dose, before opening the Dose-Expansion phase.

Section 4.2. Treatment Arms and Duration

REVISED TEXT:

1 st paragraph:

The study includes a screening period, a treatment period, and a follow-up period. Subjects will be screened for eligibility beginning approximately 4 weeks before the start of treatment. The maximum duration of treatment with GSK3174998 ~~will be 48 weeks; the maximum duration of treatment with~~ and pembrolizumab will be 2 years (Table 5) or 35 cycles whichever comes first. The follow-up period for safety assessments will be a minimum of 3 months from the date of the last dose. The post-treatment follow-up period includes disease assessments every 12 weeks until documented PD. Following PD, subjects will be contacted every 3 months to assess survival status.

Table 5 Study Treatments

REVISED TEXT:

Study Part	Study Treatment
Part 1: GSK3174998 Monotherapy	
1A – Dose escalation	GSK3174998 IV[a] Q3W for up to ~~48 weeks~~ 2 years or 35 cycles, whichever comes first
1B – Cohort expansion	GSK3174998 IV[b] Q3W for up to ~~48 weeks~~ 2 years or 35 cycles, whichever comes first
Part 2: GSK3174998 in combination with pembrolizumab	
2A – Dose escalation	GSK3174998 IV[c] Q3W for up to ~~48 weeks~~ 2 years or 35 cycles, whichever comes first Pembrolizumab 200mg IV Q3W for up to 2 years or 35 cycles, whichever comes first
2B – Cohort expansion	GSK3174998 IV[b] Q3W for up to ~~48 weeks~~ 2 years or 35 cycles, whichever comes first Pembrolizumab 200 mg IV Q3W for up to 2 years or 35 cycles, whichever comes first

a. For dose levels see Table 2.
b. At one or two dose levels shown to be tolerable in dose escalation of each part.
d. For dose levels see Table 3.
IV = Intravenous; Q3W = Every 3 weeks

Section 4.3 Type and Number of Subjects

REVISED TEXT:

1 st paragraph

The number of dose levels and the level at which the MTD is reached cannot be determined in advance. An adequate number of subjects will be enrolled into the study to establish the recommended dose(s) for further study. It is estimated that a total of up to approximately ~~180~~ 264 subjects will be enrolled in this two-part study (approximately ~~60~~144 subjects in Parts 1A and 2A [dose escalation]; approximately 120 subjects in Parts 1B and 2B [cohort expansion])

Section 4.4 Design Justification

REVISED TEXT:

This study evaluates the safety, tolerability, pharmacodynamic effects, and preliminary clinical activity of GSK3174998 as a monotherapy (Part 1) and in combination with anti-PD-1, pembrolizumab (Part 2). The safety, tolerability, and pharmacodynamics of monotherapy GSK3174998 will be evaluated in a modified 3+3 dose escalation that

includes an accelerated titration design for the first two dose levels. The dose escalation will be followed by expansion cohorts in defined subject populations. ~~Upon demonstration of clear pharmacodynamic immune activation, exploration of the combination of GSK3174998 with pembrolizumab may commence, in parallel with the continuing monotherapy exploration.~~ Dose escalation of GSK3174998 in combination with a 200 mg fixed dose of pembrolizumab will begin at a dose of 0.003 mg/kg GSK3174998 as described in Section4.5.2.~~that is at least 2 dose levels below a dose of GSK3174998 that has been demonstrated to be safe at that point in time.~~

In order to ensure sufficient safety and pharmacodynamic data were available before beginning enrollment to Part 2 of the study, available clinical data (clinical data cut-off: 17 May 2016; (see Section 2.3.5) from Part 1 of the study, including safety, PK, pharmacodynamics and efficacy, were reviewed by the Steering Committee. The Steering Committee also considered available data for other OX40 agonist antibodies as relevant background information [Hamid, 2016;Hansen, 2016;Infante, 2016]. GSK Medical Governance reviewed the same data as the Steering Committee and endorsed initiation of Part 2 of the study. The decision to initiate Part 2 was documented and reported to all participating PIs and IRBs/ IECs.

In the dose escalation phase, subjects will be enrolled with selected solid tumors that are likely to respond to anti-OX40 therapy (e.g., indications previously reported to have a response to immunotherapies, predicted immunogenicity, and/or expression of OX40). The tumor types to be evaluated in dose escalation are as follows: NSCLC, SCCHN, RCC, melanoma, bladder cancer, ~~STS,~~ TNBC, and MSI CRC.

Almost all of these histologies have demonstrated prior response to anti-CTLA-4 and/or anti-PD-1/PD-L1 therapies [Zamarin, 2015]. In addition, gene expression data [TCGA, 2014] suggest that all of these tumor types have at least moderate expression of OX40.

The inclusion of the combination with pembrolizumab is based on the preference to identify potential transformational activity early in development. Although GSK3174998 is expected to have meaningful clinical activity as a monotherapy, the full potential of the molecule is likely to be discovered in combination with other agents, particularly immunotherapies. Pembrolizumab is an ideal combination partner for GSK3174998 because it targets a different aspect of the cancer-immunity cycle, has a toxicity profile of mainly Grade 1 or 2 events, and preclinical data strongly supports the potential for synergy.

Recently reported data with OX40 agonists and other TNFR agonists [Hamid, 2016; Hansen, 2016; Infante, 2016] has highlighted the importance of understanding the impact of treatment with these agents on the tumor microenvironment. To date TNFR agonist antibodies appear to saturate receptors in the periphery at low doses, be well-tolerated, have demonstrated biological effects in the tumor microenvironment in some but not all tumors where serial fresh biopsies were available (e.g., increased CD8 infiltration, decreased Tregs), and have demonstrated modest clinical activity. In order to better understand dose-response and variables that may influence clinical response to treatment with GSK3174998 alone or in combination with pembrolizumab, it is critical that immune biomarkers in the tumor microenvironment are assessed in this study across a

range of doses and, if feasible, correlated with clinical response. In alignment with the guidance prospectively established in the Protocol, the Steering Committee proposed that dose-escalation cohorts be expanded up to a total of 12 subjects in order to further evaluate pharmacodynamic markers to aid dose selection. In order to address the need to explore the potential relationships between dose, biological effects in the tumor microenvironment, and tumor response, a "pharmacodynamic cohort" is included in each of the dose-escalation parts of the study (Part 1A and Part 2A). In order to be eligible to be enrolled in the pharmacodynamic cohorts, subjects must consent to mandatory fresh biopsy collection at baseline, on treatment (at 6 weeks), and if feasible at the time of disease progression. An additional disease assessment (at 6 weeks) and availability of a pre-baseline scan (within 24 weeks before the baseline scan), if feasible, will support exploratory investigation of tumor growth kinetics in this cohort.

~~In order to ensure sufficient safety and pharmacodynamic data are available before beginning enrollment to the GSK3174998/pembrolizumab combination (Part 2), available clinical data, including safety, pharmacodynamics and efficacy, will be reviewed by the Steering Committee. The study team will also seek endorsement from GSK Medical Governance in order to initiate Part 2 of the study. Upon deciding to open Part 2, the decision will be documented and reported to all participating PIs and IRBs/ IECs.~~

Section 4.5.2 Part 2: Starting Dose

REVISED TEXT:

2 nd paragraph:

The starting dose of GSK3174998 for the Part 2/Combination Dose-Escalation phase ~~will~~ was planned to be at least 2 dose levels below a dose that has been shown to be tolerated during the monotherapy dose escalation. This determination ~~is~~ was based on an allowance that a 10-fold lower dose of GSK3174998 should provide a sufficient safety margin when pembrolizumab is added. Using these criteria, data from Part 1 Cohort 3 (0.03 mg/kg), with a clinical data cut-off of 17 May 2016, supported a Part 2 starting dose of 0.003 mg/kg GSK3174998. The 0.03 mg/kg dose level was tolerated and transient peripheral OX40 receptor saturation was observed in 3 of 4 subjects with the fourth subject having 100% OX40 receptor saturation throughout the first dosing period (21 days). These data were reviewed by the Steering Committee and GSK Medical Governance (as described in Section 4.4) and are briefly summarized in Section 2.3.5 of the protocol.

Section 5.1 Inclusion Criteria

REVISED TEXT:

Inclusion criteria 4, 5 and 9:

4. Subjects with the following solid tumors are eligible for screening: NSCLC, SCCHN, RCC, melanoma, bladder, ~~STS~~, TNBC, and MSI CRC

1. 5.A biopsy of the tumor tissue obtained at anytime from the initial diagnosis to study entry. Although a fresh biopsy obtained during screening is preferred, archival tumor specimen is acceptable, if it is not feasible to obtain a fresh biopsy. For Part 1B and Part 2B, any archival tumor specimen must have been obtained within 3 months of starting study drug.

Note: Subjects enrolled in Part 1A or Part 2A Pharmacodynamic Cohorts must provide a fresh biopsy of a tumour lesion not previously irradiated during the screening period and must agree to provide at least one additional on-treatment biopsy.

Table 26 Definitions for Adequate Organ Function

System	Laboratory Values
Hematologic	
ANC	≥1.5x10^9/L
Lymphocyte count	>1,000/mm^3
Hemoglobin	≥9 g/dL
Platelets	≥100x10^9/L
Hepatic	
Total bilirubin *For subjects with Gilbert's Syndrome (only if direct bilirubin ≤35%)*	≤1.5xULN *≤3.0xULN*
ALT	≤1.5xULN
Renal	
Serum Creatinine **OR** Calculated CrCl[a]	≤1.5xULN > 50 mL/min
Endocrine	
TSH[b]	WNL

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

a. Estimated CrCl should be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (see Appendix 12) or per institutional standard.

b. If TSH is not within normal limits at baseline, the subject may still be eligible if total T3 or free T3 and free T4 are within the normal limits.

Section 5.2 Exclusion Criteria

REVISED TEXT:

Exclusion criteria 1:

1. Prior treatment with the following agents (from last dose of prior treatment to first dose of GSK3174998):

   - TNFR agonists, including OX40, CD27, CD137 (4-1BB), CD357 (GITR): at any time.

     NOTE: Subjects treated in Part 1/monotherapy with GSK3174998 may be enrolled into Part 2/combination with pembrolizumab upon disease progression and upon discussion and approval from the GSK Medical Monitor.

- Checkpoint inhibitors, including PD-1, PD-L1, and CTLA-4 inhibitors: within ~~8~~ 4 weeks.

Exclusion criteria 2:

~~2. Prior treatment with Receptor activator of nuclear factor-kappaB ligand (RANKL) inhibitors (e.g., denosumab) within 4 weeks of the start of study drug.~~

Exclusion criteria 3, third point:

~~4.~~3. Subjects whose toxicity related to prior treatment has not resolved to ≤Grade 1 (except alopecia, hearing loss, grade ≤ 2 neuropathy or endocrinopathy managed with replacement therapy) are not eligible.

5. Central nervous system (CNS) metastases, with the following exception:

- Subjects who have previously-treated CNS metastases, are asymptomatic, and have had no requirement for steroids ~~or anti-seizure medication~~ for 2 weeks prior to first dose of study drug.

~~13.~~ 12 Known, current drug or alcohol abuse.

18. Current or ~~H~~history of idiopathic pulmonary fibrosis, ~~pneumonitis,~~ interstitial lung disease, or organizing pneumonia~~., or evidence of active, non-infectious pneumonitis. that required steroids.~~ Note: post-radiation changes in the lung related to prior radiotherapy and/or asymptomatic radiation-induced pneumonitis not requiring treatment may be permitted if agreed by the investigator and Medical Monitor.

19. History of (non-infectious) pneumonitis that required steroids or current pneumonitis.

Section 5.4. Withdrawal/Stopping Criteria

REVISED TEXT:

Addition of Sub-Heading:

5.4.1 Treatment Discontinuation:

1st paragraph:

Subjects will receive study treatment for the scheduled time period, unless one of the following occurs earlier: disease progression (as determined by irRECIST), death, or unacceptable toxicity, including meeting stopping criteria for liver chemistry defined in Section 5.4.2. In addition, study treatment might be permanently discontinued for any of the following reasons:

- Major deviation(s) from the protocol

6th paragraph:

Once a subject has permanently discontinued from study treatment, the subject will not be allowed to be re-treated, except as described in Section 5.4.2.1 and in the following

scenario. Re-treatment of subjects who progress after a best overall response of PR or CR may be considered on a case-by-case basis for up to 1 year after discussion between the treating investigator and the Sponsor/Medical Monitor if:

- No cancer treatment was administered since the last dose of GSK3174998 ± pembrolizumab
- The subject meets the safety parameters listed in the Inclusion/Exclusion criteria
- The trial is open.

Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Response or progression in this Second Course Phase will not count towards the primary efficacy endpoint in this trial.

~~5.4.2~~ 5.4.3 QTcF Stopping Criteria:

2nd paragraph:

The QTcF should be based on single or averaged QTcF values of triplicate ECGs obtained over a brief (e.g., 5-10 minute) recording period. (i.e. single QTcF is used when a single ECG is performed, and averaged QTcF is used when triplicate ECGs are performed)

Section 5.5 Subject and Study Completion

REVISED TEXT:

Since subjects will be followed for survival in this study, only when a subject dies is he/she considered to have completed the study; consequently "death" is not listed as a reason for withdrawal from the study. Furthermore, disease progression, discontinuation of study treatment, and AEs, are not by themselves reasons for withdrawal from the study as follow-up for OS is desired. If a subject dies a copy of the death certificate should be available for review, if possible, and the cause of death should be evaluated and documented.

~~A subject will be considered to have completed the study if they complete screening assessments, received at least one dose of study treatment(s), and the TDV, or are receiving ongoing study treatment at the time of the Sponsor's decision to close the study.~~

~~For both Part 1 (dose-escalation phase) and Part 2 (expansion cohort), a completed subject is one who has discontinued study treatment for reasons listed in Section 5.4 and completed a TDV or has died while receiving study treatment.~~

The end of the study is defined as the last subject's last visit.

Section 6.1 Investigational Product and Other Study Treatment

REVISED TEXT:

Table 27 Investigational Product Dosage/Administration

	Study Treatment	
Product name:	GSK3174998	Pembrolizumab
Dosage form:	Lyophilized powder for reconstitution	Solution for infusion ~~or Lyophilized powder for reconstitution[c]~~
Unit dose strength(s)/ Dosage level(s):	40 mg lyophilized powder Dose range: 0.003 to ≤10 mg/kg	100 mg/ 4 mL solution ~~or 50 mg lyophilized powder~~ Dose range: 200 mg
Route of Administration	IV infusion – 30 min[a, b]	IV infusion – 30 min[a]
Frequency of Administration	Q3W[b]	Q3W[b]
Dosing instructions:	Make every effort to target infusion timing to be as close to 30 min as possible. However, given the variability of infusion pumps from site to site, a window of -5 min and +10 min is permitted (i.e., infusion time is 30 min: -5 min/+10 min or 25 to 40 min).	Make every effort to target infusion timing to be as close to 30 min as possible. However, given the variability of infusion pumps from site to site, a window of -5 min and +10 min is permitted (i.e., infusion time is 30 min: -5 min/+10 min or 25 to 40 min).
Manufacturer/ source of procurement	GSK	Merck

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

b. Dose levels 1 and 2 will be administered less than 30 min, please refer to the SRM for infusion directions

~~c. The dosage form of pembrolizumab will be either solution or lyophilized powder for all subjects/doses. This will be decided and communicated prior to start of the combination phase of the study.~~

Q3W = Every 3 weeks; GSK = GlaxoSmithKline

Section 6.3.1 Dose and Safety Management Guidelines

REVISED TEXT:

Table 9 General Dose Modification and Management Guidelines for Drug- related Non-Hematologic Adverse Events Not Otherwise Specified

Severity	Management	Follow-up
Grade 1	• Administer symptomatic treatment as appropriate • Continue study drug(s)[a]	*Symptoms resolve to baseline within 7 days:* • Provide close follow-up to evaluate for increased severity *Symptoms ongoing >7 days*: • Consider following algorithm for Grade 2 events
Grade 2	• Administer symptomatic treatment • Investigate etiology • Consider consulting subspecialist, biopsy, and/or diagnostic procedure • Discuss with Sponsor/Medical Monitor	*Symptoms ongoing >7 days or worsening* • Consider interruption of study drug(s)[a] o Resume study drug(s) at the same dose if symptoms have improved to Grade 1 and steroid dose is 10 mg prednisone/day or less o <u>If symptoms persist at Grade 2 for greater than 6 weeks, permanently discontinue study drug. See Section 6.3.1.13</u> • Consider starting moderate dose systemic corticosteroids (e.g., 0.5 mg/kg/day of prednisone or equivalent) o Continue steroids until improvement to Grade 1 or resolution; taper steroids as medically appropriate • If symptoms continue or worsen to Grade 3-4, see below
Grade 3-4	• Interrupt <u>or permanently discontinue</u> study drug(s)[a] • Consult subspecialist • Administer 1-2 mg/kg/day IV methylprednisolone • Discuss with Sponsor/Medical Monitor	*Symptoms improve to ≤Grade 2:* • Continue steroids until improvement to ≤Grade 1 or baseline; taper steroids over at least 1 month, then if symptoms have improved to Grade 1 and steroid dose is 10 mg prednisone/day or less, consider resumption of study drug(s) at the next lower dose level *Symptoms ongoing:* • Discuss further management with consultant and Sponsor/Medical Monitor • Consider alternative immunosuppressive therapy

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

Table 10 Guidelines for Dose Modification and Management of Hepatotoxicity

Severity	Management	Follow-up
Grade1 ALT > ULN to 3x ULN OR Total bilirubin > ULN to 1.5x ULN	**MONITOR** • Assess liver function at least weekly	Monitor the subject at least weekly until liver chemistries resolve, stabilize, or return to within baseline *Hepatotoxicity improves to ≤ Grade 1 or baseline or remains stable*: • Provide close follow-up to evaluate for increased severity. *Hepatotoxicity worsens to ≥ Grade 2:* • see below
Grade 2 ALT >3-5x ULN OR Total bilirubin >1.5-3xULN	**INTERRUPT/HOLD** • ~~Consider interruption of~~ Interrupt study drug(s) ~~after~~ and discuss~~ion~~ with Sponsor/Medical Monitor[a] • Consider treatment with IV or oral corticosteroids • Assess for infection and liver metastases • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments **within 24-72 hours** (see below) • Assess liver function at least twice weekly • Discuss with Sponsor/Medical Monitor within 24 hours • Consider consultation with a hepatologist	Monitor the subject at least twice weekly until liver chemistries resolve, stabilize, or return to within baseline *Hepatotoxicity improves to ≤ Grade 1 or baseline within 7 days*: • Resume study drug(s) (note: requirements specified in Section 5.4.2.1 must be met before treatment can restart) • Provide close follow-up to evaluate for recurrence *Hepatotoxicity ongoing > 7 days*: • Start systemic corticosteroids (e.g., 0.5 mg/kg/day of prednisone or equivalent) • Continue steroids until improvement to ≤ Grade 1 or baseline or resolution; taper steroids over at least one month • Resume study drug(s) if hepatotoxicity improves to ≤ Grade 1 or baseline and steroid dose is 10 mg prednisone/day or less (note: requirements specified in Section 5.4.2.1 must be met before treatment can restart) • Provide close follow-up to evaluate for recurrence **Discontinue study treatment if:** • Hepatotoxicity continues or worsens to ALT >5x ULN or total bilirubin to >3x ULN (follow instructions below) • ALT ≥ 3xULN but <5xULN persists for ≥4 weeks • ALT ≥ 3xULN but <5xULN **and** cannot be monitored weekly for ≥4 weeks • Unable to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks **Recurrence after rechallenge:** • **Discontinue** study drug(s) permanently • Monitor subject closely for clinical signs and symptoms • Perform full panel LFTs a weekly or more frequently if clinically indicated until ALT decreases to ≤ Grade 1 • At the time of the recurrence, complete the eCRF liver event forms.

Severity	Management	Follow-up
Grade 3 ALT >5 x ULN OR Total bilirubin >3x ULN	**DISCONTINUE** • Immediately discontinue study drug(s)[a] • Assess for infection and liver metastases • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessment **within 24 hours** (see below) • Assess liver function at least twice weekly • ~~Consider~~ Administration of 1-2 mg/kg/day IV methylprednisolone • Discuss with Sponsor/Medical Monitor within 24 hours • Consider consultation with a hepatologist	Monitor the subject at least twice weekly until liver chemistries resolve, stabilize, or return to within baseline • If ALT or bilirubin have not decreased within 72 hours in the absence of other etiologies and steroid treatment has not been administered, initiate treatment with 1-2 mg/kg/day IV methylprednisolone • Continue steroids until improvement to ≤ Grade 1 or baseline or resolution; taper steroids over at least one month • If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity.
Grade 4 ALT >20 x ULN OR Total bilirubin >10x ULN **Additional Stopping Criteria:** ALT ≥3x ULN **AND** Total bilirubin ≥2x ULN (>35% direct bilirubin)[b] ALT≥3xULN and INR>1.5, if INR measured[c] ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity[d]	**DISCONTINUE** • Immediately discontinue study drug(s)[a] • Assess for infection and liver metastases • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessment **within 24 hours** (see below) • Assess liver function at least twice weekly • Administer 1-2 mg/kg/day IV methylprednisolone • Discuss with Sponsor/Medical Monitor within 24 hours • Consider consultation with a hepatologist	Monitor the subject at least twice weekly until liver chemistries resolve, stabilize, or return to within baseline • Continue steroids until improvement to ≤ Grade 1 or baseline or resolution; taper steroids over at least one month • If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity.

a. If multiple study drugs are administered per protocol, guidance may apply to one or more study agents; discuss management on a case-by-case basis with the Sponsor/Medical Monitor.
b. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
c. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, if INR

measured which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants

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

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

Section 6.3.1.5 Management of Gastrointestinal Events (Diarrhea or Colitis)

REVISED TEXT:

Signs/symptoms may include, but are not limited to: diarrhea, constipation, abdominal pain, cramping and/or bloating, nausea and/or vomiting, blood and/or mucus in stool with or without fever, rectal bleeding, peritoneal signs consistent with bowel perforation, and ileus. All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

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

REVISED TEXT:

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

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

IV = Intravenous

Section 6.3.1.7 Management of Endocrine Events

REVISED TEXT:

Signs/symptoms may include, but are not limited to: fatigue, weakness, headache, mental status and/or behavior changes, fever, vision disturbances, cold intolerance, abdominal pain, unusual bowel habits, loss of appetite, nausea and/or vomiting, and hypotension. Endocrine events may include the following AE terms: new-onset type 1 diabetes mellitus, adrenal insufficiency, hyperthyroidism, hypophysitis, hypopituitarism, hypothyroidism, thyroid disorder, and thyroiditis.

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

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

Table 13 Guidelines for Dose Modification and Management of Endocrine Events

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

Severity	Management	Follow-up
~~**Moderate**~~**Grade 2** • Signs and/or symptoms of dysfunction • Endocrinopathies requiring hormone replacement or medical intervention	• Consider interruption of study drug(s)[a] if symptomatic • Assess endocrine function • Consider pituitary imaging • Administer up to 1-2 mg/kg/day IV methylprednisolone if clinically indicated • Initiate appropriate hormone-replacement therapy • Consider consultation with endocrinology • Discuss with Sponsor/Medical Monitor	~~• *Consider resuming study agent(s) when:*~~ • Taper steroids as clinically indicated • Consider resuming study agent(s) when ~~S~~subject is stable (on hormone-replacement therapy if indicated), symptoms have resolved or return to baseline, and the subject is receiving ≤10 mg prednisone or equivalent per day ~~• Subject is receiving ≤10 mg prednisone or equivalent per day~~
~~**Severe**~~**Grades 3-4** • Adrenal crisis or other adverse reactions requiring hospitalization, urgent medical intervention.	• Consider interruption of study drug(s)[a] • Discuss with Sponsor/Medical Monitor • Consider immediate initiation of 1-2 mg/kg/day IV methylprednisolone • Consult endocrinology • Other management as above	• Taper steroids over at least 1 month *Consider resuming study agent(s) when:* • Subject is stable (on hormone-replacement therapy if indicated) and symptoms have resolved or return to baseline • Subject is receiving ≤10 mg prednisone or equivalent per day

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

IV = Intravenous

ADDED SECTION:

Section 6.3.1.11 Renal Failure or Nephritis

Table 17 Guidelines for Dose Modification & Management of Renal Failure or Nephritis

Severity	Management	Follow-up
Grade 1	Symptomatic treatment as appropriate	*Symptoms resolve to baseline within 7 days:* • Provide close follow-up to evaluate for increased severity. *Symptoms ongoing > 7 days*: • Consider following algorithm for Grade 2 events
Grade 2	• Interrupt study drug(s)[a] • Consultation with nephrology is strongly recommended • Consider administration of oral or IV corticosteroids • Discuss with Sponsor/Medical Monitor	*Symptoms resolve to baseline within 7 days*: • resume study drug(s) *Symptoms ongoing > 7 days*: • Discontinue study drugs • If symptoms continue or worsen to Grade 3-4, see below
Grade 3	• Interrupt study drug(s) [a] • Administer 1-2 mg/kg/day IV methylprednisolone • Consultation with nephrologist is strongly recommended • Discuss with Sponsor/Medical Monitor	*Symptoms improve to ≤ Grade 2:* • continue steroids until improvement to ≤ Grade 1 or baseline; taper steroids over at least one month *Symptoms ongoing ≥12 weeks* • permanently discontinue study drugs
Grade 4	• Discontinue study drug(s) • Immediately inform Sponsor/Medical Monitor	• Management as per Grade 3

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

IV = Intravenous

Section 6.3.1.12, Table 18

REVISED TEXT

Table 18 Biomarker Panel

Biomarker	Relationship to Adverse Event
Serum tryptase[a]	IgE-related infusion reaction (Allergic/anaphylaxis) [Schwartz, 2006]
Serum CRP[a]	Elevated in CRS [Lee, 2014]
Serum ferritin[a]	Elevated in CRS [Lee, 2014]
~~Serum~~ Plasma cytokine panel[b] (IFN-γ*^, TNF-α*^, IL-2*, IL-4, IL-5*, IL-6*^, IL-8*, IL-10*, IL-12p70, IL-13, and IL-17)	* Reported to be elevated in CRS [Lee, 2014] ^ consistently reported as elevated in CRS [Lee, 2014]

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

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

Section 6.8.2 Pembrolizumab Overdose

REVISED TEXT:

An overdose of pembrolizumab will be defined as ≥1000 mg (5 times the dose) of pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, any overdose of pembrolizumab, or follow up to an overdose, whether or not related to the Sponsor's product, must be reported within 5 days to GSK as an AESI, either by electronic media or paper.

Section 6.10 Concomitant Medications and Non-Drug Therapies

ADDED TEXT:

Medications or vaccinations specifically prohibited (see Section 6.10.2) are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination

rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject

Section 6.10.1 Permitted Medications and Non-Drug Therapies

REVISED TEXT:

Supportive Care: Subjects should receive full supportive care during 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. Intra-nasal flu vaccine is excluded. Elective ~~palliative~~ surgery or palliative radiation may be permitted on a case-by-case basis in agreement with the Medical Monitor, if these do not include any "target" lesions.~~are not performed to alleviate symptoms resulting from disease progression.~~

Growth Factors and Bisphosphonates: The use of growth factors, RANK-L inhibitors, and bisphosphonates (if on a stable dose for at least 4 weeks) is permitted while participating in this study. However, the initiation of growth factors and bisphosphonates is not allowed during the first 4 weeks of study treatment, unless used in the management of toxicity and agreed upon by the investigator and Medical Monitor.

Section 6.10.2 Prohibited Medications and Non-Drug Therapies

4th bullet:

DELETED TEXT:

~~RANKL inhibitors (e.g. denosumab).~~

Section 7 Study Assessments and Procedures

REVISED TEXT:

If assessments are scheduled for the same nominal time, it is recommended that ~~then~~ the assessments should occur in the following order: 12-lead ECG, vital signs, and blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time.

Section 7.1 Time and Events Table

REVISED TEXT:

Table 19 Time and Events Table – Monotherapy and Combination Therapy

	Scrn[a/b]			Treatment[a]										Follow-up	
Week[a]	**≤4**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**9**	**12**	**> 12 - 48[c]**	**≥49 -105[c]**	**TDV[d]**	**DFS FU[e]**	**SFU[f]**
Day	**≤28**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**64**	**85**	**106-337**	**≥344-736**	**30d after last dose**	**Q12W**	**Q12W**
Dose		**1**			**2**			**3**	**4**	**5**	**6-17**	**18-36**			
Informed Consent	X														
Inclusion/Exclusion	X	X													
Demographics, Medical History, Prior Medications	X														
Concomitant Medications		Assess at each visit from first dose until the TDV visit													
Subject Registration		X													
Anti-Cancer Treatment													X	X	X
Part I Study Treatment Monotherapy															
Administer GSK3174998 (± ~~2~~3 days)[g]		X			X			X	X	X	X	X			
Part 2 Study Treatment Combination Therapy (note: administer pembrolizumab 1 hour after the end of the GSK3174998 infusion)															
Administer GSK3174998[g]		X			X			X	X	X	X	X			
Administer Pembrolizumab[g]		X			X			X	X	X	X	X			
Safety															
AE/SAE Assessment		Assess at each visit from first dose until the TDV visit for AEs and until 90 days after last dose for AESI and SAEs[d]													
ECOG PS	X	X	X	X	X	X	X	X	X	X	Q6w	Q6w	X		
Physical Examination	X	X			X			X	X	X	Q6w	Q6w	X		
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X	X	X		
12-lead ~~ECG~~[k]ECG[l]	X	X[l]			X[l]			X	X	X[l]	Q12w	Q12w	X		
Laboratory Assessments (Safety) – perform assessments pre-dose on each dosing day															
Hepatitis B and C	X														
Pregnancy Test: Serum β-hCG	≤3d	~~As clinically indicated~~ Monthly (urine or serum)													
Clinical Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X		
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X		
Thyroid function tests	X							X		X	~~X~~Q6W	Q6W	X		
Calculated CrCl	X				X			X	X	X	X	X	X		
Urinalysis	X		X	X	X	X	X	X	X	X	X	X	X		
Disease Assessments															
Tumor imaging [h]	X							X[j]		X	Q12W				
Telephone call for survival															X

	Scrn[a/b]			Treatment[a]										Follow-up	
Week[a]	**≤4**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**9**	**12**	**> 12 - 48[c]**	**≥49 -105[c]**	**TDV[d]**	**DFS FU[e]**	**SFU[f]**
Day	**≤28**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**64**	**85**	**106-337**	**≥344-736**	**30d after last dose**	**Q12W**	**Q12W**
Dose		**1**			**2**			**3**	**4**	**5**	**6-17**	**18-36**			
status[f]															
Tumor Biopsies															
Archived tumor [i]	X														
Fresh tissue sample[i]	X							X					~~X~~		
PD tissue sample[~~k~~i]								X[~~k~~i]							

Foot notes d, g, h, i and j

d. The treatment discontinuation visit should be completed 30 days from the last dose of study treatment. The window for this visit is +10 days. All AEs and concurrent medications will be collected until at least 30 days after the last dose of study treatment. All AESIs and SAEs and any concurrent medications relevant to the reported AESIs and SAEs will be collected until at least 90 days after the last dose of study treatment. If another anti-cancer agent is started during the 90 day reporting period, only AESI and SAEs that occur within 30 days from the last dose of study drug(s) should be recorded. ~~or until the start of new anticancer therapy, whichever occurs first. Any drug or study-related SAEs occurring after the 90-day window will be reported according to directions provided in~~(see Section7.4.1.1)

g. Dosing of GSK3174998 and pembrolizumab at every 3-week intervals is shown in the Time and Events Table; however, dosing of GSK3174998 may be delayed due to toxicity. During the combination phase, GSK3174998 should be administered first, and pembrolizumab should be administered at least 1 hour and no more than 2 hours following the end of the GSK3174998 infusion. GSK3174998 ~~will be dosed for a maximum of 48 weeks. P~~and pembrolizumab will be dosed for a maximum of 2 years or 35 cycles, whichever comes first

h. Screening tumor imaging must be obtained within 28 days of the first dose. Tumor imaging will be performed every 12 weeks (±1 week) until disease progression has been confirmed by irRECIST; Subjects whose disease progresses must have a confirmatory scan performed at least 4 weeks after the date of assessment during which the first indication of PD was demonstrated. ~~additional scans may be obtained if PD is suspected but not confirmed~~ Immune-related RECIST will be used to determine treatment decisions for PD and the primary endpoint analysis will use irRECIST. If a subject has achieved a CR or PR in the previous radiologic assessment, a repeat scan should be performed as a part of the confirmation of response, within at least 4 ~~6~~ weeks to confirm the response. At the TDV, tumor imaging is only required if the last disease assessment did not show PD and was performed ≥6 weeks before TDV. During the DFS FU visits (performed when a subject has permanently discontinued study treatment before disease progression has been documented), tumor imaging will be obtained every 12 weeks (±1 week) until PD, initiation of a new anticancer treatment, or death, whichever comes first

i. A fresh tumor biopsy should be attempted at screening (before first dose) and at Week 6 (after the 3rd dose of study treatment ~~±~~+1 week). Fresh biopsies are mandatory for all patients in the Pharmacodynamic Cohort and the Dose Expansion phase. During the Dose Expansion phase, ~~O~~once evaluable paired tumor biopsies are collected for up to 10 subjects in the dose expansion phases, this requirement may be waived. Tumor lesions planned for biopsy must not be used as indicator lesions for assessment of disease, unless discussed and agreed with the GSK Medical Monitor. For subjects in the initial dose escalation cohorts, where biopsy is not mandatory, , a recent archival tumor specimen is acceptable if it is not feasible to obtain a fresh biopsy.

j. The 6-week disease assessment for patients in the Pharmacodynamic Cohort is timed to coincide with the on-treatment (6 week) tumor biopsy. The disease assessment should be performed after the tumor biopsy.

Table 19 Time and Events Table – Pharmacokinetics, Antidrug Antibodies, and Pharmacodynamics (Parts 1 and 2).

		Treatment													
Day	**1**	**2**	**8**	**15**	**22**	**23**	**29**	**36**	**43**	**64**	**85**	**106**	**≥148**	**30 D after Last Dose**	**12 Wks Post-Treatment ±1 week**
Dose	**1**				**2**				**3**	**4**	**5**	**6**	**≥8**		
Pharmacogenetics (6 mL)[a]	X														
Receptor occupancy and phenotyping panels(10 mL)	Pre EOI+4h[g]	EOI+24h	X	X	Pre EOI+4h[g]				Pre EOI + 4h[g]					X	X
Plasma + PBMC prep (20 mL)[b]	Pre		X		Pre				Pre					X	X
Cytokines (5 mL)	Pre EOI+4h	EOI+24h	X		Pre EOI+4h				Pre EOI+4h						
Plasma for cfDNA + exosomes (10 mL)	Pre								At time of biopsy if done						
Serum (5 mL)	Pre														
GSK3174998 Pharmacokinetics (1 mL)	Pre EOI+30m EOI+4h	EOI+24h[d]	X	X	Pre EOI+30m EOI+4h	EOI+24	X	X	Pre EOI+30m	Pre EOI+30m	Pre EOI+30m	Pre EOI+30m	Pre[e]	X	X
Part 2 only: Pembrolizumab Pharmacokinetics (3 mL)	Pre EOPI+30m	EOI+24h	X	X	Pre					Pre		Pre	Pre[e]	X	X
Anti- GSK3174998 antibodies[c,f] (5 mL)	Pre				Pre				Pre		Pre		Pre[e]	X	X[f]
Part 2 only: Anti-Pembrolizumab antibodies[c,f] (~~5~~6 mL)	Pre				Pre					Pre		Pre	Pre[e]	X	X[f]

Foot note no. f and g:

f. In the event of a hypersensitivity reaction that is either 1) clinically-significant in the opinion of the investigator, or 2) leads to the subject withdrawing from the study, blood samples should be taken from the subject for immunogenicity testing at the time of the event and again 30 days, 12 weeks, and 24 weeks after.

g. If the EOI+4h RO sample is scheduled to be collected after the last lab courier pick-up time of the day, the sample should be collected as late as possible to enable processing and shipping on the same day as collection.

Section 7.2.2 Baseline Documentation of Target and Non-Target Lesions

Last paragraph

REVISED TEXT:

Confirmation of CR and PR are required per protocol. Confirmation assessments must be performed ~~within 4 to~~ at least 4 weeks after the criteria for response have initially been met and may be performed at the next protocol scheduled assessment. If a confirmation assessment is performed prior to the next protocol schedule assessment, the next protocol scheduled evaluation is still required (e.g., evaluations must occur at each protocol scheduled time point regardless of unscheduled assessments).

Section 7.3.1 Evaluation of Anticancer Activity

REVISED TEXT:

7 and 8 bullet points:

- Subjects whose disease responds (either CR or PR) should have a confirmatory disease assessment performed at least 4 weeks after the date of assessment during which the response was demonstrated. ~~More frequent disease assessments may be performed at the discretion of the investigator~~.
- Subjects whose disease progresses (PD) must have a confirmatory scan performed at least 4 weeks after the date of assessment during which the first indication of PD was demonstrated.

Section 7.4.1.1 Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information.

REVISED TEXT:

Any AESI and SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to 90 days after the last dose of study drug(s). If another anti-cancer agent is started during ~~this time~~ the 90 day reporting period, only AESI and SAEs that occur within 30 days from the last dose of study drug(s) should be recorded. ~~until 30 days after the last dose, or initiation of other anti-cancer agent (whichever is later).~~ SAEs must be reported within 24 hours to the Sponsor either by electronic media or paper.

Section 7.4.2 Pregnancy

REVISED TEXT:

1 st bullet point:

- Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of dosing until 120 days after the last dose of study medication.

Section 7.4.3 Physical Exams

REVISED TEXT:

- A complete physical examination will be done at screening and will include assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- A brief, targeted physical examination will be done at all other timepoints, unless physician's judgement requires a full exam ~~include 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.
- For melanoma subjects, a full body dermatological examination will be performed by a dermatologist (or suitably qualified physician) to identify abnormal skin lesions within the 28 day screening period. All findings will be photographed and identified during screening. Subsequently, ~~B~~brief skin examinations ~~will be performed as indicated in the~~ will be included in the PE exams as per the Time and Events Table (Section7.1, Table 19) or more frequently as necessitated.

Section 7.4.4 Vital Signs

REVISED TEXT:

2 nd point:

~~Three readings of blood pressure and pulse rate should be taken, the first reading should be rejected and the second and third averaged to give the measurement to be recorded in the eCRF.~~

Section 7.4.6 Clinical Safety Laboratory Assessments

REVISED TEXT:

Added Thyroid Function Tests

Table 29 Clinical Laboratory Assessments

Added Chloride and Carbon Dioxide in Clinical chemistry assessment

Added urine β-hCG Pregnancy test to Other Screening Tests

Section 7.6.1 Blood Biomarkers:

REVISED TEXT:

2 nd paragraph:

Blood samples will also be collected for isolation of PBMC ~~and~~ plasma, and serum. Plasma and serum samples will be used for an analysis of circulating soluble factors in relation to T-cell activation, cfDNA, exosomes circulating proteins, and may be analyzed for soluble OX40 and soluble OX40-drug complex depending on the availability of the assays. Factors to be analyzed may include but are not limited to: the presence of IFN-γ, TNF-α, IL-2, IL-4, IL-5, IL-6, IL 10, IL-8, IL-12p70, IL-13, and IL-17 as well as antibodies against tumor, self tumor mutations, gene expression (RNA or protein) or viral antigens.

Section 7.6.2 Tumor Tissue

REVISED TEXT:

Archival tumor tissue, as well as fresh pre- and ~~post~~ on-treatment biopsies in subjects in the pharmacodynamic cohorts, at least 10 subjects of the dose-expansion cohorts and if possible in the dose escalation cohorts will be evaluated by IHC for expression of phenotypic and functional immune cell markers on tumor infiltrating lymphocytes (TILs) and other immune cells and as well as immune signaling markers on the surface of tumor cells (e.g. including, but not limited to PD-L1), to understand antitumor immune responses. In addition, when possible, similar analyses will be performed on tumor tissue samples obtained upon progression. Additionally, tumor tissue may be sequenced to assess TCR diversity as well as evaluated for any DNA/RNA/protein changes correlating with response.

In the pharmacodynamic cohort mandatory fresh pre- and on treatment biopsies are required (see Table 18 for timing). These mandatory biopsy samples will be evaluated as previously described for the archival, pre and post treatment, and progression biopsies.

If feasible, for all of the fresh pre-and on-treatment biopsies the same tumor site should be used for both samples. If not possible, the post treatment biopsy should be obtained from the same anatomical site as the pre-dose biopsy. The tumor site chosen for biopsy must not be the used as an indicator lesion for assessment of disease unless otherwise discussed and agreed upon with the GSK medical monitor.

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

Blood and tumor samples may be used for purposes related to the quality assurance of the laboratory tests described in this protocol, or for the development of a diagnostic assay.

ADDED SECTIONS:

Section 7.7 Anti-Drug Antibodies

Section 7.7.1 Blood Sample Collection

Serum samples will be collected and tested for the presence of antibodies that bind to GSK3174998 and pembrolizumab. Serum samples for testing anti-GSK3174998 and anti-pembrolizumab antibodies will be collected as described in the Time and Events schedule (Section 7.1). The actual date and time of each blood sample collection will be recorded. Details of blood sample collection (including volume to be collected), processing, storage, and shipping procedures are provided in the SRM.

The timing and number of planned immunogenicity samples may be altered during the course of the study, based on newly-available data to ensure appropriate safety monitoring. In the event of a hypersensitivity reaction that is either 1) clinically-significant in the opinion of the investigator, or 2) leads to the subject withdrawing from the study, blood samples should be taken from the subject for immunogenicity testing at the time of the event and again 30 days, 12 weeks, and 24 weeks after. For subjects who prematurely withdraw from the study, immunogenicity testing will occur at withdrawal and at follow-up 30 days, 12 weeks, and 24 weeks after the last dose.

Section 9.1.2 Part 1: Monotherapy Dose Expansion (GSK3174998)

REVISED TEXT:

The null hypothesis for the secondary endpoint- overall response rate is:

H_0: $p \leq 10\%$.

The alternative hypothesis is:

H_A: $p > 10\%$.

Section 9.2 Sample Size Considerations

REVISED TEXT:

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

The study will enroll up to approximately ~~186~~ 264subjects with tumor types that may include NSCLC, SCCHN, RCC, melanoma, bladder cancer, ~~STS,~~ TNBC, and MSI CRC

Section 9.3 Data Analysis Considerations

REVISED TEXT:

1 st paragraph:

In the dose escalation cohorts, the dose will be escalated based on all available data, including biomarker and PK data and the safety profile of prior cohorts. In addition, the recommended dose from a Continuous Reassessment Method (N-CRM) analysis [Neuenschwander, 2008] will~~may~~ be calculated. The N-CRM is a type of Bayesian adaptive dose-escalation scheme. The method is fully adaptive and makes use of all the DLT information available at the time of each dose assignment. The Fixed and Adaptive Clinical Trial Simulator (FACTS) will be used to conduct the N-CRM analysis. The DLT information on all subjects enrolled in the trial are used to update the estimated dose-toxicity relationship and provide supportive information in addition to the 3+3 design in the next escalation/de-escalation decision. ~~; the 3+3 algorithm is expected to be used as the primary criteria for dose escalation.~~

Section 9.3.2 Interim Analysis

ADDED TEXT:

No formal interim analyses will be performed using the data generated from dose escalation cohorts. Preliminary safety and available PK/PD data will be performed and reviewed by study team (to include at minimum, the GSK medical monitor and investigator) after completion of each dose cohort. This review will support the decision on the dose level in the next dose cohort. Dose escalation decisions making will be based on the rules as described in section 4.1 and section 9.3. The Steering Committee will guide the transition of the study from dose escalation to cohort expansion for both monotherapy and combination therapies.

For dose expansion cohorts, continuous assessment of efficacy and safety will be performed after first interim analysis based upon a minimum of 10 subjects in at least one of the disease-specific cohort with available unconfirmed Overall Response data. The Steering Committee will monitor safety and efficacy over the course of the study following the randomization and futility rules for expansion cohorts as described in section 4.1 and section 9.3.

Section 9.4.1.6 Primary Analyses

DELETED SECTION:

~~9.4.1.6 Anticancer Activity Analyses~~

~~The All Treated Population will be used for anticancer activity analyses. Since this is a Phase I study, anticancer activity will be evaluated based on clinical evidence and response criteria. If data warrant, the response data will be summarized by dose level.~~

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

Section 9.4.2 Secondary Analyses

ADDED SECTION:

9.4.2.1 Anticancer Activity Analyses

The All Treated Population will be used for anticancer activity analyses. Since this is a Phase I study, anticancer activity will be evaluated based on clinical evidence and response criteria. If data warrant, the response data will be summarized by dose level. irRECIST is the primary measure of clinical activity for response endpoints and PFS; RECIST v1.1 guidelines are used for disease measurements.

If the data warrant, ORR, DCR, TTR, DOR, PFS and OS will be calculated and listed for each subject.

ORR is defined as the percentage of subjects with a best overall confirmed CR or PR at any time as per disease-specific criteria (refer to Appendix 12.5). DCR is defined as the percentage of subjects with a confirmed CR + PR at any time, plus SD ≥12 weeks.

DOR will be summarized for subjects with a confirmed CR or PR and is defined as the first documented evidence of CR or PR until disease progression or death due to any cause among subjects 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 is defined as time from the date of first dose to the date of disease progression according to clinical or radiological assessment or death due to any cause, whichever occurs earliest. For the analysis of PFS, if the subject received subsequent anti-cancer therapy prior to the date of documented events, PFS will be censored at the last adequate assessment (e.g. assessment where visit level response is CR, PR or SD) prior to the initiation of therapy. Otherwise, if the subject does not have a documented date of event, PFS will be censored at the date of the last adequate assessment.

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

Further details on rules of censoring will be provided in the RAP. PFS and OS will be summarized using the Kaplan-Meier method if the data warrant.

Section 9.4.2.4 Immunogenicity Analyses

DELETED TEXT:

First two paragraphs:

~~Serum samples will be collected and tested for the presence of antibodies that bind to GSK3174998 and pembrolizumab. Serum samples for testing anti-GSK3174998 and anti-pembrolizumab antibodies will be collected as described in the Time and Events schedule (Section7.1). The actual date and time of each blood sample collection will be recorded. Details of blood sample collection (including volume to be collected), processing, storage, and shipping procedures are provided in the SRM.~~

~~The timing and number of planned immunogenicity samples may be altered during the course of the study, based on newly available data to ensure appropriate safety monitoring. In the event of a hypersensitivity reaction that is either 1) clinically-significant in the opinion of the investigator, or 2) leads to the subject withdrawing from the study, blood samples should be taken from the subject for immunogenicity testing at the time of the event and again 30 days, 12 weeks, and 24 weeks after. For subjects who prematurely withdraw from the study, immunogenicity testing will occur at withdrawal and at follow-up 30 days, 12 weeks, and 24 weeks after the last dose.~~

Section 9.4.3 Other Analyses

ADDED SECTION:

9.4.3.3 Longitudinal tumor size modelling

Longitudinal tumor size data will be analyzed using a non-linear mixed effects model to determine tumor kinetic constants. These parameters may be related to other patient characteristics, such as dose group, GSK3174998 exposure, or biomarkers.

Section 11 References

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Topalian SL, Drake CG, Pardoll DM. Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity. *Curr Opin Immunol*. 2012; 24:207-212.

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Hamid O, Thompson JA, Dlab A, Ros W, Eskens ALM, et al. First in Human Study of an OX40 Agonist Monoclonal Antibody PF-04518600 (PF-8600) in Adult Patients With Select Advanced Solid Tumors: Preliminary Safety and Pharmacokinetic /Pharmacodynamic Results. Abstract J Clin Oncol 34, 2016 (suppl; abstr 3079)

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REVISED REFERENCES:

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Section 12.1 Appendix 1 Abbreviations and Trademarks

REVISED TEXT:

Added Abbrevations		**Deleted abbrevations**	
CTC	Circulating Tumor Cell		
DOR	Duration of Response	~~STS~~	~~Soft tissue sarcoma~~
TTR	Time to Response		

Section 12.5 Appendix 5: Guidelines for Assessment of Disease, Disease Progression and Response Criteria – adapted from RECIST version 1.1.

REVISED TEXT:

Evaluation of target lesions

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

a. Measureable according to RECIST v1.1.
b. Treatment decisions will be based upon the immune-related RECIST criteria.

Table 23 Evaluation of Overall Response for Subjects with Measurable Disease at Baseline.

REVISED TEXT:

Evaluation of best overall response:

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

- To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after the first dose at a minimum interval of 84 days.

If the minimum time for SD is not met, best response will depend on the subsequent assessments. For example if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement the best response will be PD. Alternatively, subjects lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

Section 12.7 Appendix 7: Genetic Research

REVISED TEXT:

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including GSK3174998 or pembrolizumab or any concomitant medicines;
- NSCLC, SCCHN, RCC, melanoma, bladder, ~~STS,~~ TNBC or MSI CRC, susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate

Section 12.8.1 Definition of Adverse Events

2nd box, 5th bullet

REVISED TEXT:

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). <u>See Section 6.8.2 for details on an overdose with pembrolizumab</u>

Section 12.8 Appendix 8 Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events.

REVISED TEXT:

Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and email to ~~usnaps~~ PPD or fax to PPD .Site will enter the SAE data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information to the Medical Monitor by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

Section 12.11 Appendix 11: Adverse Events of Special Interest

REVISED TEXT:

1 st paragraph

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

Added Text following the table:

Pembrolizumab-specific events of clinical interest for this trial include:

- An overdose of pembrolizumab, as defined in Section 6.8.2 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
- An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

12.13.3. Amendment 3 Protocol Changes for Amendment 3 (16-MAR-2018) from the Protocol Amendment 2 (16-AUG-2016)

Where the Amendment Applies

This amendment applies to all sites and countries.

Summary of Amendment Changes with Rationale

Amendment 3 includes the addition of preliminary clinical, safety, PK and PD data; updated pembrolizumab background and dose rationale, study design, with description of cohort expansion populations for Part 2B, modified dose rationale for cohort expansion (Part 2B). Updated risk assessment, Inclusion/Exclusion Criteria to define cohort expansion population. Consolidated Section 6.3 Dose and Safety Management Guidelines and minor changes to Time & Events tables. Modified Section 9 (Statistical Considerations and Data Analysis) – updated hypothesis, sample size considerations, futility analysis and stopping rules. Throughout the document minor editorial and document formatting revisions were made (minor, therefore have not been summarized [e.g. Table no., figure no., section no. etc]).

Changes are noted below with strikethrough to identify deleted text and underlining to identify new or replacement text.

List of Specific Changes

Section TITLE PAGE

Rationale for Change

The sponsor information was updated based on internal GSK team personnel changes.

REVISED TEXT:

PPD [redacted]

Section MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Rationale

Medical monitor information was updated

REVISED TEXT:

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/Serious Adverse Event (SAE) Contact Information:

Role	Name	Office Phone Email Address	Mobile	Fax
Primary Medical Monitor	PPD, MD	PPD	PPD	
Secondary Medical Monitors	PPD, MD, PhD PPD, MD	PPD PPD	PPD PPD	
SAE contact information		PPD		PPD

Section PROTOCOL SYNOPSIS Objective/Endpoints

Rationale for Change

Additional pharmacodynamic endpoints added

REVISED TEXT:

- **Pharmacodynamic endpoints:** Assessment of lymphocyte OX40 receptor membrane expression and occupancy by GSK3174998, along with the phenotype, quantity, and activation state of T cells in the periphery, T-cell receptor (TCR) diversity, expression of circulating soluble factors, and changes in genomic DNA and gene expression, and mutational load. Assessment of tumor biopsies via immunohistochemistry (IHC) for the numbers of tumor-infiltrating lymphocytes and other immune cells expressing key phenotypic markers. Changes in gene expression (RNA and protein), TCR diversity or mutational load (genomic DNA).~~.~~

Section PROTOCOL SYNOPSIS Type and Number of Subjects

Rationale for Change

Added new tumor type

REVISED TEXT

The study will enroll up to approximately 264 subjects with tumor types that may include NSCLC, squamous cell carcinoma of the head and neck (SCCHN), renal cell carcinoma

(RCC), melanoma, bladder cancer, soft tissue sarcoma (STS), triple-negative breast cancer (TNBC), and colorectal carcinoma displaying high microsatellite instability (MSI CRC).

Section 2.3.5. Preliminary Clinical Data for GSK3174998

Rationale for Change

Preliminary clinical data updated based on data from the ongoing study

REVISED TEXT

Data are summarized for the ongoing first time in human study with a clinical data cut-off of ~~17 May 2016~~ 09 Jan 2018. Data are reported for 104 subjects. 45 subjects received doses up to 10 mg/kg of GSK3174998 monotherapy and 61 subjects received doses up to ~~1.0~~ 10 mg/kg of GSK3174998 + 200 mg of pembrolizumab. Two subjects crossed over from monotherapy to combination therapy.

~~Data are reported for six subjects enrolled at the following GSK3174998 dose levels: 0.003 mg/kg (Cohort 1, n=1), 0.01 mg/kg (Cohort 2, n=1), and 0.03 mg/kg (Cohort 3, n=4). At the time of reporting, three subjects had discontinued treatment due to disease progression (one at each dose level).~~

Section 2.3.5.1.1. Safety Data - Part 1

Rationale for Change

Preliminary safety data updated based on data from the ongoing study

REVISED TEXT:

No dose-limiting toxicities, or treatment-related Grade 4, or Grade 5 toxicities were reported. Grade 3 asthenia and Grade 3 lymphocytopenia were reported in a single patient and attributed to study treatment. A single event in another subject led to treatment discontinuation~~,~~; Grade 5 stroke manifested as aphasia, attributed to disease progression. ~~No dose-limiting toxicities, treatment-related Grade 3 or 4 toxicities,~~The most common AEs regardless of attribution were fatigue (13, 29%), back pain (9, 20%), diarrhea (9, 20%), nausea (9, 20%), vomiting (9, 20%), asthenia (8, 18%), anemia, (7, 16%), headache (6, 13%), constipation (5, 11%), cough (5, 11%), dyspnoea (5, 11%), myalgia (5, 11%), pain in extremity (5, 11%), and pyrexia (5, 11%). The most common AEs attributed to treatment by the investigator included diarrhea (5, 11%) and fatigue (5, 11%). ~~and no treatment discontinuations due to AEs were reported. One SAE was reported (Grade 3 urinary tract infection and Grade 4 hydronephrosis) in a subject with bladder cancer treated at the 0.003 mg/kg dose level; the SAE was attributed to disease progression. The subject discontinued study treatment due to disease progression and at that time had received 2 doses of GSK3174998. All other AEs were Grade 1 or 2 in severity. One AE (fatigue) was reported in two subjects; all other events were reported once each: Actinic keratosis, anemia, arthralgia, asthenia, blood creatinine increased,~~

~~cough, diarrhea, dizziness, dry mouth, fall, headache, hernia, hyperkalemia, hypoesthesia, myalgia, nausea, pain in extremity, vomiting. Two events (Grade 1 dry mouth, Grade 1 nausea) were considered treatment-related.~~

Section: 2.3.5.1.2. Safety Data - Part 2

Rationale for Change

Preliminary safety data updated based on data from the ongoing study

REVISED TEXT:

No treatment related Grade 4 or Grade 5 toxicities were reported. Three patients reported Grade 3 treatment-related AEs.-Two dose limiting toxicities were reported. One patient with bladder cancer reported asymptomatic Grade 3 cardiac troponin and Grade 1 myocarditis occurring 16 days after the first and only dose of study treatments. Both events were attributed to study treatments, resulted in discontinuation of treatment, and resolved with a short course of 500 mg methylprednisolone. Other treatment-related Grade 3 events included Grade 3 fatigue in one patient with colorectal cancer (resulting in treatment discontinuation), and Grade 3 diarrhea in a patient with bladder cancer. The diarrhea lasted a single day, three days after the second dose of study drugs. A second dose limiting toxicity of Grade 2 pleural effusion was reported in a patient with triple negative breast cancer (0.03 mg/kg dose cohort). Adverse events leading to treatment discontinuation included the Grade 3 myocarditis and Grade 3 fatigue described above, and Grade 3 abdominal pain not related to treatment in a patient with colorectal cancer. The most common AEs regardless of attribution were fatigue (15, 25%), decreased appetite, (12, 20%), pleural effusion (9, 15%), arthralgia (8, 13%), nausea (7, 11%), asthenia (6, 10%), cough (6, 10%), and diarrhea (6, 10%). The most common AEs attributed to treatment by the investigator included fatigue (12, 20%), nausea (4, 7%), and pruritus (4, 7%).

For further details on the safety of GSK3174998, please refer to the IB [GlaxoSmithKline Document Number GlaxoSmithKline Document Number 2014N212091_00]

Section 2.3.5.2. Preliminary Pharmacokinetic Data (ENGAGE-1, Part 1A and 2A)

Rationale for Change

Preliminary PK data updated based on data from the ongoing study

REVISED TEXT:

Section 2.3.5.2 Preliminary Pharmacokinetic Data (ENGAGE-1, Part 1A and 2A~~:~~ ~~Part 1~~)

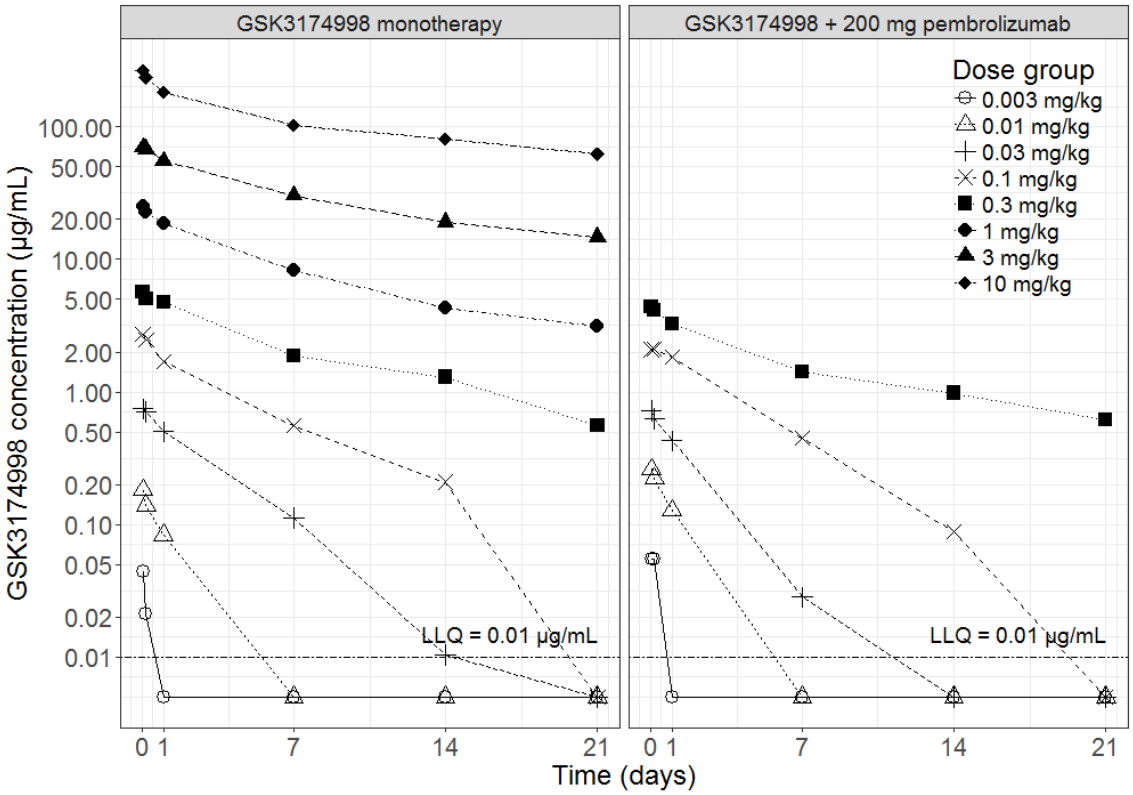
~~Maximum observed concentrations (Cmax) of GSK3174998 in plasma were in the predicted range anticipated for each dose level (44 ng/mL for 0.003 mg/kg, 267 ng/mL for 0.01 mg/kg, 458-1624 ng/mL for 0.03 mg/kg). Clearance was greater than anticipated~~

~~at the lower dose levels; this was considered to be due to target mediated clearance. Subject 4, dosed at 0.03 mg/kg was the heaviest subject treated (119 kg), thus received the largest dose and had the highest GSK3174998 exposure (1624 ng/mL).~~The PK of GSK3174998 was evaluated after IV administration at doses of 0.003 mg/kg to 10 mg/kg every 3 weeks in patients with solid tumors in Study 201212. Plasma PK samples (cut-off date 28 July 2017) were analyzed with a validated analytical method based on immunocapture and trypsin digestion, followed by ultra-high pressure liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) analysis with a lower limit of quantitation (LLOQ) of 10 ng/mL.

The median first cycle concentration-time profiles for Part 1A and Part 2A presented in Figure 2 initially exhibited a biexponential decline typical for mAbs- administered IV. At lower GSK3174998 concentrations, faster elimination and shorter half-lives were observed, indicating target-mediated disposition. Consequently, AUC and trough concentrations were increasing more than proportionally with dose. Concentration-time profiles were similar between GSK3174998 alone and combination therapy, indicating that co-administration of pembrolizumab did not affect the PK of GSK3174998. Cmax values were approximaely dose-proportional and typical for mAbs.

At the time of data cut off (22 June 2017) 49% of subjects with available post-treatment data tested positive for anti-GSK3174998 anti-drug antibodies (ADA) across dose levels 0.003–10 mg/kg GSK3174998 in Part 1A and 0.003–0.1 mg/kg in Part 2A. Positive ADA titers were detectable as early as three weeks after the first dose of GSK3174998. Of the 30 subjects with positive ADA titers, two subjects experienced infusion related reactions beginning with administration of the third dose of GSK3174998; no other infusion reactions were reported in the study.

Figure 2 Median (range) time-concentrations profiles by dose group for GSK3174998 alone or in combination with pembrolizumab



Notes:
1. Preliminary data from Study 201212 (cut-off date 28 July 2017).
2. Samples reported below the limit of quantitation (0.01 µg/mL) were assigned a value of 0.005 µg/mL for the purposes of this graphical summary.

Section 2.3.5.3. Preliminary Receptor Occupancy Data (ENGAGE-1, Part 1A and 2A)

Rationale for Change

Preliminary receptor occupancy data updated based on data from the ongoing study

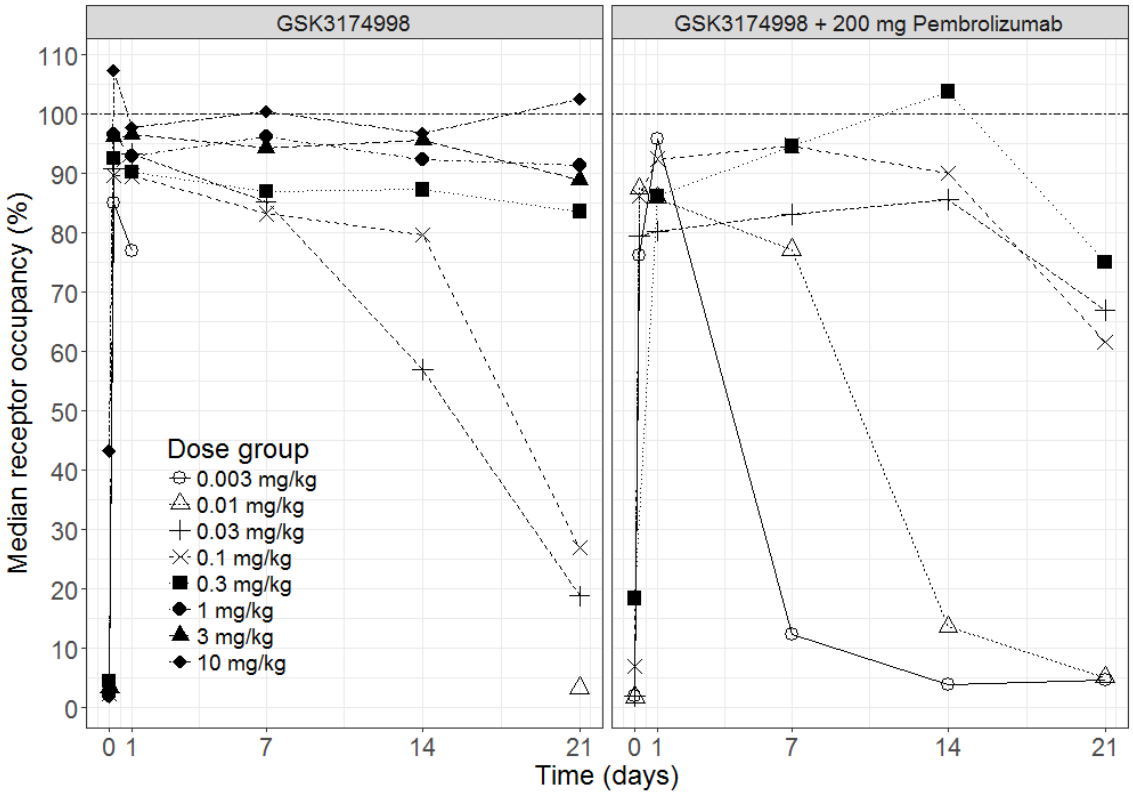
REVISED TEXT:

Section 2.3.5.3. Preliminary Receptor Occupancy Data (ENGAGE-1, Part 1A and 2A: ~~Part 1~~)

~~Receptor occupancy (RO) was assessed for CD3+ cells from peripheral blood. Preliminary receptor occupancy (RO) data after the first dose was higher than predicted; approximately 85% RO was seen in Subject 1 who received the lowest dose of GSK3174998 (0.003 mg/kg). Subject 4, who had the largest GSK3174998 exposure, had >90% RO throughout the first dosing period (21 days); while Subjects 6, 7, and 502, treated with the same dose level (0.03 mg/kg) had >90% RO for approximately 8 days during the first dosing period.~~Receptor occupancy (RO) was assessed for peripheral

blood CD3+ T cells in Part1A and 2A. Preliminary data indicated that a high degree (≥80%) of receptor occupancy is achieved initially (≤1 day after dosing) even for the lowest dose of 0.003 mg/kg GSK3174998 (Figure 3). For doses of 0.1 mg/kg or smaller receptor occupancy subsequently declines towards the end of the dosing cycle. Starting with 0.3 m/kg GSK3174998 continuously high receptor occupancy levels are observed over the whole 21-day dosing cycle. Qualitatively similar receptor occupancy profiles were observed when GSK3174998 was administered in combination with 200 mg pembrolizumab Q3W (Figure 3)

Figure 43 Median receptor occupancy profiles for varying doses of GSK3174998 alone or in combination with pembrolizumab



Notes:
1. Preliminary data from Study 201212.

Section 2.3.5.4. Preliminary Clinical Activity Data (ENGAGE-1)

Rationale for Change

Preliminary clinical data updated based on data from the ongoing study

REVISED TEXT:

2.3.5.4. Preliminary Clinical Activity Data (ENGAGE-1~~: Part 1~~)

~~Due to the frequency of disease assessments (every 12 weeks), few subjects had their first post-baseline disease assessments performed at the time of clinical data cut-off (17 May~~

~~2016) and no objective responses were observed. Subject 1 (0.003 mg/kg), 3 (0.01 mg/kg) and 4 (0.03 mg/kg) discontinued treatment due to disease progression after 2, 4, and 3 doses of GSK3174998, respectively.~~

2.3.5.4.1. Clinical Activity - Part 1A

At the time of the clinical data cut-off (09 Jan2018), one confirmed PR was reported at week 24 in a subject with STS (0.3 mg/kg GSK3174998), who subsequently discontinued treatment for PD at week 30. A subject with NSCLC (0.3 mg/kg GSK3174998) was reported to have SD for 24 weeks, and discontinued treatment with PD after 39 weeks. An additional 5 subjects were reported to have SD at week 12, but subsequently discontinued treatment for PD prior the next imaging assessment.

2.3.5.4.2. Clinical Activity - Part 2A

At the time of the clinical cut-off (09 Jan 2018), clinical responses were reported for the combination of GSK3174998 and pembrolizumab. At the 0.01 mg/kg GSK3174998 + 200 mg pembrolizumab dose level, one subject demonstrated a CR (MSI-CRC) and one subject with SCCHN demonstrated SD at week 24, and continues on treatment at week 54. At the 0.1 mg/kg GSK3174998 + 200 mg pembrolizumab dose level, 3 subjects demonstrated a PR (melanoma, bladder and MSI-CRC). At the 0.3 mg/kg GSK3174998 + 200 mg pembrolizumab dose level, 1 subject with NSCLC demonstrated a PR, while a second subject with NSCLC demonstrated SD at week 15 and remained on treatment as of week 27.

Section 2.4 Pembrolizumab

Rationale for Change

Updated language as required

REVISED TEXT:

2.4.1 Pembrolizumab Background and Clinical Trials

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical *in vitro* data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator brochure.[Merck Sharp & Dohme Corp, 2015] .

~~Pembrolizumab, a humanized monoclonal antibody against the PD-1 protein, has been developed by Merck & Co for the treatment of patients with cancer. Pembrolizumab is approved for treatment of patients with melanoma in several countries; in the US and EU~~

~~it is approved for the treatment of patients with advanced (unresectable or metastatic) melanoma in adults. Pembrolizumab has also been approved for treatment of patients with NSCLC in several countries; in the US it is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with NSCLC and EGFR or ALK genomic tumor aberrations should also have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab. In the US, pembrolizumab is also approved for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after platinum-containing chemotherapy.~~

~~Pembrolizumab has demonstrated initial clinical efficacy in single arm monotherapy trials in subjects with non-small cell lung cancer, head and neck squamous cell carcinoma, urothelial cancer, gastric cancer, triple negative breast cancer and Hodgkin's Lymphoma as determined by response rate. Ongoing clinical trials are being conducted in advanced melanoma, NSCLC, head and neck cancer, urothelial cancer, gastric cancer, TNBC, Hodgkin's lymphoma and a number of other advanced solid tumor indications and hematologic malignancies. For study details please refer to the IB~~

2.4.2 Rationale for Pembrolizumab Dose Selection

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

~~The dose of pembrolizumab planned to be studied in this trial is 200 mg Q3W. The dose recently approved in the United States and several other countries for treatment of melanoma subjects is 2 mg/kg Q3W. Information on the rationale for selecting 200 mg Q3W is summarized below.~~

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

~~An integrated body of evidence suggests that 200 mg every 3 weeks (Q3W) is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in subjects with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with 2 mg/kg Q3W dose.~~

~~A population pharmacokinetic (PK) model, which characterized the influence of body weight and other patient covariates on exposure, has been developed. The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose and importantly will maintain individual patient~~

~~exposures within the exposure range established in melanoma as associated with maximal clinical response. Pharmacokinetic properties of pembrolizumab, and specifically the weight-dependency in clearance and volume of distribution are consistent with no meaningful advantage to weight-based dosing relative to fixed dosing.~~

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

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

Section 3 OBJECTIVE AND ENDPOINTS

Rationale for Change

Addition of TCR diversity and mutational load

REVISED TEXT:

Second and Fourth Exploratory Objective and Endpoint

Exploratory	
• To evaluate the pharmacodynamic activity of GSK3174998 in the peripheral blood and to explore the utility of these measures to enrich for clinical efficacy and development of a diagnostic test.	• Assessment of lymphocyte OX40 receptor membrane expression and occupancy by GSK3174998. Measures of immune function in blood (e.g. phenotype, quantity, and activation state of T cells in the periphery, TCR diversity, expression of circulating soluble factors such as cytokines and stress-related proteins). Assessment of changes in genomic DNA, gene expression (RNA and protein), (e.g., using cfDNA, exosomes or circulating tumor cells [CTCs]), and mutational load.

• Pharmacogenetics (PGx): To evaluate the association of genetic variations in the host DNA and response to therapy or disease characterization.
•
	• Germline genetic evaluations may be conducted for:
	  • Medicine response, including GSK3174998 or any concomitant medicines.
	  • Disease susceptibility, severity, and progression and related conditions.

Section 4.1 Overall Design

Rationale for Change

Additional tumor type of STS added

REVISED TEXT:

Second paragraph

The study will be conducted in 2 parts, ~~each part consisting of~~ starting with a dose-escalation phase followed by a cohort expansion phase. Part 1 will evaluate GSK3174998 monotherapy, while Part 2 will evaluate GSK3174998 in combination with pembrolizumab. As shown in Figure 5 , GSK3174998 will first be evaluated as monotherapy in escalating doses. Once a dose of GSK3174998 has been identified that is both tolerable and demonstrates pharmacodynamic activity, enrollment of Part 2 may begin. In Part 2, escalating doses of GSK3174998 will ~~first~~ be evaluated with fixed doses of pembrolizumab. Part 1A and 2A will also include a Pharmacodynamic Cohort, which requires mandatory fresh pre- and on-treatment biopsies and an additional disease assessment at week 6. ~~Each~~ Part 2 ~~part~~ will also include expansion cohorts for ~~up to three different~~specified tumor types.

Third paragraph

The study will enroll up to approximately 264 subjects with tumor types that may include NSCLC, SCCHN, RCC, melanoma, bladder cancer, STS, TNBC, and MSI CRC. In the dose-escalation phase of the study, subjects with any of the aforementioned tumor types may be included; whereas in the cohort expansion phase of the study, each expansion cohort will enroll subjects with one specific tumor type selected from the aforementioned list. ~~Up to three expansion cohorts may be included for each part of the study.~~

Figure 5 Information of part 1B is deleted

Section 4.1.4 Dose Limiting Toxicity

Rationale for Change

Consolidated dose modifications guidelines

REVISED TEXT:

Last Paragraph

Guidance for the management of toxicity, including dose modification algorithms, is provided in Section 6.3.1 and is based on the experience of management of immune-related adverse events (irAEs) since the development of ipilimumab and PD-1 inhibitors such as pembrolizumab~~. Section 6.3.1 includes general guidance for the management of non-hematologic AEs (Table 9), general guidance for the management of irAEs (Section 6.3.1.1), general principles of irAE identification and evaluation (Section 6.3.1.2), and specific guidance for: hepatotoxicity (Section 6.3.1.4), gastrointestinal events (Section 6.3.1.5), skin toxicity (Section 6.3.1.6), endocrine events (Section 6.3.1.7), pneumonitis (Section 6.3.1.8), hematologic events (Section 6.3.1.9), uveitis/iritis (Section 6.3.1.10), infusion reactions or severe cytokine release (Section 6.3.1.11) and dose delay (Section 6.3.1.13).~~

Section 4.1.5. Cohort Expansion

Rationale for Change

New details added to define the dose expansion cohorts

REVISED TEXT:

~~Any dose level(s) in Parts 1A and 2A (dose escalation) may be selected for cohort expansion in Parts 1B and 2B of the study in order to collect additional data on safety, PK, pharmacodynamic activity, and clinical activity.~~

~~Each expansion cohort will include subjects with a single tumor type and will enroll up to approximately 20 subjects who will be treated at the selected dose level. In both Part 1B and Part 2B, up to three expansion cohorts will be enrolled with one indication per cohort. Selection of tumor indications will be based in part on data generated in Part 1A and Part 2A, respectively. The Steering Committee will review the available preliminary safety, PK, pharmacodynamic, and clinical activity data before selecting the dose level indications for all 3 cohorts. Criteria that may be~~ In accordance with the Steering Committee Charter and based upon a review of pertinent data with input from the study team and investigators, the Steering Committee recommended initiation of Part 2B expansion cohorts, including the selection of tumor types and the dose of GSK3174998 to be administered to subjects who enter the expansion cohorts as described below. Criteria considered in the determination of which dose level(s) to expand and which tumor types to select for cohort expansion ~~may include~~included:

- ~~**Target engagement and pharmacodynamic activity:** Observed OX40 receptor occupancy and pharmacodynamic activity. Pharmacodynamic activity will be determined by an evaluation of markers of T-cell activation and proliferation in whole blood. The changes in numbers and activation state of lymphocytes will also be assessed and correlated with individual responses as well as immune cell populations within the tumor (see Section 7.6).~~

- ~~**Tolerability**~~**Target engagement and PK:** Observed OX40 receptor occupancy and GSK3174998 exposure.

- **Safety and tolerability:** The frequency of DLT, and frequency and severity of treatment-related AEs~~of special interest (AESI), and the extent of dose modifications for either GSK3174998 or the combination agent~~.

- **Clinical activity:** Evidence of clinical response, including SD of at least 12 weeks and/or minor responses.

~~After 10 subjects have been enrolled in a given~~ The preliminary clinical data supporting initiation of the expansion ~~cohort, the Steering Committee may recommend continued accrual in that~~ cohorts are summarized in Section 2.3.5.

The initial expansion ~~cohort up to a total of~~ cohorts in Part 2B will evaluate one dose level of 0.3 mg/kg GSK3174998 (see Section 4.5.3) in tumor types where confirmed response or prolonged SD (≥12 weeks) was observed in Part 1A or 2A of this study. Tumor types selected for initial evaluation in expansion cohorts are melanoma and dedifferentiated liposarcoma (seeTable 5). Additional tumor types may be included in Part 2B in accordance with existing inclusion/exclusion criteria. A maximum of approximately ~~20~~120 subjects~~. While it is~~will be included in Part 2B.

Table 5 Part 2B Expansion Cohorts

	Population	Prior PD-(L)1 Treatment	GSK3174998 Dose	N
Study Part 2B	Melanoma	Yes	0.3 mg/kg	10-30
	Dedifferentiated liposarcoma[a]	No	0.3 mg/kg	10-30
	Additional tumor types [b]	TBD	TBD	10-60

a. Dedifferentiated liposarcoma will be the initial target; however, additional sarcoma sub-types may be included
b. Any of the tumor types studied in Part A (may be enriched for selected biomarkers if validated biomarker selection assays are available)

Subsequent expansion cohorts are anticipated ~~that the additional 10 subjects in each cohort will be treated at the same dose level as~~to receive 0.3 mg/kg GSK3174998, unless emerging data from Parts A or B of the ~~initial 10 subjects, the Steering Committee may recommend~~study support further exploration of ~~a different~~an alternative tested dose ~~level~~. These cohorts may include any of the tumor types studied in Part A, including additional subtypes of STS, and may be enriched for selected biomarkers if validated biomarker selection assays are available (e.g., PD-(L)1 expression, OX40 expression on ~~the basis of emerging data.~~ selected T cell populations, high mutational load, etc). The selection of any additional dose level(s) or dosing schedules and tumor types for cohort expansion will be communicated to the sites in writing.

A minimum of 10 subjects will be enrolled in each cohort. The first futility analysis of each expansion cohort will be conducted after approximately 10 subjects are enrolled for

whom overall response data at approximately week 12 is available. Enrollment will continue while evaluating the tumor responses from the first 10 evaluable subjects.

Any expansion cohort passing futility criteria may be selected to expand up to a total of 30 subjects per cohort. Interim analyses for futility will be conducted with decision rules for the 10^{th} to 30^{th} evaluable subjects (see Table 17 and Table 18). These decision rules provide a guideline only; actual decisions will depend upon the totality of the data. For example, a cohort may be expanded if at least 1 melanoma subject or 2 STS subjects of the initial 10 subjects enrolled in each cohort demonstrate a confirmed response (per cohort). Please refer to Section 9.3.2 for details of the futility analysis.

~~The selection of dose level(s) and tumor types selected for cohort expansion will be communicated to the sites in writing~~. For any of the expansion cohorts tested, if the observed clinical benefit appears to be associated with specific patient characteristics and/or biomarkers, a new cohort may be opened for further investigation with subjects enriched with these specific patient characteristics and/or biomarkers. Expansion cohorts will require mandatory fresh pre- and on-treatment biopsies (see Secition 7.6.2) and an additional disease assessment at Week 6. This disease assessment is timed to coincide with the on-treatment (Week 6) tumor biopsy. If feasible, the disease assessment should be performed after the tumor biopsy.

Section 4.1.6 Intra-Subject Dose Escalation

Rationale for Change

Part 1B was removed from the study design

REVISED TEXT:

There will be no intra-subject dose escalation.~~, except as follows. Upon determination of the dose selected for Part 1B, subjects being treated at lower doses in Part 1A may be considered for escalation/titration to the Part 1B dose. For such subjects, the decision whether to dose escalate will be made on a case-by-case basis after agreement by the investigator and the GSK Medical Monitor.~~

~~There will be no intra-subject dose escalation in Part 2 of the study.~~

Section 4.2. Treatment Arms and Duration

Rationale for Change

Part 1B was removed from the study design

REVISED TEXT:

Table 6 Study Treatments

Study Part	Study Treatment
Part 1: GSK3174998 Monotherapy	
1A – Dose escalation	GSK3174998 IV[a] Q3W for up to 2 years or 35 cycles, whichever comes first
~~1B – Cohort expansion~~	~~GSK3174998 IVb Q3W for up to 2 years or 35 cycles, whichever comes first~~
Part 2: GSK3174998 in combination with pembrolizumab	
2A – Dose escalation	GSK3174998 ~~IVc~~ IV[b] Q3W for up to 2 years or 35 cycles, whichever comes first Pembrolizumab 200mg IV Q3W for up to 2 years or 35 cycles, whichever comes first
2B – Cohort expansion	GSK3174998 ~~IVb~~ IV[b] Q3W for up to 2 years or 35 cycles, whichever comes first Pembrolizumab 200 mg IV Q3W for up to 2 years or 35 cycles, whichever comes first

a. For dose levels see Table 2.

~~b. At one or two dose levels shown to be tolerable in dose escalation of each part.~~

c. For dose levels see Table 3.

Alternative dosing schedules may be explored if the data warrants. This will be communicated to the sites in writing prior to implementation.

IV = Intravenous; Q3W = Every 3 weeks

Section 4.3 Type and Number of Subjects

Rationale for Change

Part 1B was removed from the study design

REVISED TEXT:

First paragraph second sentence

It is estimated that a total of up to approximately 264 subjects will be enrolled in this two-part study (approximately 144 subjects in Parts 1A and 2A [dose escalation]; approximately 120 subjects in ~~Parts 1B and~~ Part 2B [cohort expansion]).

Section 4.4. Design Justification

Rationale for Change

Minor corrections and addition of STS

REVISED TEXT:

First paragraph second sentence

The safety, tolerability, and pharmacodynamics of monotherapy GSK3174998 will be evaluated in a modified CRM~~3+3~~ dose escalation that includes an accelerated titration design for the first two dose levels.

Third paragraph second sentence

The tumor types to be evaluated in dose escalation are as follows: NSCLC, SCCHN, RCC, melanoma, bladder cancer, STS, TNBC, and MSI CRC.

Section 4.5.3 Dose Rationale for Cohort Expansion (Part 2B)

Rationale for Change

Data added to support dose selection decision for expansion cohorts.

REVISED TEXT:

GSK3174998 will be administered intravenously at a dose of 0.3 mg/kg once every 3 weeks (Q3W) on Day 1 of each 21-day cycle in combination with 200 mg pembrolizumab Q3W.

For GSK3174998 doses of ~~(~~0.3 mg/kg and higher ~~appears to be the threshold for linear PK and~~ peripheral receptor occupancy saturation over the whole dose interval was observed ~~(~~see Figure 3~~ Figure 2 and Figure 3~~). ~~–~~Peripheral OX40 receptor occupancy on circulating CD3+ T cells, provides a measure of target engagement. While the relationship between the extent of peripheral receptor occupancy and clinical response has not been established, clinical activity was observed in Part 1A at this dose level for monotherapy as described in Section 2.3.5.4.1~~ 2.3.5.4~~. In Part 2A at GSK3174998 dose levels 0.01 to 0.3 mg/kg in combination with pembrolizumab (see Section 2.3.5.4.2) at the time of the clinical data cut off (09 Jan 2018).

Safety data were reported for the full dose range of GSK3174998 monotherapy (0.003 to 10 mg/kg) and for GSK3174998 (0.003 to 10 mg/kg) when administered in combination with pembrolizumab 200 mg at the time of the clinical data cut-off (09 Jan 2018). No DLTs were reported for monotherapy. Two DLTs (pleural effusion and myocarditis) were reported in the combination setting. Out of 9 subjects dosed at GSK31748998 0.03 mg/kg + pembrolizumab, one DLT of pleural effusion was reported. Out of 4 subjects dosed at GSK3174998 10 mg/kg + pembrolizumab, one DLT of myocarditis was reported. Overall, there did not appear to be a dose-relationship for AEs and the 0.3 mg/kg dose level for the combination treatment was well tolerated. Safety data are described in more detail in Section 2.3.5.1.

In summary, the 0.3 mg/kg GSK3174998 dose level was well tolerated during dose escalation, demonstrated target engagement on circulating T cells and clinical activity

was observed at this dose level for both monotherapy and in combination with pembrolizumab.

Section 4.6.1 Risk Assessment GSK3174998 ± pembrolizumab

Rationale for Change

Addition of embryo-fetal toxicity risk and mitigation strategy.

REVISED TEXT:

Section 4.6.1. Risk Assessment GSK3174998 ± pembrolizumab

Table ~~6~~7 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hypersensitivity reaction	• Risk for infusion reactions and hypersensitivity is inherent to many mAbs [Brennan, 2010]	Subjects Severe hypersensitivity to another mAb are not eligible for participation in this study See Section ~~6.3.1.11~~ 6.3.1.2
Severe cytokine release syndrome (sCRS)	• OX40 is a costimulatory receptor that can stimulate proliferation and activation of T cells • GSK3174998 is an OX40 agonist that can costimulate T-cell activation in the context of TCR signal and CD28 cosignal. • An anti-CD28 super agonist (TGN1412) induced rapid-onset catastrophic CRS in 6 healthy volunteers	See Section ~~6.3.1.11~~ 6.3.1.2
Other immune-related AEs	Inflammatory AEs such as diarrhea/colitis, pneumonitis, and hepatotoxicity are well established after treatment with immune-modulating agents, and are consistent with the immune-stimulatory mechanism of action of these agents.	• Subjects with the following medical history are not eligible for participation in this study o Toxicity (≥Grade 3) related to prior immunotherapy leading to study treatment discontinuation o Severe hypersensitivity to another mAb ~~See Table 9, Non-Hematologic AEs; Table 10, Hepatotoxicity; Table 11, Gastrointestinal Events; Table 12, Skin Toxicity; Table 13, Endocrine Events; Table 14, Pneumonitis; Table 16,~~

		~~Uveitis/Iritis~~See Section 6.3.1.1
Embryo-fetal toxicity	Currently there are a number of monoclonal antibodies targeting immune checkpoints approved for use in humans (e.g., ipilimumab, nivolumab, durvalumab and pembrolizumab). These agents have embryo-fetal toxicity documented in the Warnings and Precautions section of the USPI and in Section 4.6 of the EU-SPC. This risk has been identified in a variety of animal species (generally cynomolgus monkeys or experiments in mice with PD-(L)1 antagonism), and link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. Human IgG4 (immunoglobulins) are known to cross the placenta; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus. There are no available human data informing the risk of embryo-fetal toxicity.	Advise females of reproductive potential of the potential risk to a fetus. Women of child-bearing potential and their male partners are required to use highly effective contraception as described in Section 5.1
TCR = T-cell receptor; mAb = Monoclonal antibody; AEs = Adverse Events		

Section 5.1. Inclusion Criteria

Rationale for Change

Criteria updated to define expansion cohorts

REVISED TEXT:

Subjects eligible for enrollment in the study must meet all of the following criteria:

1. Provide signed, written informed consent.
2. Male and female subjects, age ≥18 years (at the time consent is obtained).

3. Histological documentation of locally advanced, recurrent or metastatic solid malignancy that has progressed after standard therapy appropriate for the specific tumor type, or for which standard therapy has proven to be ineffective, intolerable, or is considered inappropriate (with the possible exception of the PD-(L)1 naive populations described in inclusion criterion 4). Subjects should not have received more than 5 prior lines of therapy for advanced disease including both standards of care and investigational therapies. Subjects whose cancers harbor molecular alterations for which targeted therapy is standard of care should have received health authority-approved appropriate targeted therapy for their tumor types before enrollment.
4. Subjects with the following solid tumors are eligible for screening: NSCLC, SCCHN, RCC, melanoma, bladder, STS, TNBC, and MSI CRC.

   In Part 2B (Cohort Expansion), specific subgroups of the above solid tumors will be studied. These subgroups may be defined by specific lines of treatment, types of prior treatment, histological subtypes, and may be enriched for selected biomarkers or patient characteristics. Populations to be studied in Amendment 3 include but are not limited to the following. Enrolment of additional populations will be communicated in writing.

   - Subjects with dedifferentiated liposarcoma who have not received prior treatment with a PD-(L)1 inhibitor
   - Subjects with melanoma who have received a prior PD-(L)1 inhibitor, had a CR, PR or SD and subsequently progressed while on PD-(L)1 therapy.
   - Subjects who have received prior treatment with a PD-(L)1 inhibitor must have documented disease progression as defined by meeting all of the following criteria:
     - Has received at least 2 doses of an approved PD-(L)1 inhibitor
     - Has demonstrated disease progression as defined by RECIST v1.1. The initial evidence of disease progression is to be confirmed by a second assessment no less than four weeks from the date of the first documented PD, in the absence of rapid clinical progression.
     - Progressive disease has been documented within 18 weeks from the last dose of the PD-(L)1 inhibitor.
5. In Parts 1A and 2A, ~~A~~a biopsy of the tumor tissue obtained at anytime from the initial diagnosis to study entry. Although a fresh biopsy obtained during screening is preferred, archival tumor specimen is acceptable if it is not feasible to obtain a fresh biopsy.~~:~~ ~~For Part 1B and Part 2B, any archival tumor specimen must have been obtained within 3 months of starting study drug.~~

   ~~Note:~~ Subjects enrolled in Part 1A or Part 2A Pharmacodynamic Cohorts or in Part 2B of the study must provide a fresh biopsy of a tumo~~ur~~ lesion not previously irradiated during the screening period and must agree to provide at least one additional on-treatment biopsy. In addition, an archived tumor tissue should be submitted for subjects in Part 2B, if available.

The criterion for collection of fresh biopsies may be waived once GSK has determined an appropriate number of viable tissue samples have been analysed.

6. Measurable disease per RECIST version 1.1 - please refer to Appendix 5. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilized as the only measurable lesion

7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1.
8. Life expectancy of at least 12 weeks.
9. Adequate organ function (see Table 8):

Table 8 Definitions for Adequate Organ Function

System	Laboratory Values
Hematologic	
ANC	≥1.5x10^9/L
Lymphocyte count	≥~~>1,000~~800/mm^3
Hemoglobin	≥9 g/dL
Platelets	≥100x10^9/L
Hepatic	
Total bilirubin *For subjects with Gilbert's Syndrome (only if direct bilirubin ≤35%)*	≤1.5xULN *≤3.0xULN*
Part 1A and 2A: ALT	≤1.5xULN
Part 2B: ALT	≤2.5xULN
Renal	
Serum Creatinine **OR** Calculated CrCl[a]	≤1.5xULN > 50 mL/min
Endocrine	
TSH[b]	WNL

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

c. Estimated CrCl should be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (see Appendix 12) or per institutional standard.
d. If TSH is not within normal limits at baseline, the subject may still be eligible if total T3 or free T3 and free T4 are within the normal limits.

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

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

Section 5.2. Exclusion Criteria

Rationale for Change

Criteria updated to define expansion cohorts

REVISED TEXT:

First Exclusion criteria second bullet point

- Checkpoint inhibitors, including PD-1, PD-L1, and CTLA-4 inhibitors: within 4 weeks. NOTE: Subjects entering the PD-(L)1 naive expansion cohort may not have received any prior PD-(L)1 anti-cancer treatment.

Twenty third Exclusion criteria

History of severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients

Section 5.4.1. Treatment Discontinuation

Rationale for Change

Addition of window for TDV

REVISED TEXT:

Second Paragraph (NOTE) second sentence

The treatment discontinuation visit (TDV) should be conducted within 30 days (+10 days) of the decision to discontinue study drug(s).

Section 6.1. Investigational Product and Other Study Treatment

Table ~~8~~9 Investigational Product Dosage/Administration

	Study Treatment	
Product name:	GSK3174998	Pembrolizumab
Dosage form:	Lyophilized powder for reconstitution	Solution for infusion
Unit dose strength(s)/ Dosage level(s):	40 mg lyophilized powder Dose range: 0.003 to ≤10 mg/kg	100 mg/ 4 mL solution Dose range: 200 mg
Route of Administration	IV infusion – 30 min[a, b]	IV infusion – 30 min[a]
Frequency of Administration	Q3W[b, c]	Q3W[b]
Dosing instructions:	Make every effort to target infusion timing to be as close to 30 min as possible. However, given the variability of infusion pumps from site to site, a window of -5 min and +10 min is permitted (i.e., infusion time is 30 min: -5 min/+10 min or 25 to 40 min).	Make every effort to target infusion timing to be as close to 30 min as possible. However, given the variability of infusion pumps from site to site, a window of -5 min and +10 min is permitted (i.e., infusion time is 30 min: -5 min/+10 min or 25 to 40 min).

Manufacturer/ source of procurement	GSK	Merck

a. Infusions may be prolonged in the event of an infusion reaction. If multiple subjects experience clinically significant infusion reactions, the infusion rate may be slowed for all future administrations of study drug(s) for all subjects. Should this global change in infusion rate be required, it will be communicated to the sites in writing.
b. Dose levels 1 and 2 will be administered less than 30 min, please refer to the SRM for infusion directions
c. Alternative dosing schedules may be explored if emerging data warrants. This will be communicated to the sites in writing prior to implementation.
Q3W = Every 3 weeks; GSK = GlaxoSmithKline

Section 6.3. Planned Dose Adjustments

Rationale for Change

Dose modification guidelines consolidated for sake of efficiency.

REVISED TEXT:

Section 6.3 of previous amendment (Amendment 2) is modified extensively (many sections have been deleted or modified) in the current amendment (Amendment 3).

6.3.1 Dose and Safety Management Guidelines

6.3.1.1. Dose modification and toxicity management for immune-related AEs associated with GSK3174998 ± pembrolizumab

AEs associated with treatment with GSK3174998 ± pembrolizumab exposure may be immune-mediated. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of GSK3174998 ± pembrolizumab treatment, or anywhere in between, and may affect more than on 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 study 201212, most irAEs were reversible and could be managed with interruptions of GSK3174998 ± pembrolizumab, administration of corticosteroids and/or other supportive care. 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 GSK3174998 ± pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for ir AEs associated with GSK3174998 ± pembrolizumab are provided in Table 10.

Table 10 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 GSK3174998 ± pembrolizumab has been withheld, GSK3174998 ± pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered.

GSK3174998 ± pembrolizumab 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	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to GSK3174998 ± pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg methylprednisolone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent grade 2	Permanently discontinue		
Diarrhea / colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg methylprednisolone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of enterocolitis (i.e. diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. peritoneal signs and ileus). • Subjects with ≥ Grade 2 diarrhea suspecting colitis
	Grade 4	Permanently discontinue		

				should consider GI consultation and performing endoscopy to rule out colitis. • Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
AST / ALT elevation or increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg methylprednisolone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg methylprednisolone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for subjects with T1DM • Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or Permanently		

		discontinue		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g. levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (methylprednisolone 1-2mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes •
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Grade 3, or intolerable/ persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 4 or recurrent Grade 3	Permanently discontinue		

NOTES:

1. The decision whether to withhold or permanently discontinue GSK3174998 ± pembrolizumab is at the discretion of the investigator or treating physician.
2. For subjects with Grade 3 or 4 immune-related endocrinopathy where interruption of GSK3174998 ± pembrolizumab is required, treatment with GSK3174998 ± pembrolizumab may be resumed when the event resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or, for T1DM, metabolic control has been achieved.

Table 11 Biomarker Panel

Biomarker	**Relationship to Adverse Event**
Serum tryptase[a]	IgE-related infusion reaction (Allergic/anaphylaxis) [Schwartz, 2006]
Serum CRP[a]	Elevated in CRS [Lee, 2014]
Serum ferritin[a]	Elevated in CRS [Lee, 2014]
Plasma cytokine panel[b] (IFN-γ*^, TNF-α*^, IL-2*, IL-4, IL-5*, IL-6*^, IL-8*, IL-10*, IL-12p70, IL-13, and IL-17)	* Reported to be elevated in CRS [Lee, 2014] ^consistently reported as elevated in CRS [Lee, 2014]

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

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

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

Table 12 GSK3174998 ± Pembrolizumab 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 subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for <24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of study drugs with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical 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 subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated.	No subsequent dosing

	In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further study drug treatment.	
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 v4.0 (CTCAE) at http://ctep.cancer.gov		

6.3.1.3 Dose Delay

GSK3174998 ± pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

If there is a dose delay between 1 and 49 days (2 dosing cycles + 7 days), the procedures at the original scheduled visit (including dosing) should be performed as soon as possible. All subsequent visits will follow a Q3W calendar schedule. Subjects with infusion delays causing 2 consecutive missed doses due to toxicity should discontinue study drug(s) unless the treating investigator and Sponsor/Medical Monitor agree there is strong evidence supporting continued treatment. While no washout from study treatments is required for subjects requiring elective surgery or palliative radiation therapy while on study, investigators and site staff are encouraged to schedule these procedures to fall in between dosing days (see Section 6.10.1. for details on permitted medications and non-drug therapies).

Section 6.8.1. GSK3174998 Overdose

Rationale for Change

Length of follow up adjusted to be consistent with the T&E table

REVISED TEXT:

Second bullet point

- Closely monitor the subject for AEs/SAEs and laboratory abnormalities for at least ~~130~~90 days.

Section 6.10.1. Permitted Medications and Non-Drug Therapies

Rationale for Change

Adjustments to guidelines for palliative radiation

REVISED TEXT:

Supportive Care: Subjects should receive full supportive care during the study, including transfusion of blood and blood products, palliative radiation to non-target lesions, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate. Seasonal flu vaccine is permitted as an injection only. Intra-nasal flu vaccine is excluded. Elective surgery or non-palliative radiation may be permitted on a case-by-case basis in agreement with the Medical Monitor. ~~, if these do not include any "target" lesions.~~

Growth Factors and Bisphosphonates: The use of growth factors, RANK-L inhibitors, and bisphosphonates (if on a stable dose for at least 4 weeks) is permitted while participating in this study. However, the initiation of growth factors and bisphosphonates is not allowed during the first 4 weeks of study treatment, unless used in the management of toxicity and agreed upon by the investigator and Medical Monitor.

Steroids: Use of steroids is permitted for treatment of AEs (~~as per~~ ~~Table 9, Non-Hematologic AEs;~~ Table 10, Hepatotoxicity; Table 11, Gastrointestinal Events;~~ ~~Table 12, Skin Toxicity;~~ ~~Table 13, Endocrine Events~~; ~~Table 14~~, Pneumonitis, and Table 16, ~~Uveitis/Iritis) while the subject is undergoing treatment on this study.~~ Table 10 ***and*** Table 12***, Dose Modification Guidelines for Immune-Related AEs or Infusion Reactions.***

Section 7.1 Time and Events Table

Rationale for Change

Minor changes to clarify footnotes and define expansion cohorts

REVISED TEXT:

Time and Evnts Table and Footnotes

Table 13 Time and Events Table – Monotherapy and Combination Therapy

Tumor Biopsies															
Archived tumor [i]	X														
Fresh tissue sample[i, m]	X							X							
PD tissue sample[k]			X[k]												

g. Dosing of GSK3174998 and pembrolizumab at every 3-week intervals is shown in the Time and Events Table; however, dosing of GSK3174998 may be delayed due to toxicity. During the combination phase, GSK3174998 should be administered first, and pembrolizumab should be administered at least 1 hour and no more than 2 hours following the end of the GSK3174998 infusion. GSK3174998 and pembrolizumab will be dosed for a maximum of 2 years or 35 cycles, whichever comes first. Alternative dosing schedules of GSK3174998 and pembrolizumab may be explored if the data warrants. This will be communicated in writing to sites prior to implementation.

h. Screening tumor imaging must be obtained within 28 days of the first dose. Tumor imaging will be performed every 12 weeks (±1 week) until disease progression has been confirmed by irRECIST; Subjects whose disease progresses must have a confirmatory scan performed at least 4 weeks after the date of assessment during which the first indication of PD was demonstrated. Immune-related RECIST will be used to determine treatment decisions for PD and the primary endpoint analysis will use irRECIST. If a subject has achieved a CR or PR in the previous radiologic assessment, a repeat scan should be performed as a part of the confirmation of response, within at least 4 weeks to confirm the response. At the TDV, tumor imaging is only required if the last disease assessment did not show PD and was performed ≥6 weeks before TDV. During the DFS FU visits (performed when a subject has permanently discontinued study treatment before disease progression has been documented), tumor imaging will be obtained every 12 weeks (±1 week) until PD, initiation of a new anticancer treatment, or death, whichever comes first. Pre-baseline scans (within 24 weeks before the baseline scan) may be collected to assess tumor growth rate in selected subjects to support exploratory investigation of tumor growth kinetics.

i. A fresh tumor biopsy should be attempted at screening (before first dose) and at Week 6 (after the 3rd dose of study treatment +1 week). Fresh biopsies are mandatory for all patients in the Pharmacodynamic Cohort and the Dose Expansion phase. ~~During the Dose Expansion phase, once evaluable paired tumor biopsies are collected for up to 10 subjects in the dose expansion phases, this requirement may be waived.~~ Tumor lesions planned for biopsy must not be used as indicator lesions for assessment of disease, unless discussed and agreed with the GSK Medical Monitor. For subjects in the initial dose escalation cohorts, where biopsy is not mandatory, a recent archival tumor specimen is acceptable if it is not feasible to obtain a fresh biopsy.

j. The 6-week disease assessment will be performed for subjects enrolled in Part A ~~for patients~~ in the Pharmacodynamic Cohort and in all Part B expansion cohorts. This disease assessment is timed to coincide with the on-treatment (6 week) tumor biopsy. If feasible, t~~T~~he disease assessment should be performed **after** the tumor biopsy.
k. Progressive Disease Tissue Sample: An optional fresh tumor biopsy should be attempted at the time of disease progression.
l. For Part 1A only: On Day 1 ECG measurements will be performed in triplicate predose and at the following times after the infusion: EOI+30m, EOI + 4h, EOI +24h, on Day 22 ECG measurements will be performed in triplicate predose and on Day 85 ECG measurements will be performed in triplicate predose and at the following times after the infusion: EOI+30m.
m. With subject consent and agreement by the PI and GSK Medical Monitor, additional, optional fresh biopsies may be obtained during the study. One example of when this may be considered is when a mixed response occurs and tumor biomarker data are anticipated to inform why some lesions are, and some are not, responding to the treatment.

Time and Events Table – Pharmacokinetics, Antidrug Antibodies, and Pharmacodynamics (Parts 1 and 2)

		Treatment													
Day	**1**	**2**	**8**	**15**	**22**	**23**	**29**	**36**	**43**	**64**	**85**	**106**	**≥148**	**30 D after Last Dose**	**12 Wks Post-Treatment ±1 week**
Dose	**1**				**2**				**3**	**4**	**5**	**6**	**≥8**		
Pharmacogenetics (6 mL)[a]	X														
Receptor occupancy and phenotyping panels(10 mL)[i]	Pre EOI+4h[g]	EOI+24h	X	X	Pre EOI+4h[g]				Pre EOI + 4h[g]					X	X
Plasma + PBMC prep (20 mL)[b]	Pre		X		Pre				Pre		Pre			X	X
Cytokines (5 mL)	Pre EOI+4h	EOI+24h	X		Pre EOI+4h				Pre EOI+4h		Pre EOI+4h				
Plasma for cfDNA + exosomes (~~10~~ 20 mL)[h]	Pre								At time of biopsy if done						
Serum (5 mL)	Pre														
GSK3174998 Pharmacokinetics (1 mL)	Pre EOI+30m EOI+4h	EOI+24h[d]	X	X	Pre EOI+30m EOI+4h	EOI+24[d]	X	X	Pre EOI+30m	Pre EOI+30m	Pre EOI+30 m	Pre EOI+30m	Pre[e]	X	X

Part 2 only: Pembrolizumab Pharmacokinetics (3 mL)	Pre EOPI+30 m	EOI+24h	X	X	Pre					Pre		Pre	Pre[e]	X	X
Anti- GSK3174998 antibodies[c,f] (~~45~~ mL)	Pre				Pre				Pre	Pre	Pre	Pre	Pre[e]	X	X[f]
Part 2 only: Anti-Pembrolizumab antibodies[c,f] (6 mL)	Pre				Pre					Pre		Pre	Pre[e]	X	X[f]

Timepoint Definitions:
X = Anytime during visit
Pre = within 60 min before the start of the GSK3174998 infusion
EOI+30m = within 30 minutes of the end of the GSK 3174998 infusion
EOPI+30m = within 30 minutes of the end of the pembrolizumab infusion
EOI +4h = within 4 hours ±10 minutes of the end of the GSK3174998 infusion
EOI+24h = 24 hours ± 4 hours after the end of the GSK3174998 infusion

a. Informed consent for optional pharmacogenetics research must be obtained before collecting a sample. It is recommended that the blood sample be taken at the first opportunity after a subject has met all eligibility requirements, and can be done up to 28 days before Day 1.
b. If the baseline/pre-dose sample is not viable, samples for PBMCs are not needed at subsequent visits.
c. In addition to these scheduled immunogenicity assessments, "event-driven" testing will also be employed for those subjects that experience anaphylaxis, serious hypersensitivity, or AEs related to study drug administration that led to withdrawal from the study. See Section 9.4.2.4 for full details.
d. Day 2 PK samples are only required during the dose-escalation phases of the study.
e. Dose 8 and every 4 dosing cycles
f. In the event of a hypersensitivity reaction that is either 1) clinically-significant in the opinion of the investigator, or 2) leads to the subject withdrawing from the study, blood samples should be taken from the subject for immunogenicity testing at the time of the event and again 30 days, 12 weeks, and 24 weeks after.
g. If the EOI+4h RO sample is scheduled to be collected after the last lab courier pick-up time of the day, the sample should be collected as late as possible to enable processing and shipping on the same day as collection.
h. <u>If a tumor biopsy is taken at the time of PD, then a plasma sample should also be collected for cfDNA + exosomes,</u>
i. <u>Receptor Occupancy and phenotyping panels will only be collected in Parts 1A and 2A of the study</u>

D = Days; PBMC = Peripheral blood mononuclear cell; EOI = End of infusion
Procedures for blood sample collection, processing, storage, and shipping are described in the SRM.

Section 7.3.1. Evaluation of Anticancer Activity

Rationale for Change

Additional details needed for expansion cohorts

REVISED TEXT:

Third Bullet point and last bullet point

- The baseline disease assessment will be completed within 4 weeks prior to the first dose of GSK3174998, then every 12 weeks thereafter, and at the final study visit. For subjects enrolled in the Part A "Pharmacodynamic Cohort" and in all Part B expansion cohorts an additional disease assessment will be performed at Week 6. See the Time and Events Table (Section 7.1, Table 13) for the schedule of assessments of anticancer activity.
- Pre-baseline scans (within 24 weeks before the baseline scan) may be collected to assess tumor growth rate in selected subjects to support exploratory investigation of tumor growth kinetics.

Section 7.4.5. Electrocardiogram (ECG)

Rationale for Change

Additional details needed for expansion cohorts

REVISED TEXT:

Third paragraph first sentence

For Part ~~1~~1A of the study, ECG measurements will be performed in triplicate at specified times (see Table 13, including footnotes).

Section 7.5.2 Blood Sample Analysis

Rationale for Change

Name of analysis name changed

REVISED TEXT:

Plasma or serum analysis for GSK3174998 and pembrolizumab will be performed under the control of Department of Bioanalysis, Immunogenicity and Biomarkers (BIB), IVIVT, PTS, GSK~~PTS-DMPK/Scinovo, GSK~~ or Merck Sharp & Dohme Corp the details of which will be included in the SRM. Concentrations of GSK3174998 and pembrolizumab will be determined in plasma and serum samples, respectively, using the

currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM). Once the plasma or serum has been analyzed for GSK3174998 and pembrolizumab any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate BIB, PTS~~PTS-DMPK/Scinovo~~, GSK or Merck Sharp & Dohme protocol.

Section 7.6.1. Blood Biomarkers

Rationale for Change

Addition of tumor mutational load to be consistent with other sections of the protocol

REVISED TEXT:

Second paragraph third sentence

Factors to be analyzed may include but are not limited to: the presence of IFN-γ, TNF-α, IL-2, IL-4, IL-5, IL-6, IL 10, IL-8, IL-12p70, IL-13, and IL-17 as well as antibodies against tumor, self tumor mutations, i.e., tumor mutational load, gene expression (RNA or protein) or viral antigens.

Section 7.6.2. Tumor Tissue

Rationale for Change

Additional details needed for expansion cohorts

REVISED TEXT:

Archival tumor tissue, as well as fresh pre- and on-treatment biopsies in subjects in the pharmacodynamic cohorts, ~~at least 10 subjects of the~~ dose-expansion cohorts, and if possible in the dose escalation cohorts will be evaluated by IHC for expression of phenotypic and functional immune cell markers on tumor infiltrating lymphocytes (TILs) and other immune cells and as well as immune signaling markers on the surface of tumor cells (e.g. including, but not limited to PD-L1), to understand antitumor immune responses. In addition, when possible, similar analyses will be performed on tumor tissue samples obtained upon progression. Additionally, tumor tissue may be sequenced to assess TCR diversity as well as evaluated for any DNA/RNA/protein changes correlating with response, such as but not limited to tumor mutational burden.

In the pharmacodynamic cohort and expansion cohorts, mandatory fresh pre- and ~~on~~ on-treatment biopsies are required (see Table 13 for timing). These mandatory biopsy samples will be evaluated as previously described for the archival, pre- and ~~ontreatment,~~on-treatment and progression biopsies.

If feasible, for all of the fresh pre-and on-treatment biopsies, both samples should be obtained from the same tumor lesion ~~site should be used for both samples~~. If not possible, the on-treatment biopsy should be obtained from the same ~~anatomical site~~ organ as the pre-treatment biopsy. The tumor site chosen for biopsy must not be the used as an

indicator lesion for assessment of disease unless otherwise discussed and agreed upon with the GSK medical monitor.

With subject consent and agreement by the PI and GSK Medical Monitor, additional, optional fresh biopsies may be obtained during the study. One example of when this may be considered is when a mixed response occurs and tumor biomarker data are anticipated to inform why some lesions are, and some are not, responding to the treatment. In this case, the additional biopsies are not required to be obtained from the same lesion or organ as the pre-treatment biopsy. .

Section 9.1 Hypotheses

Rationale for Change

Additional details needed to define the analysis plan for the expansion cohorts

REVISED TEXT:

Section 9.1.1. to Section 9.3.2.

9.1.1. Part 1: Monotherapy Dose Escalation (GSK3174998)

With respect to the primary objectives and endpoints, no specific statistical hypotheses are being tested. The primary focus will be on determining the recommended dose for further exploration, the safety profile, and antitumor activity of GSK3174998.

~~**9.1.2.** Part 1: Monotherapy Dose Expansion (GSK3174998)~~

~~The null hypothesis for the secondary endpoint- overall response rate is:~~

~~H_0: p≤10%.~~

~~The alternative hypothesis is:~~

~~H_A: p>10%.~~

9.1.2. Part 2: Combination Dose Escalation (GSK3174998 + Pembrolizumab)

No formal statistical hypotheses are being tested. Analysis of the data obtained from this study will be focused on comparison between dose cohorts and only descriptive methods will be used in analysis of the data obtained from this study.

9.1.3. Part 2: Combination Dose Expansion (GSK3174998 + Pembrolizumab)

~~In the dose-expansion phase, for each cohort the primary goal is to test the null hypothesis that the overall response rate for the combination of GSK3174998 + pembrolizumab is equal to the historical response rate of monotherapy pembrolizumab, expected to be 15% to 40% according to which tumor types are selected for study. The~~

~~goal will be to detect an improvement in the overall response rate on the combination therapy in the range of 25% over the null, with power of at least 80% and no more than a 15% type 1 error rate. In populations resistant to pembrolizumab, the goal would be to observe a response rate of 20% to 30% to the combination of GSK3174998 + pembrolizumab.~~

The expansion cohorts of GSK3174998 + pembrolizumab are designed to evaluate preliminary clinical activity. Futility assessments will be conducted to evaluate accumulating data including safety, responses, PK and pharmacodynamics. The methodology is based on the predictive probability of success if enrollment continues until all planned subjects are recruited [Lee, 2008].

There are mutiple dose expansion cohorts being planned for STS, melanoma and other cancers types in the dose-expansion phase. For each cohort the objective is to test the null hypothesis that the overall response rate for the combination of GSK3174998 + pembrolizumab is equal to the historical response rate of monotherapy pembrolizumab.

The observed monotherapy pembrolizumb overall response rate was apprioxmately 18% for STS [Burgess, 2017]. The observed monotherapy pembrolizumb overall response rate was assumed to be apprioxmately 10% for melanoma in the pretreated population[Robert, 2014].

The sample size is chosen based on an improvement of 20% in the overall response rate on the combination therapy over the null hypotheiss, with power of at least 80% and no more than a 10% type 1 error rate. In the population previously treated with pembrolizumab, the goal would be to observe a response rate of 30% to the combination of GSK3174998 and pembrolizumab.

Therefore, the hypothesis for both **PD-(L)1** naïve and **PD-(L)1** pretreated cohorts are shown as below:

For **PD-(L)1** naïve dose expansion cohorts (e.g., STS),

the null hypothesis for ORR is:

H_0: p=18%

The alternative hypothesis is:

H_A:p=38%

For **PD-(L)1** pretreated dose expansion cohorts (e.g., melanoma),

the null hypothesis for ORR is:

H_0: p=10%

The alternative hypothesis is:

H_A:p=30%

9.2. Sample Size Considerations

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

The study will enroll up to approximately ~~264subjects~~264 subjects with tumor types that may include NSCLC, SCCHN, RCC, melanoma, STS, bladder cancer, TNBC, and MSI CRC.

Up to 72 subjects will be enrolled in each of the two dose escalation parts of the study (Parts 1A and 2A); up to 30 subjects will be enrolled in each of dose expansion cohorts. The sample size of each expansion cohort at a given dose level will be minimum of 10 subjects and maximum of 30 subjects based on the overall response assessments.

The trial is not designed to stop early for efficacy but is designed to continusly assess futility if the predictive probability of success is 10% or less. The type I error rate, power, and predictive probability for assessing futility were determined from stating the minimum and maximum sample size, futility stopping rate, and the optimizing criterion as minimizing the sample size under null hypothesis. A weak informative prior distribution with a mean response rate equal to the target response rate is assumed. Thus, the predictive probability for the response rate will be primarily driven by the data. The detailed decision criteria for all cohorts are documented in section 9.3.2.

Table 16 Expansion Cohorts Power and Type I Error

	Power	Type I error
STS PD-(L)1 naïve population: p0=18% and p1=38%	0.802	0.062
Melanoma pretreated PD1/PDL1 population: p0=10% and p1=30%	0.831	0.051

For the PD-(L)1 naïve combination expansion cohorts in STS, starting with 10 subjects in each cohort and allowing for a maximum sample size of 30 for each cohort, this design will have approximately 80.2% power with an overall type I error rate (α) of 6.2%. Under null hypotheses with an 18% ORR, the probability of early termination (PET) is 43% after data from 10 subjects evaluable for response are available and 77% after data from 20 evaluable subjects are available. Under the alternative hypothesis, if the true response rate is 38%, PET is 6% after data from 10 evaluable subjects are available and 13% after data from 20 evaluable subjects are available.

For the expansion cohorts in PD-(L)1 pretreated melanoma, starting with 10 subjects in each cohort and allowing for a maximum sample size of 30 for each cohort, this design will have approximately 83.1% power with an overall type I error rate (α) of 5.1%. Under null hypotheses with a 10% ORR, PET is 35% and 80% when data for 10 and 20 evaluable subjects are available. Under the alternative hypothesis, if the true response rate is 30%, PET is 3% by 10 subjects evaluated and 13% by 20 subjects evaluated.

9.2.1. Sample Size Re-estimation or Adjustment

Up to ~~20~~30 subjects/cohort are expected to be enrolled in each dose-expansion phase of Part ~~1 and Part~~ 2. ~~In Part 2, the~~There is no other sample size ~~may be increased up to approximately 40 subjects per cohort, once the tumor types are chosen and the null/alternative hypotheses determined, to maintain power of at least 80% with no more than a 15% type 1 error rate.~~re-estimation or adjustment planned.

9.3. Data Analysis Considerations

In the dose escalation cohorts, the dose will be escalated based on all available data, including biomarker and PK data and the safety profile of prior cohorts. In addition, the recommended dose from a Continuous Reassessment Method (N-CRM) analysis [Neuenschwander, 2008] will be calculated. The N-CRM is a type of Bayesian adaptive dose-escalation scheme. The method is fully adaptive and makes use of all the DLT information available at the time of each dose assignment. The Fixed and Adaptive Clinical Trial Simulator (FACTS) will be used to conduct the N-CRM analysis. The DLT information on all subjects enrolled in the trial are used to update the estimated dose-toxicity relationship and provide supportive information in addition to the 3+3 design in the next escalation/de-escalation decision.

The expansion phases are designed to evaluate preliminary efficacy. A futility assessment will be conducted and enrollment may be paused in order to evaluate accumulating data including safety, responses and pharmacodynamic data. The methodology is based on the predictive probability of success if enrollment continues until all planned subjects are recruited [Lee, 2008].

In addition, a Bayesian hierarchical model may be used to share information across cohorts if PK and biomarker data suggest a strong similarity in clinical activity among cohorts.

~~For Part 1: MonotherapyIn the Dose Expansion cohorts, after 10 subjects have been enrolled in each cohort (for pre-treatment , the number of observed responses may be used to guide further enrollment according to the rules summarized in Table 22 Table 17 and Table 18. However, all available data will be considered in making enrollment decisions.~~

Table 22 Monotherapy Expansion Cohort Enrollment Guidance

	Number of Responses				
Number of Subjects[a]	0	1	2	3	≥4
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					

a. The shaded regions are the specific regions for pausing enrollment.

Starting with 10 subjects and allowing for a maximum sample size of 20, this design will have a type I error rate (α) of 0.128 and 88% power when the true response rate is 30%. The trial is not designed to stop early for efficacy but is designed to assess futility if the predictive probability of success is 1% or less. The type I error rate, power, and predictive probability of success to assess futility were derived from explicitly stating the minimum and maximum sample size, futility stopping rate, and selection of the optimizing criterion as the maximization of power under the alternative hypothesis. The Bayesian prior used in determining the design was Beta (0.1, 0.9), a relatively non-informative distribution with a mean response rate of 10%. Under the null hypothesis, if the true response rate is 10%, the expected sample size of the design is 16 subjects per expansion cohort and the probability of early termination is 73%. Under the alternative hypothesis, if the true response rate is 30%, the expected sample size of the design is 20 subjects per expansion cohort and the probability of early termination is 6%.
These operating characteristics assume that the futility assessment rules are followed. If not and the trial continues to enroll until 20 subjects are evaluated, the overall type 1 error rate increases from 0.128 to 0.133, with an increase in power from 88% to 89%.

The statistical approach for creating futility assessment rules for the expansion phase of the combination cohorts will be similar to that of the monotherapy phase, determined according to which tumor types are selected for study. In addition, a Bayesian hierarchical model may be used to share information across cohorts if PK and biomarker data suggest a strong similarity in clinical activity among cohorts.

CRM-recommended dose-escalation levels, futility assessment rules, and posterior probabilities are only guidelines and the totality of the data will be considered by the team in decision making.

9.3.1. Analysis Populations

The **All Treated Population** is defined as all subjects who receive at least one dose of GSK3174998. Safety and anticancer activity will be evaluated based on this analysis population.

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

9.3.2. Interim Analysis

No formal interim analyses will be performed using the data generated from dose escalation cohorts. Preliminary safety and available PK/PD data will be performed and reviewed by study team (to include at minimum, the GSK medical monitor and investigator) after completion of each dose cohort. This review will support the decision on the dose level in the next dose cohort. Dose escalation decisions making will be based on the rules as described in Section 4.1.1 and Section 9.3. The Steering Committee will guide the transition of the study from dose escalation to cohort expansion for both monotherapy and combination therapies.

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

Futility interim analysis decision rules for the 10^{th} to 30^{th} evaluable subjects are presented in Table 17 and Table 18, which specify the number of subjects with an unconfirmed response required for continuing enrolment when total sample size is up to 30. Additional futility looks may be performed, if necessary. These rules are intended as a guideline only. If applicable, appropriated data from dose escalation may be integrated into dose expansion decisions.

Actual decisions will depend on the totality of the data. Any additional decision rules will be documented in the RAP before the nterim analysis. Should the recommendation to stop for futility be disregardedp in favor of a decision to continue the trial based on the totality of the data, the overall type I error rate of the expansion phase will be inflated. The Steering Committee will monitor safety and efficacy over the course of the study following the randomization and futility rules for expansion cohorts.

Table 17 Futility Boundary for PD(L)-1 naive Pembrolizumab Combination Therapy Expansion Cohorts in STS.

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

a. Shaded regions indicate enrollment pause based on meeting futility

Table 18 Futility Boundary for PD(L)-1 Experienced Pembrolizumab Combination Therapy Expansion Cohorts in Melanoma

Number of Subjects[a]	Number of Responders					
	0	1	2	3	4	5
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						
29						
30						

a. Shaded regions indicate enrollment pause based on meeting futility

Section 11 References

Rationale for Change

New references added

REVISED TEXT:

Burgess MA, Bolejack V, Van Tine BA, et al. Multicenter phase II study of pembrolizumab (P) in advanced soft tissue (STS) and bone sarcomas (BS): final results of SARC028 and biomarker analyses. *J Clin Oncol*. 2017;35(suppl; abstr 11008)..

Garon EB, Rizvi NA, Hui R, Leighl NL, Balmanoukian AS, Eder JP, Patnaik A, Aggarwal A, et al. Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer. *N Engl J Med* 2015; 372:2018-2028.

KEYTRUDA (pembrolizumab) prescribing information. Merck Sharp & Dohme Corporation, Whitehouse Station, New Jersey, USA, ~~October 2015~~ November 2017.

Section 12.1. Appendix 1: Abbreviations and Trademarks

Rationale for Change

Clarification of MSI CRC and addition of STS

REVISED TEXT:

MSI CRC	Colorectal carcinoma displaying high microsatellite instability
STS	Soft Tissue Sarcoma

Section 12.5.3.1. Evaluation of best overall response

Rationale for Change

Aligned wording to be consistent with T&E table

REVISED TEXT:

First bullet

- To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after the first dose at a minimum interval of ~~84~~ 77 days.

Section 12.7 Appendix 7: Genetic Research

Genetic Research Objectives and Analyses

Rationale for Change

Addition of STS expansion cohort

REVISED TEXT:

Second bullet point

- NSCLC, SCCHN, RCC, melanoma, bladder, STS, TNBC or MSI CRC, susceptibility, severity, and progression and related conditions

Section 12.11. Appendix 11: Adverse Events of Special Interest

Rationale for Change

Minor change to wording

REVISED TEXT:

First paragraph fifth sentence

Please note this table lists known AESI, additional events may be identified during the course of the study.

12.13.4. Amendment 4 Protocol Changes

Where the Amendment Applies

This amendment applies to all sites and countries.

Summary of Amendment Changes with Rationale

Amendment 4 documents the closure of Part 2B expansion cohorts, removes the requirement for future disease assessments and survival follow-up, and clarifies the impact of ending enrolment of expansion cohorts on the study objectives and efficacy analysis.

For expansion cohorts, enrolment of 10 subjects/cohort was initially planned, with a possibility of further enrolment if the cohorts passed planned futility analyses. However, in February 2019, a strategic decision was made not to initiate any new clinical investigations with the GSK3174998/pembrolizumab combination, including halting further expansion beyond 10 subjects/cohort. This decision was based upon the modest clinical activity observed within the study at that time, in addition to published data for other OX40 agonist antibodies combined with PD-1 or PD-L1 inhibitors reporting low/modest clinical activity for these combinations. As a consequence, the futility analyses (described in Section 4.1.5) were deemed unnecessary. Ultimately, the three expansion cohorts in Melanoma, STS and NSCLC treated a total of 9, 9, and 5 subjects, respectively. As of 5 November 2019, all subjects have completed treatment and are in post-treatment follow-up; no responses were observed in subjects enrolled in the expansion cohorts. Given the lack of responses in the expansion cohorts (Part 2B) and the modest clinical activity observed in dose escalation (Part 1A and 2A), no time-to-event summaries and analyses (TTR, DOR, PFS, OS) will be performed for efficacy data.

Minor clarifications, formatting and typographical errors were also addressed in this amendment.

Changes are noted with ~~strikethrough~~ to identify deleted text and <u>underlining</u> to identify new or replacement text.

Overall change: The protocol has been updated to reflect the most recent IBs throughout the document.

Section TITLE PAGE

Rationale for Change

The sponsor information was updated based on internal GSK team personnel changes.

REVISED TEXT:

PPD

Section Sponsor Signatory

Rationale for Change

The sponsor information was updated based on internal GSK team personnel changes.

REVISED TEXT:

~~Li Yan, MD~~

~~VP, Head Unit Physician~~
Hesham A. Abdullah, MD, MSc, RAC
SVP, Head of Clinical Development, Oncology

Section MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Rationale

Medical monitor information was updated

REVISED TEXT:

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/Serious Adverse Event (SAE) Contact Information:

Role	Name	Office Phone Email Address	Mobile	Fax
Primary Medical Monitor	PPD , MD	PPD	PPD	
Secondary Medical Monitors	PPD , MD, PhD PPD ~~, MD~~	PPD	PPD	
SAE contact information		PPD		PPD

Section PROTOCOL SYNOPSIS Objectives/Endpoints (Antitumour activity)

Rationale for Change

Given the modest clinical activity observed in dose escalation (Part 1A and 2A), no time-to-event summaries and analyses (TTR, DOR, PFS, OS) will be performed for efficacy data.

REVISED TEXT

- **Antitumor activity endpoints:** Objective response rate (ORR) and Disease Control Rate (DCR) (complete response [CR]+partial response [PR]+stable disease [SD] ≥12 weeks~~), time to response (TTR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS~~). Unless otherwise specified, all response endpoints will be assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and by irRECIST (immune-related RECIST); the primary endpoint analysis will use irRECIST.

Section PROTOCOL SYNOPSIS Treatment Arms and Duration (Second paragraph)

Rationale for Change

This decision was based upon the modest clinical activity observed in the study.

REVISED TEXT

With the implementation of Amendment 04, there will be no requirement to perform future disease assessments or survival follow-up. In Part 1, dose escalation for GSK3174998 monotherapy will begin with a starting dose of 0.003 mg/kg GSK3174998 administered once every 3 weeks (Q3W).

Section 2.3.5. Preliminary Clinical Data for GSK3174998

Rationale for Change

Updates in the Investigators' Brochure. Removal of text within the protocol that is a duplicate of the Investigators' Brochure.

REVISED TEXT

2.3.5. Preliminary Clinical Data for GSK3174998

Data are summarized for the ongoing first time in human study with a clinical data cut-off of ~~09 Jan 2018.~~13 August 2019 in the Investigator's Brochure [2014N212091_06]. Data are reported for ~~104~~138 subjects.; 45 subjects received doses up to 10 mg/kg of GSK3174998 monotherapy and ~~61~~96 subjects received doses up to 1.0 10 mg/kg of GSK3174998 + 200 mg of pembrolizumab. ~~Two~~Three subjects crossed over from monotherapy to combination therapy.

~~**2.3.5.1. Preliminary Safety Data (ENGAGE-1)**~~

~~**2.3.5.1.1. Safety Data - Part 1**~~

~~No dose-limiting toxicities, or treatment-related Grade 4, or Grade 5 toxicities were reported. Grade 3 asthenia and Grade 3 lymphocytopenia were reported in a single patient and attributed to study treatment. A single event in another subject led to treatment discontinuation; Grade 5 stroke manifested as aphasia, attributed to disease progression.~~

~~The most common AEs regardless of attribution were fatigue (13, 29%), back pain (9, 20%), diarrhea (9, 20%), nausea (9, 20%), vomiting (9, 20%), asthenia (8, 18%), anemia, (7, 16%), headache (6, 13%), constipation (5, 11%), cough (5, 11%), dyspnoea (5, 11%), myalgia (5, 11%), pain in extremity (5, 11%), and pyrexia (5, 11%). The most common AEs attributed to treatment by the investigator included diarrhea (5, 11%) and fatigue (5, 11%).~~

~~2.3.5.1.2. Safety Data - Part 2~~

~~No treatment related Grade 4 or Grade 5 toxicities were reported. Three patients reported Grade 3 treatment-related AEs.Two dose limiting toxicities were reported. One patient with bladder cancer reported asymptomatic Grade 3 cardiac troponin and Grade 1 myocarditis occurring 16 days after the first and only dose of study treatments. Both events were attributed to study treatments, resulted in discontinuation of treatment, and resolved with a short course of 500 mg methylprednisolone. Other treatment-related Grade 3 events included Grade 3 fatigue in one patient with colorectal cancer (resulting in treatment discontinuation), and Grade 3 diarrhea in a patient with bladder cancer. The diarrhea lasted a single day, three days after the second dose of study drugs. A second dose limiting toxicity of Grade 2 pleural effusion was reported in a patient with triple negative breast cancer (0.03 mg/kg dose cohort). Adverse events leading to treatment discontinuation included the Grade 3 myocarditis and Grade 3 fatigue described above, and Grade 3 abdominal pain not related to treatment in a patient with colorectal cancer. The most common AEs regardless of attribution were fatigue (15, 25%), decreased appetite, (12, 20%), pleural effusion (9, 15%), arthralgia (8, 13%), nausea (7, 11%), asthenia (6, 10%), cough (6, 10%), and diarrhea (6, 10%). The most common AEs attributed to treatment by the investigator included fatigue (12, 20%), nausea (4, 7%), and pruritus (4, 7%).For further details on the safety of GSK3174998, please refer to the IB [GlaxoSmithKline Document Number GlaxoSmithKline Document Number 2014N212091_00]~~

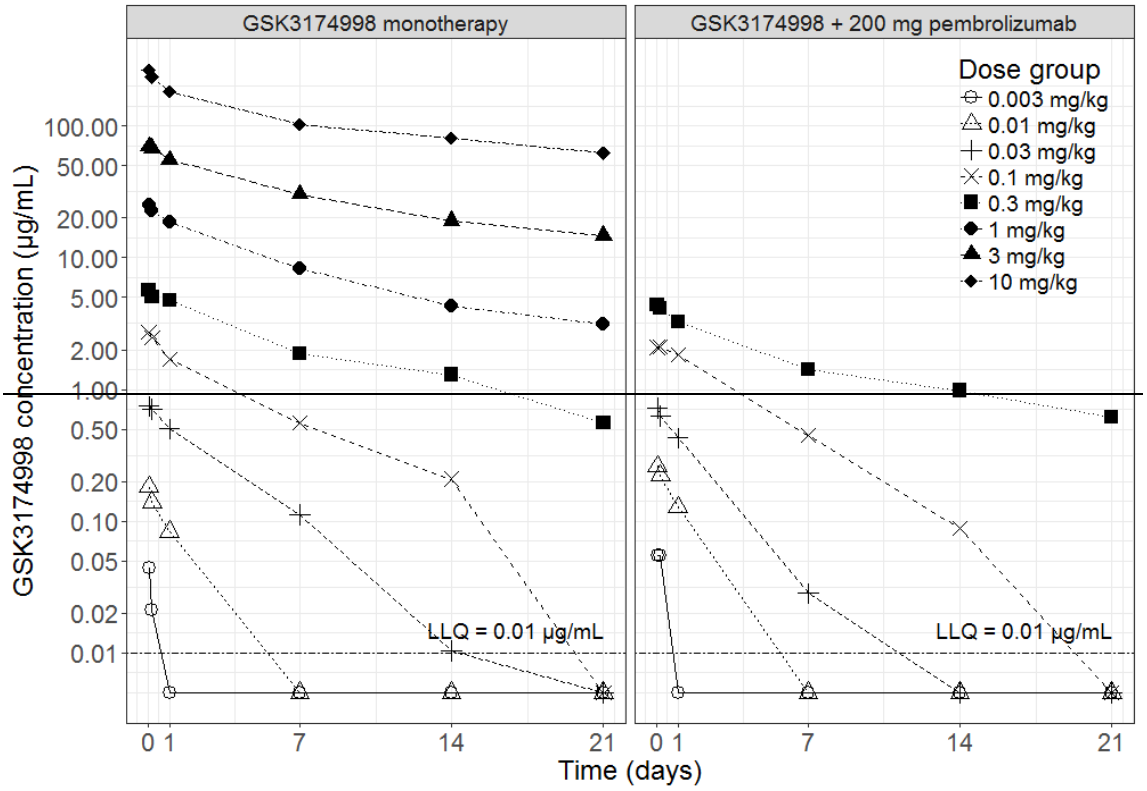
~~2.3.5.2. Preliminary Pharmacokinetic Data (ENGAGE-1, Part 1A and 2A)~~

~~The PK of GSK3174998 was evaluated after IV administration at doses of 0.003 mg/kg to 10 mg/kg every 3 weeks in patients with solid tumors in Study 201212. Plasma PK samples (cut-off date 28 July 2017) were analyzed with a validated analytical method based on immunocapture and trypsin digestion, followed by ultra-high pressure liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) analysis with a lower limit of quantitation (LLOQ) of 10 ng/mL.~~

~~The median first cycle concentration-time profiles for Part 1A and Part 2A presented in Figure 2 initially exhibited a biexponential decline typical for mAbs administered IV. At lower GSK3174998 concentrations, faster elimination and shorter half-lives were observed, indicating target-mediated disposition. Consequently, AUC and trough concentrations were increasing more than proportionally with dose. Concentration-time profiles were similar between GSK3174998 alone and combination therapy, indicating that co-administration of pembrolizumab did not affect the PK of GSK3174998. Cmax values were approximaely dose-proportional and typical for mAbs.~~

~~At the time of data cut off (22 June 2017) 49% of subjects with available post-treatment data tested positive for anti-GSK3174998 anti-drug antibodies (ADA) across dose levels 0.003–10 mg/kg GSK3174998 in Part 1A and 0.003–0.1 mg/kg in Part 2A. Positive ADA titers were detectable as early as three weeks after the first dose of GSK3174998. Of the 30 subjects with positive ADA titers, two subjects experienced infusion related reactions beginning with administration of the third dose of GSK3174998; no other infusion reactions were reported in the study.~~

~~Figure 2 Median (range) time-concentrations profiles by dose group for GSK3174998 alone or in combination with pembrolizumab~~



~~Notes:~~

~~1. Preliminary data from Study 201212 (cut-off date 28 July 2017).~~

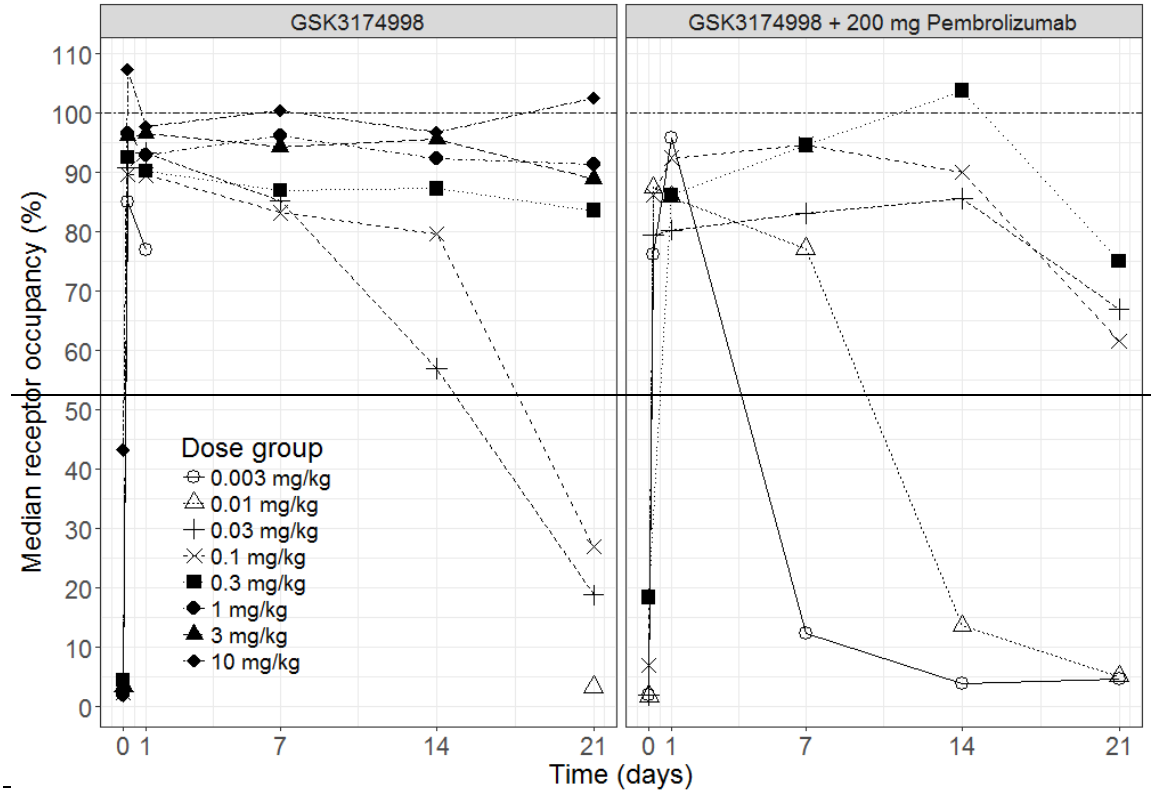
2. ~~Samples reported below the limit of quantitation (0.01 µg/mL) were assigned a value of 0.005 µg/mL for the purposes of this graphical summary.~~

~~2.3.5.3. Preliminary Receptor Occupancy Data (ENGAGE-1, Part 1A and 2A)~~

~~Receptor occupancy (RO) was assessed for peripheral blood CD3+ T cells in Part1A and 2A. Preliminary data indicated that a high degree (≥80%) of receptor occupancy is achieved initially (≤ 1 day after dosing) even for the lowest dose of 0.003 mg/kg GSK3174998 (Figure 3). For doses of 0.1 mg/kg or smaller receptor occupancy subsequently declines towards the end of the dosing cycle. Starting with 0.3 m/kg GSK3174998 continuously high receptor occupancy levels are observed over the whole 21-day dosing cycle. Qualitatively similar receptor occupancy profiles were observed~~

~~when GSK3174998 was administered in combination with 200 mg pembrolizumab Q3W (Figure 3)~~

~~Figure 3 Median receptor occupancy profiles for varying doses of GSK3174998 alone or in combination with pembrolizumab~~



~~Notes:~~
~~1. Preliminary data from Study 201212.~~

~~2.3.5.4. Preliminary Clinical Activity Data (ENGAGE-1)~~

~~2.3.5.4.1. Clinical Activity - Part 1A~~

~~At the time of the clinical data cut-off (09 Jan2018), one confirmed PR was reported at week 24 in a subject with STS (0.3 mg/kg GSK3174998), who subsequently discontinued treatment for PD at week 30. A subject with NSCLC (0.3 mg/kg GSK3174998) was reported to have SD for 24 weeks, and discontinued treatment with PD after 39 weeks. An additional 5 subjects were reported to have SD at week 12, but subsequently discontinued treatment for PD prior the next imaging assessment.~~

~~2.3.5.4.2. Clinical Activity - Part 2A~~

~~At the time of the clinical cut-off (09 Jan 2018), clinical responses were reported for the combination of GSK3174998 and pembrolizumab. At the 0.01 mg/kg GSK3174998 + 200 mg pembrolizumab dose level, one subject demonstrated a CR (MSI-CRC) and one subject with SCCHN demonstrated SD at week 24, and continues on treatment at week 54. At the 0.1 mg/kg GSK3174998 + 200 mg pembrolizumab dose level, 3 subjects~~

~~demonstrated a PR (melanoma, bladder and MSI-CRC). At the 0.3 mg/kg GSK3174998 + 200 mg pembrolizumab dose level, 1 subject with NSCLC demonstrated a PR, while a second subject with NSCLC demonstrated SD at week 15 and remained on treatment as of week 27.~~

Section 3 Objectives and Endpoints

Rationale for Change

Given the modest clinical activity in the study, no time-to-event summaries and analyses (TTR, DOR, PFS, OS) will be performed for efficacy data. TTR and DOR will be calculated and considered as exploratory endpoints.

REVISED TEXT

Objectives	Endpoints
Part 1: GSK3174998 Monotherapy	
Primary	
• To evaluate the safety and tolerability and identify the MTD[a] or the MAD of GSK3174998 administered intravenously to subjects with selected advanced or recurrent solid tumors.	• AEs, SAEs, DLT, withdrawals due to AEs, dose reductions or delays, and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters).
Secondary	
• To evaluate the antitumor activity of GSK3174998 in subjects with selected advanced or recurrent solid tumors. • To characterize the PK of GSK3174998 monotherapy. • To determine the immunogenicity of GSK3174998.	• ORR and DCR (CR+ PR+ SD ≥12 weeks~~), TTR, DOR, PFS, and OS.~~)[b] • GSK3174998 concentrations in plasma and PK parameters including Cmax, AUC(0-τ), and Cmin. • Number and percentage of subjects who develop detectable ADA.
Exploratory	
• To explore the relationship between antitumor activity, PK parameters, pharmacodynamic activity and other patient characteristics. • <u>To explore onset and durability of response</u>	• Evaluation of antitumor activity (CR, PR, SD, PD), tumor kinetic parameters, PK parameters, pharmacodynamic activity, and other patient characteristics. • <u>TTR and DOR</u>

Objectives	Endpoints
Part 1: GSK3174998 Monotherapy	
• To evaluate the pharmacodynamic activity of GSK3174998 in the peripheral blood and to explore the utility of these measures to enrich for clinical efficacy and development of a diagnostic test.	• Assessment of lymphocyte OX40 receptor membrane expression and occupancy by GSK3174998. Measures of immune function in blood (e.g. phenotype, quantity, and activation state of T cells in the periphery, TCR diversity, expression of circulating soluble factors such as cytokines and stress-related proteins). Assessment of changes in genomic DNA, gene expression (RNA and protein), (e.g. using cfDNA, exosomes or circulating tumor cells [CTCs]), and mutational load.
~~**Part 1: GSK3174998 Monotherapy**~~	
Exploratory	

• To evaluate the pharmacodynamic activity of GSK3174998 in the tumor microenvironment and to explore the utility of these measures to enrich for clinical efficacy and development of a diagnostic test.
 	
• Pharmacogenetics (PGx): To evaluate the association of genetic variations in the host DNA and response to therapy or disease characterization.
	• Assessment of tumor biopsies via IHC for the numbers of tumor-infiltrating lymphocytes and other immune cells expressing key phenotypic markers. Changes in gene expression (RNA and protein), TCR diversity, or mutational load (genomic DNA).
	
	• Germline genetic evaluations may be conducted for:
	  • Medicine response, including GSK3174998 or any concomitant medicines.
	  • Disease susceptibility, severity, and progression and related conditions.

Hypothesis	
For the primary objective, no formal statistical hypothesis will be tested; analysis will be descriptive and exploratory	

c. In the final determination of the MTD, all available safety and tolerability data will be considered
d. Unless otherwise specified, all response endpoints will be assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and by irRECIST (immune-related RECIST); irRECIST will be used to determine treatment decisions.

RNA = Ribonucleic acid; DNA = Deoxyribonucleic acid

Objectives	Endpoints
PART 2: Combination GSK3174998 plus pembrolizumab	
Primary	
• To evaluate the safety and tolerability and identify the MTD[a] or the MAD of GSK3174998 administered intravenously in combination with IV pembrolizumab to subjects with selected advanced or recurrent solid tumors.	• AEs, SAEs, DLTs, withdrawals due to AEs, dose reductions or delays, and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters).
Secondary	
• To evaluate the antitumor activity of GSK3174998 in combination with pembrolizumab in subjects with selected advanced or recurrent solid tumors.	• ORR and DCR (CR+PR+SD ≥12 weeks~~),~~ ~~TTR, DOR, PFS, and OS.~~).[b]
• To characterize the PK of GSK3174998 and pembrolizumab when administered in combination.	• Plasma GSK3174998 and serum pembrolizumab concentrations and PK parameters including Cmax, AUC(0-τ), and Cmin.
• To determine the immunogenicity of GSK3174998 and pembrolizumab when administered in combination.	• Number and percentage of subjects who develop detectable ADA.
Exploratory	
• To explore the relationship between antitumor activity, PK parameters, pharmacodynamic activity and other patient characteristics.	• Evaluation of antitumor activity (CR, PR, SD, PD), tumor kinetic parameters, PK parameters, pharmacodynamic activity, and other patient characteristics.
• To explore onset and durability of response	• TTR and DOR
• To evaluate the pharmacodynamic activity of GSK3174998 in combination with pembrolizumab in the peripheral blood and to explore the utility of these measures to enrich for clinical efficacy and development of a diagnostic test.	• Assessment of lymphocyte OX40 receptor membrane expression and occupancy by GSK3174998. Measures of immune function in blood (e.g. phenotype, quantity, and activation state of T cells in the periphery, TCR diversity, expression of circulating soluble factors such as cytokines and stress related proteins). Assessment of changes in genomic DNA, gene expression (RNA and protein), (e.g. using cfDNA, exosomes or CTCs), and mutational load.

Objectives	Endpoints
PART 2: Combination GSK3174998 plus pembrolizumab	
~~**PART 2: Combination GSK3174998 plus pembrolizumab**~~	
Exploratory	
• To evaluate the pharmacodynamic activity of GSK3174998 in combination with pembrolizumab in the tumor microenvironment and to explore the utility of these measures to enrich for clinical efficacy and development of a diagnostic test.	• Assessment of tumor biopsies via IHC for the numbers of tumor-infiltrating lymphocytes and other immune cells expressing key phenotypic markers. Changes in gene expression (RNA and protein), TCR diversity, or mutational load (genomic DNA).
• PGx: To evaluate the association of genetic variations in the host DNA and response to therapy or disease characterization.	• Germline genetic evaluations may be conducted for: • Medicine response, including GSK3174998 and pembrolizumab or any concomitant medicines. • Disease susceptibility, severity, and progression and related conditions.
Hypothesis	
For the primary objective, no formal statistical hypothesis will be tested; analysis will be descriptive and exploratory	

d. In the final determination of the MTD, all available safety and tolerability data will be considered
e. Unless otherwise specified, all response endpoints will be assessed by RECIST v1.1 and by irRECIST; irRECIST will be used to determine treatment decisions.

RNA = Ribonucleic acid; DNA = Deoxyribonucleic acid

Section 4.1.5. Cohort Expansion (Fifth paragraph onwards)

Rationale for Change

Given the modest clinical activity observed in the study a decision was made not to initiate any new clinical investigations with the GSK3174998/pembrolizumab combination.

REVISED TEXT

A minimum of 10 subjects will be enrolled in each cohort. ~~The~~Until implementation of Amendment 4, the first futility analysis of each expansion cohort ~~will be conducted~~was planned to occur after approximately 10 subjects are enrolled for whom overall response data at approximately week 12 ~~is~~was available. ~~Enrollment will continue while evaluating~~

~~the tumor responses from the first 10 evaluable~~After implementation of Amendment 4, no further subjects were enroled in the study, and no futility analyses were performed.

~~Any expansion cohort passing futility criteria may be selected to expand up to a total~~Until implementation of ~~30 subjects per cohort. Interim analyses for futility will be conducted with decision rules for the 10th to 30th evaluable subjects (see Table 17 and Table 18). These decision rules provide a guideline only; actual decisions will depend upon the totality of the data. For example, a cohort may be expanded if at least 1 melanoma subject or 2 STS subjects of the initial 10 subjects enrolled in each cohort demonstrate a confirmed response (per cohort). Please refer to Section 9.3.2 for details of the futility analysis.~~

~~For~~ Amendment 4, for any of the expansion cohorts tested, if the observed clinical benefit ~~appears~~appeared to be associated with specific patient characteristics and/or biomarkers, a new cohort may ~~be~~have been opened for further investigation with subjects enriched with these specific patient characteristics and/or biomarkers. After implementation of Amendment 4, no further subjects were enroled in the study.

Expansion cohorts will require mandatory fresh pre- and on-treatment biopsies (see ~~Secition~~Section 7.6.2) and an additional disease assessment at Week 6. This disease assessment is timed to coincide with the on-treatment (Week 6) tumor biopsy. If feasible, the disease assessment should be performed after the tumor biopsy.

Section 4.2. Treatment Arms and Duration (Second Paragraph onwards)

Rationale for Change

Given the modest clinical activity observed in the study, no time-to-event summaries and analyses will be performed for efficacy data.

REVISED TEXT

The study includes a screening period, a treatment period, and a follow-up period. Subjects will be screened for eligibility beginning approximately 4 weeks before the start of treatment. The maximum duration of treatment with GSK3174998 and pembrolizumab will be 2 years (Table 6) or 35 cycles whichever comes first. The follow-up period for safety assessments will be a minimum of 3 months from the date of the last dose. The post-treatment follow-up period includes disease assessments every 12 weeks until documented PD. Following PD, subjects will be contacted every 3 months to assess survival status.

~~Subjects with confirmed PR or CR will be followed for response duration and may be eligible for additional treatment with GSK3174998 at the time of relapse/progression. The decision whether a subject will receive additional treatment will be discussed and agreed upon by the treating investigator and the Sponsor/Medical Monitor on a case-by-case basis.~~

With the implementation of Amendment 04, there will be no requirement to perform future disease assessments or survival follow-up.

Section 5.4.1. Treatment Discontinuation (Fourth Paragraph last point onward)

Rationale for Change

Given the modest clinical activity observed in the study, no time-to-event summaries and analyses will be performed for efficacy data.

REVISED TEXT

- Study closure/termination (with implementation of Protocol Amendment 4).

A subject with a CR requires confirmation of response via imaging at least 4 weeks after the first imaging showed a CR. Early discontinuation of GSK3174998 and/or pembrolizumab may be considered for subjects who have attained a confirmed complete response per RECIST 1.1 that have been treated for at least 6 months and had at least two treatments beyond the date when the initial CR was declared.

Once a subject has permanently discontinued from study treatment, the subject will not be allowed to be re-treated~~, except as described in Section 5.4.2.1 and in the following scenario. Re-treatment of subjects who progress after a best overall response of PR or CR may be considered on a case-by-case basis for up to 1 year after discussion between the treating investigator and the Sponsor/Medical Monitor if:~~

- ~~No cancer treatment was administered since the last dose of GSK3174998 ± pembrolizumab~~
- ~~The subject meets the safety parameters listed in the Inclusion/Exclusion criteria~~
- ~~The trial is open.~~

~~Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Response or progression in this Second Course Phase will not count towards the primary efficacy endpoint in this trial.~~

~~All subjects who permanently discontinue study treatment will be followed for a minimum of 6 months from the date of the last dose.~~ The follow-up period for safety assessments will be a minimum of 3 months from the date of the last dose. The post treatment follow-up period includes disease assessments every 12 weeks until documented PD. Following PD, subjects will be contacted every 3 months to assess survival status.

With the implementation of Amendment 04, there will be no requirement to perform future disease assessments or survival follow-up. If the subject voluntarily discontinues from treatment due to toxicity, 'AE' will be recorded as the primary reason for permanent discontinuation on the eCRF.

All subjects who discontinue from study treatment will undergo safety assessments at the time of discontinuation and during post-study treatment follow-up as specified in the Time and Events Table (see Section 7.1, Table 13 and Table 14).

Section 5.5 Subject and Study Completion

Rationale for Change

Given the modest clinical activity observed in the study, no time-to-event summaries and analyses will be performed for efficacy data.

REVISED TEXT

~~Since~~ Upon Protocol Amendment 4 implementation, ongoing subjects will be considered withdrawn due to study closure and will be followed for ~~survival in this study, only~~up to 3 months after the last dose. Only when a subject dies is he/she considered to have completed the study; consequently "death" is not listed as a reason for withdrawal from the study. Furthermore, disease progression, discontinuation of study treatment, and AEs, are not by themselves reasons for withdrawal from the study~~ as follow-up for OS is desired.~~. If a subject dies a copy of the death certificate should be available for review, if possible, and the cause of death should be evaluated and documented.

Section 6.9. Treatment after the End of the Study

Rationale for Change

Given the modest clinical activity observed in the study, no time-to-event summaries and analyses will be performed for efficacy data.

REVISED TEXT

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

Refer to Section 5.4 and Section 7.1 for follow-up assessments ~~of subjects who are to be followed for disease progression and/or survival after they permanently discontinue from study treatment.~~

Section 7.1. Time and Events Table

(Table 13 Time and Events Table – Monotherapy and Combination Therapy

Footnote e, f, h)

Rationale for Change

Given the modest clinical activity observed in the study, no time-to-event summaries and analyses will be performed for efficacy data.

REVISED TEXT

e. If study treatment has been permanently discontinued in the absence of PD, the subject will return for disease assessments every 12 weeks until PD is documented (by irRECIST), another anticancer treatment is initiated, or death, whichever occurs first. These visits are described as Disease Free Survival Follow-up (DFS FU) visits. Upon implementation of Protocol Amendment 4, no future disease assessments are required.

f. The Survival FU visit should be completed every 12 weeks after documented disease progression (or after initiation of another anticancer treatment). Subjects should be contacted every 12 weeks (±2 weeks) until death occurs. Upon implementation of Protocol Amendment 4, no future survival follow-up is required.

h. Screening tumor imaging must be obtained within 28 days of the first dose. Tumor imaging will be performed every 12 weeks (±1 week) until disease progression has been confirmed by irRECIST; Subjects whose disease progresses must have a confirmatory scan performed at least 4 weeks after the date of assessment during which the first indication of PD was demonstrated. Immune-related RECIST will be used to determine treatment decisions for PD and the primary endpoint analysis will use irRECIST. If a subject has achieved a CR or PR in the previous radiologic assessment, a repeat scan should be performed as a part of the confirmation of response, within at least 4 weeks to confirm the response. At the TDV, tumor imaging is only required if the last disease assessment did not show PD and was performed ≥6 weeks before TDV. During the DFS FU visits (performed when a subject has permanently discontinued study treatment before disease progression has been documented), tumor imaging will be obtained every 12 weeks (±1 week) until PD, initiation of a new anticancer treatment, or death, whichever comes first. Pre-baseline scans (within 24 weeks before the baseline scan) may be collected to assess tumor growth rate in selected subjects to support exploratory investigation of tumor growth kinetics. Upon implementation of Protocol Amendment 4, no future disease assessments are required.

Section 7.3.1. Evaluation of Anticancer Activity (Fifth bullet point)

Rationale for Change

Given the modest clinical activity observed in the study, no time-to-event summaries and analyses will be performed for efficacy data.

REVISED TEXT

- For post-baseline assessments, a window of ±7 days is permitted to allow for flexible scheduling. If the last radiographic assessment was more than 12 weeks prior to the subject's withdrawal from study and PD has not been documented, a disease assessment should be obtained at the time of withdrawal from the study. Upon implementation of Protocol Amendment 4, no future disease assessments are required.

Section 9.3.2. Interim Analysis

Rationale for Change

Given the modest clinical activity observed in the study, no time-to-event summaries and analyses will be performed for efficacy data.

REVISED TEXT

No formal interim analyses will be performed using the data generated from dose escalation cohorts. Preliminary safety and available PK/PD data will be performed and reviewed by study team (to include at minimum, the GSK medical monitor and investigator) after completion of each dose cohort. This review will support the decision on the dose level in the next dose cohort. Dose escalation decisions making will be based on the rules as described in Section 4.1.1 and Section 9.3. The Steering Committee will guide the transition of the study from dose escalation to cohort expansion for both monotherapy and combination therapies

For dose expansion cohorts, continuous assessment of efficacy and safety ~~will~~was planned to be performed after first interim analysis based upon a minimum of 10 subjects in at least one of the disease-specific cohorts with available unconfirmed overall response data for at least 12 weeks. However, after implementation of Amendment 4, no further subjects were enroled in the study; therefore, no futility analyses were performed. ~~of the disease-specific cohort with available unconfirmed overall response data.~~

~~Futility~~ Planned futility interim analysis decision rules for the 10th to 30th evaluable subjects are presented in Table 17 and Table 18, which specify the number of subjects with an unconfirmed response required for continuing enrolment when total sample size is up to 30. Additional futility looks may ~~be~~have been performed, if necessary. These rules ~~are~~were intended as a guideline only. If applicable, appropriated data from dose escalation may ~~be~~have been integrated into dose expansion decisions.

Section 9.4.2.1 Anticancer Activity Analyses

Rationale for Change

Given the modest clinical activity observed in the study, no time-to-event summaries and analyses (TTR, DOR, PFS, OS) will be performed for efficacy data. TTR and DOR will be calculated and considered as exploratory endpoints.

REVISED TEXT

The All Treated Population will be used for anticancer activity analyses. Since this is a Phase I study, anticancer activity will be evaluated based on clinical evidence and response criteria. If data warrant, the response data will be summarized by dose level. irRECIST is the primary measure of clinical activity for response endpoints~~and PFS~~; RECIST v1.1 guidelines are used for disease measurements.

If the data warrant, ORR, DCR, TTR, ~~DOR, PFS~~ and ~~OS~~DOR will be calculated and listed for each subject.

ORR is defined as the percentage of subjects with a best overall confirmed CR or PR at any time as per disease-specific criteria (refer to Appendix 5). DCR is defined as the percentage of subjects with a confirmed CR + PR at any time, plus SD ≥12 weeks.

DOR will be ~~summarized~~ calculated and listed for subjects with a confirmed CR or PR and is defined as the first documented evidence of CR or PR until disease progression or death due to any cause among subjects 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. DOR and TTR are considered as exploratory endpoints. No summary tables for DOR and TTR will be provided.

~~PFS is defined as time from the date of first dose to the date of disease progression according to clinical or radiological assessment or death due to any cause, whichever occurs earliest. For the analysis of PFS, if the subject received subsequent anti-cancer~~

~~therapy prior to the date of documented events, PFS will be censored at the last adequate assessment (e.g. assessment where visit level response is CR, PR or SD) prior to the initiation of therapy. Otherwise, if the subject does not have a documented date of event, PFS will be censored at the date of the last adequate assessment.~~

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

Further details ~~on rules of censoring~~ will be provided in the RAP. ~~PFS and OS will be summarized using the Kaplan-Meier method if the data warrant.~~

Section 9.4.2.2.1. Pharmacokinetic Parameters

Rationale for Change

Update to PK analyses to be conducted.

REVISED TEXT

PK analysis of GSK3174998 and pembrolizumab will be the responsibility of the Clinical Pharmacology Modeling and Simulation (CPMS) Department, GSK or Merck Sharp and Dohme Corp.

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

- Cmax
- time to Cmax (tmax)
- Cmin
- area under the plasma concentration-time curve ~~(AUC(0-t)~~, AUC(0-τ) (repeat dosing~~) and/or AUC(0-∞) (single dose)~~
- ~~apparent terminal phase elimination rate constant (λz) (single dose)~~
- apparent terminal phase half-life (t½) (single dose)
- systemic clearance of parent drug (CL)
- <u>steady-state volume of distribution (Vss)</u>

Section 12.7 Apeendix 7 Genetic Research (12.7.2. Study Assessments and Procedures)

Rationale for Change

Clarification on length of time for sample storage.

REVISED TEXT

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or ~~GSK may destroy~~ the ~~samples sooner~~study closure/termination. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.