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Protocol Title: A Phase I/II, Open-Label Study to Investigate the Safety, Clinical Activity, Pharmacokinetics, and Pharmacodynamics of GSK3145095 Administered Alone and in Combination with Anticancer Agents Including Pembrolizumab in Adult Participants with Selected Advanced Solid Tumors

Protocol Number: 205013 / Amendment 01

Study Phase: I/II

Short Title: First-time-in-human study of GSK3145095 alone and in combination with other anticancer agents in adults with advanced solid tumors

Compound Number: GSK3145095

Sponsor Name and Legal Registered Address:

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Medical Monitor Name and Contact Information [will be provided separately OR can be found in the Study Reference Manual]

Regulatory Agency Identifying Number(s): IND138899

Approval Date: 25-OCT-2018

2019N419040_00

SPONSOR SIGNATORY:

PPD

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Oct 25, 2018
Date

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY List dates of original protocol and all amendments in reverse chronological order.		
Document	**Date**	**DNG Number**
Amendment 1	25-OCT-2018	2017N343207_03
Original Protocol (republished)	06Aug2018	2017N343207_02
Original Protocol (republished)	28Jun2018	2017N343207_01
Original Protocol	22Jun2018	2017N343207_00

Amendment 1: 25-OCT-2018

Overall Rationale for the Amendment: Protocol Amendment 1 is an administrative amendment only which includes the summary of changes information, as well as a change in the title of the protocol (i.e. "Amendment 01"). The changes listed below were previously made in the 06Aug18 republished version of the original protocol in response to FDA feedback from the initial FDA IND Application 138899 (original republished protocol dated 28Jun2018) submitted on 2 July 2018.

Section # and Name	Description of Change	Brief Rationale
Synopsis (table)	Added dose proportionality/time invariance to Parts 1/2 secondary endpoints Added exploratory PK endpoint (relationship between GSK3145095 exposure and safety/QTcF parameters)	FDA requested changes from IND submission
1. Synopsis Treatment Groups/Duration	Change to starting dose (100mg) and change in dose levels (100, 200, 400, 800, and 1600 mg per day)	FDA requested changes (modification of starting dose and dose intervals) from IND submission
2. Schedule of Activities	Addition of Genetics (PGx) sample to Mono and Combo tables	Item inadvertently omitted from previous protocol version
3.2.1. GSK3145095	Change starting dose from 50mg to 100mg and corresponding increase in level of Rip1 inhibition	FDA requested change (modification of starting dose)
3.3.1.1. GSK3145095 risk assessment	Hepatox in vivo data inadvertently placed in wrong section (cardiac); moved to correct section (hepatotox)	Administrative change
3.3.2 benefit assessment	Change starting dose from 50mg to 100mg and corresponding increase in level of Rip1 inhibition	FDA requested change (modification of starting dose)
4. Objectives and Endpoints	Added dose proportionality/time invariance to Parts 1/2 secondary endpoints Added exploratory PK endpoint (relationship between GSK3145095 exposure and safety/QTcF parameters)	FDA requested changes from IND submission
5.1.1.1. Monotherapy Dose Escalation	revision of dosing language, DLT, and statistical language, and grammatical corrections	FDA requested changes from IND submission
5.1.1.3 Dose Limiting Toxicity	Change CTCAE version to 5.0	GSK administrative change
Table 1 (DLT)	Add tox language to definitions (<80% doses)	FDA requested changes from IND submission
5.1.1.4 Max Dose Increment	Change to language regarding dose levels/increments	FDA requested changes from IND submission

Section # and Name	Description of Change	Brief Rationale
5.1.1.5 Planned Dose Levels	Change to language regarding dose levels/increments	FDA requested changes from IND submission
5.1.1.7 Alternative Dosing Schedules for GSK3145095	Clarification of wording in section	GSK administrative change
5.7 Justification for Starting Dose	Change to language regarding starting dose and pharmacology	FDA requested changes from IND submission
6.1 Inclusion Criteria #3	Revision of eligibility criteria to include only patients who have received prior therapy (not include those who have refused prior)	FDA requested changes from IND submission
7.2 Toxicity Management Guidelines	Section 7.2 has been edited to clarify that guidelines in Section 7.2.1 are intended for management of immune-related adverse events associated with pembrolizumab use; revised reference to CTCAE 5.0	FDA requested changes from IND submission
7.2.1 General Guidelines for Immune-Related Adverse Events (irAEs)	Clarify language that an irAE is defined as a clinically significant AE of any organ that is associated with pembrolizumab exposure	FDA requested changes from IND submission
7.2.1.1 Overview of Management of irAEs	Clarify language that patients who experience a life-threatening adverse event should discontinue study treatment.	FDA requested changes from IND submission
7.2.1.2 General Principles of Immune-Related Adverse Events Identification and Evaluation	Clarify that AESIs are subset of irAEs	GSK administrative change
Table 4 Dose Mod/Tox Mgmt Guidelines irAEs	Change to CTCAE v.05	FDA requested change from IND submission
7.2.2. General Guidelines	Addition of language (last paragraph) to provide guidance on permanent discontinuation of subjects and life-threatening AEs	FDA requested changes from IND submission, and GSK administrative changes

Section # and Name	Description of Change	Brief Rationale
Table 5 Dose Mod/Tox Mgmt Guidelines	Revision to criteria (Grades 2-4), including clarify that patients with Grade 2 toxicities lasting > 7 days should interrupt study treatment	FDA requested changes from IND submission
7.7.2 Prohibited Medications	Addition of drugs that are strong inducers of CYP3A4, removal of multivitamins	FDA requested changes from IND submission, GSK administrative changes
8.1 Discontinuation of Study Treatment	Addition of 12-week language, clarification of language	FDA requested changes from IND submission, GSK administrative changes
9.9 Immunogenicity assessments	Clarification of wording that samples may be collected	GSK administrative change
10.4.1	Revision to NCRM language, dose levels, scenarios/simulations	GSK administrative changes
10.6.2.2 Adverse Events	Change to CTCAE v.05	FDA requested changes from IND submission
10.6.2.3 Clinical Lab Evaluations	Change to CTCAE v.05	FDA requested changes from IND submission
10.6.3.2 PK/PD Analyses	Language added regarding additional exploratory endpoint	FDA requested changes from IND submission
12.2.3 Dose Escalation Committee	Revision of wording regarding collection of data from minimum 3 subjects	GSK administrative change
12.4 Appendix 4: Adverse Events	Change to CTCAE v.05	FDA requested changes from IND submission

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1. SYNOPSIS

Protocol Title: A Phase I/II, Open-Label Study to Investigate the Safety, Clinical Activity, Pharmacokinetics, and Pharmacodynamics of GSK3145095 Administered Alone and in Combination with Anticancer Agents Including Pembrolizumab in Adult Participants with Selected Advanced Solid Tumors

Short Title: First-time-in-human study of GSK3145095 alone and in combination with other anticancer agents in adults with advanced solid tumors

Rationale:

Pancreatic ductal adenocarcinoma (PDAC) is the 4th leading cause of cancer deaths worldwide with a 5-year survival rate of less than 5%. A major therapeutic barrier for PDAC is the highly immunosuppressive myeloid infiltrate that is a hallmark of the pancreatic tumor microenvironment (TME). This immunosuppressive innate infiltrate is largely responsible for PDAC resistance to current immunotherapies that target the adaptive immune system. To overcome this barrier, the next generation of immunotherapies for pancreatic cancer and other tumors with a similar cellular phenotype will need to modulate the innate infiltrate to increase sensitivity to T cell checkpoint inhibitors.

Nonclinical evidence suggests that there is therapeutic potential for inhibition of receptor interacting protein 1 (RIP1), encoded by the RIPK1 gene, across multiple therapeutic areas, including oncology. RIP1 kinase activity in pancreatic oncogenesis reveals that within the pancreatic TME, RIP1 inhibition leads to the replacement of tumor-permissive myeloid infiltrates with innate cells that promote an effective anti-tumor response by the adaptive immune system (Seifert, 2016). Furthermore, in an unbiased screen, RIPK1 was identified as a top gene contributing to resistance to immunotherapy (Manguso, 2017). These data suggest that the small molecule RIP1 inhibitor GSK3145095 may have therapeutic potential in multiple tumor types.

Study 205013 is a Phase 1 first-time-in-human (FTIH) study of GSK3145095 alone and in combination with other anticancer agents including pembrolizumab in participants with PDAC and other selected tumors, e.g. non-small cell lung cancer (NSCLC), triple-negative breast cancer, or melanoma. These tumor types were chosen based on preclinical evidence supporting a role for RIP1 kinase activity promoting oncogenesis and/or their phenotypic similarity to PDAC characterized by high infiltrates of immunosuppressive innate infiltrates (Seifert, 2016; Manguso, 2017; Santoni, 2018; Liu, 2015; Lievense, 2013; Hartwig, 2017). The study includes up to 4 parts: Parts 1 and 2 will be conducted as dose escalation as monotherapy and in combination with pembrolizumab), Part 3 will explore dose expansion with pembrolizumab, and Part 4 will explore dose expansion of GSK3145095 in combination with other anticancer therapies.

Objectives and Endpoints:

In the following tables, primary and secondary objectives are presented separately for Dose Escalation (Parts 1 and 2) and Dose Expansion (Parts 3 and 4), while exploratory objectives are presented together for all parts.

Parts 1 & 2: Dose Escalation		
	Objectives	**Endpoints**
Primary	To evaluate the safety and tolerability and identify the maximum tolerated dose (MTD) or the maximum administered dose (MAD) of GSK3145095 administered orally alone and in combination with other agents such as pembrolizumab to participants with selected advanced or recurrent solid tumors.	Frequency and severity of adverse events including frequency of dose-limiting toxicities (DLTs).
Secondary	To evaluate the antitumor activity of GSK3145095 alone and in combination with other agents such as pembrolizumab in participants with selected advanced or recurrent solid tumors.	Best overall response based on RECIST 1.1 criteria
	To characterize the pharmacokinetics (PK) of GSK3145095 alone and in combination with other agents such as pembrolizumab in participants with selected advanced or recurrent solid tumors.	Derived PK parameters for GSK3145095 including area under the plasma drug concentration versus time curve ($AUC_{(0-t)}$, $AUC_{(0-\tau)}$), maximum observed plasma drug concentration (C_{max}), minimum observed plasma drug concentration (C_{min}), time to maximum observed plasma drug concentration (t_{max}), clearance (CL/F), volume of distribution (V/F) and terminal half-life ($t_{1/2}$) following single and repeat doses, and evaluation of dose proportionality, accumulation ratio and time invariance where data allow
	To characterize the pharmacokinetics (PK) of pembrolizumab when administered in combination with GSK3145095.	Serum pembrolizumab concentrations and PK parameters including C_{max}, $AUC_{(0-\tau)}$, and C_{min}.

Parts 3 & 4: Dose Expansion		
	Objectives	**Endpoints**
Primary	To evaluate the antitumor activity of GSK3145095 in combination with other agents such as pembrolizumab in participants with selected advanced or recurrent solid tumors.	Overall Response Rate (ORR; % of participants achieving CR or PR) based on RECIST 1.1 criteria.
Secondary	To further evaluate the safety and tolerability of GSK3145095 administered orally in combination with other agents such as pembrolizumab to participants with selected advanced or recurrent solid tumors.	Frequency and severity of adverse events.
	To further evaluate the antitumor activity of GSK3145095 in combination with other agents such as pembrolizumab in participants with selected advanced or recurrent solid tumors.	Progression-Free Survival and Overall Survival.
	To characterize the PK of GSK3145095 in combination with other agents such as pembrolizumab in participants with selected advanced or recurrent solid tumors.	Derived PK parameters for GSK3145095 and combination agent including $AUC_{(0-t)}$, $AUC_{(0-\tau)}$, C_{max}, t_{max}, and $t_{1/2}$ following single and repeat doses, and evaluation of dose proportionality, accumulation ratio and time invariance where data allow

Parts 1, 2, 3, & 4: Exploratory Objectives	
Objectives	**Endpoints**
To explore the inter-relationship between antitumor activity, PK parameters, pharmacodynamic activity, and other participant characteristics	Assessment of antitumor activity (CR, PR, SD, progressive disease [PD]), tumor kinetic/PK parameters, pharmacodynamic activity, and other participant characteristics
To evaluate the pharmacokinetic and pharmacodynamic activity of GSK3145095 in the periphery and the tumor microenvironment	Assessment of GSK3145095 tumor penetration, RIP1 target engagement, activation, and pathway inhibition may be explored.
To evaluate the relationship between GSK3145095 and safety parameters, including QTcF following single and repeated administration.	Relationship between GSK3145095 exposure (e.g. concentration, Cmax, AUC) and safety parameters including change from baseline QTcF.
To explore the effect of RIP1 inhibition on the tumor microenvironment and the immune response within the tumor and periphery	May include assessment of: • Tumor biopsies via immunohistochemistry (IHC) • Changes in gene expression (ribonucleic acid [RNA] and protein), T cell receptor [TCR] diversity, tumor microenvironment or mutational load (genomic deoxyribonucleic acid [DNA]) • Measures of immune function in peripheral blood mononuclear cells (PBMCs) • Expression of circulating soluble factors
To investigate the mechanism of action and indicators of sensitivity and resistance to GSK3145095 alone or in combination with other agents such as pembrolizumab	Assessment of DNA, RNA, and/or protein markers in tumor or periphery and their association with anti-tumor activity for potential use in the development of a predictive biomarker and/or diagnostic test
To characterize the metabolite profile of GSK3145095 after single or repeated oral dosing in some participants	Identification and quantitative estimates of parent GSK3145095 and metabolites in plasma and/or urine following single or repeat doses
To assess potential effect of repeat doses of GSK3145095 on Cytochrome P450 3A4 (CYP3A4) enzyme activity in some participants	Plasma 4βhydroxycholesterol to cholesterol ratio pretreatment and following repeat dosing of GSK3145095
To evaluate disease and treatment related symptoms and impact on function and health-related quality-of-life (Parts 3 & 4 only)	Qualitative telephone interview(s)
To investigate the relationship between genetic variants in candidate genes, PK, and safety profile of GSK3145095 alone or in combination with other agents such as pembrolizumab	Pharmacogenomic (PGx) study using blood samples

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 GSK3145095 orally administered twice daily (BID) to participants with selected advanced or recurrent solid tumors.

The study will utilize a staged approach consisting of at least four parts. In Part 1, GSK3145095 monotherapy will be assessed in escalating doses in participants with advanced or metastatic pancreatic cancer. Part 2 will assess escalating doses of GSK3145095 in combination with a fixed dose of pembrolizumab in participants with selected solid tumors that may include PDAC, NSCLC, triple-negative breast cancer, and/or melanoma. Initiation of Part 2 will occur after emerging data from Part 1 demonstrate the safety of GSK3145095 monotherapy. Part 2 will begin with a GSK3145095 dose below the highest Part 1 dose shown to have an acceptable toxicity profile in at least 3 participants. Part 3 may evaluate the combination of one or more doses of GSK3145095 and pembrolizumab in disease-specific expansion cohorts via protocol amendment. All available safety, pharmacodynamic, PK, and efficacy data will be used to select 1 or more doses of GSK3145095 to evaluate in Part 3. The population of participants selected for Part 3 will also be determined by data emerging from Part 2. The protocol may be amended to include investigation of additional anticancer agent combinations with GSK3145095 in Part 4.

All participants in Parts 1 and 2 must be willing to undergo mandatory fresh biopsy collection at baseline, on treatment, and if feasible at the time of disease progression.

Exploration of lower dose levels (or expansion of a previously tested dose level) will be allowed if agreed upon by the Medical Monitor and treating investigators. The Neuenschwander Continual Reassessment Method (NCRM) (Neuenschwander, 2008) will be used to guide dose escalation for monotherapy and the modified Toxicity Probability Interval (mTPI) procedure (Ji, 2013) will be used for combination therapy. The final dose escalation decision will be made by the study team based 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 in the study files.

Criteria that may be considered in the determination of which dose level(s) to expand and which tumor types to enroll in Parts 3 and 4 may include target engagement and pharmacodynamic activity, tolerability, and clinical activity, including stable disease of at least 12 weeks.

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

Number of Participants:

The study will enroll up to approximately 220 participants (Parts 1 and 2 [approximately 30 participants each], Parts 3 and 4 [approximately 80 each]) with tumor types that may include PDAC, NSCLC, triple-negative breast cancer, and/or melanoma.

Treatment Groups and Duration:

The study includes a screening period, a treatment period, and a follow-up period. Participants will be screened for eligibility beginning approximately 21 days before the start of treatment. The maximum duration of treatment with GSK3145095 alone and GSK3145095 plus pembrolizumab will be 2 years. The follow-up period for safety assessments will be a minimum of 3 months from the date of the last dose of any study drug. The post-treatment follow-up period includes disease assessments every 12 weeks until documented PD, initiation of another anticancer therapy, or death. Following PD or initiation of another anticancer therapy, participants will be contacted every 12 weeks to assess survival status until death occurs.

Participants with confirmed PR or CR will be followed for response duration and may be eligible for additional treatment with GSK3145095 at the time of relapse/progression. The decision whether a participant will receive additional treatment will be discussed and agreed upon by the treating investigator and the Sponsor/Medical Monitor on a case-by-case basis.

In Part 1, dose escalation for GSK3145095 monotherapy will begin with a total daily dose of 100 mg GSK3145095 administered by mouth in two equally divided doses (50 mg po BID). Planned dose levels are 100, 200, 400, 800, and 1600 mg per day but intermediate doses or schedules other than BID may be explored if exposure differs significantly from that predicted, if there is excessive toxicity, or if further evaluation of pharmacodynamic markers to aid dose selection is warranted. Dose escalation of GSK3145095 in combination with 200 mg pembrolizumab (Part 2) will begin with a GSK3145095 dose below the highest Part 1 dose shown to have acceptable toxicity profile in at least 3 participants.

Analyses:

No formal statistical hypothesis will be tested in the dose escalation phase.

For the combination therapy, in the dose expansion phase, the anti-tumor activity of combination therapy will be tested using the predictive probability design of Lee and Liu (Lee 2008). The response rates to be tested for null and alternative hypotheses for the secondary endpoint of overall response rate (ORR) will be specified prior to initiation of the expansion phase. These rates will depend on the target tumor type and the choice of anti-cancer agent.

2. SCHEDULE OF ACTIVITIES (SOA)

Monotherapy Schedule														
Visit Week		**1**		**2**	**3**		**4**	**5**	**6**	**7+**		**Follow Up**		
Visit Day	**SCR**	**1**	**2**	**8**	**15**	**16**	**22**	**29**	**36**	**43+**	**EOT**	**Response**	**Survival**	**Notes**
Office Visit	X	X[1]	X[1]	X	X	X	X	X	X	X[2]	X	X		Visit Types/Windows - see Section 9.1 [1] On Week 1, Day 3, sites will call participants to assess AEs. [2] After the first 6 weeks, office visits to occur every 3 weeks
Inclusion/ Exclusion	X	X												I/E checked prior to first dose on Day 1 See Section 6.1 and Section 6.2 re: I/E criteria
Screening	X													Participant Registration, IC, Demographics, MHx, Prior Medications Refer to the Study Reference Manual (SRM)
Anti-Cancer Treatment	X											X	X	Any anti-cancer treatments administered prior to signing consent and/or during study follow-up periods will be collected.
Administer GSK3145095		See notes												Day 1 – single morning dose only; Day 2 – begin BID schedule. See Section 7.1 for treatment schedule. Dosing may be delayed due to toxicity (Section 7.2). See Section 8 for treatment discontinuation criteria. GSK3145095 will be dosed for a maximum of 2 years.
Con Meds		See notes												Concomitant medications to be collected at all office visits (Day 1 through Response Follow Up). See Section 9.1 and Section 9.3 for more details.

Monotherapy Schedule														
Visit Week		**1**		**2**	**3**		**4**	**5**	**6**	**7+**		**Follow Up**		
Visit Day	**SCR**	**1**	**2**	**8**	**15**	**16**	**22**	**29**	**36**	**43+**	**EOT**	**Response**	**Survival**	**Notes**
AE/SAE Assessment	See notes													On Week 1, Day 3, sites will call participants to assess AEs. All other AE assessments will be done at office visits (weekly for the first 6 weeks and then q3wks). AEs: Dose 1 – EOT. SAEs: Consent - 90d post last dose AESIs: Dose 1 – 90d post last dose. See Section 9.1 and Section 9.3 for more details.
PS, PE, VS, Weight	X	X		X	X		X	X	X	X	X			Weekly for first 6 wks, then every 3 wks and at EOT visit; see Section 9.5.1 and Section 9.5.2 for more details.
12-lead ECG	X	X	X	X	X	X	X		X	X	X	X		Days 1,2,8,15,16,22, and 36: triplicate 12-lead ECGs to coincide with PK timepoints. Other days: single 12-lead ECGs. PK samples will be collected directly after ECG, not during the recordings.
HIV, HCV, HBVAb, UA	X													

Monotherapy Schedule													
Visit Week		**1**		**2**	**3**		**4**	**5**	**6**	**7+**		**Follow Up**		
Visit Day	**SCR**	**1**	**2**	**8**	**15**	**16**	**22**	**29**	**36**	**43+**	**EOT**	**Response**	**Survival**	**Notes**
Pregnancy Test	X	X					X			X	X			Women of child bearing potential only. Serum test is required at screening & EOT visits. Urine pregnancy test is adequate at other visits. Day 1 test should be done within 24 hours before the first dose of any study drug. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. After starting study treatment, participants will undergo urine pregnancy testing every 3 weeks and whenever a menstrual cycle is missed or when pregnancy is otherwise suspected. If the participant hasn't been on an acceptable method of contraception for at least 2 weeks prior to start of therapy, pregnancy testing must be done weekly for the first month of treatment.
CBC, Chemistry, LFT	X	X		X	X		X	X	X	X	X			Weekly for the first 6 weeks, then q3wks, and at the EOT visit. See Table 9 for more details regarding Clinical Safety Laboratory Assessments.
TFT	X								X	X				At screening, q6wk and as clinically indicated. See Table 9 for more details regarding Clinical Safety Laboratory Assessments.

Monotherapy Schedule													
Visit Week		**1**		**2**	**3**		**4**	**5**	**6**	**7+**		**Follow Up**		
Visit Day	**SCR**	**1**	**2**	**8**	**15**	**16**	**22**	**29**	**36**	**43+**	**EOT**	**Response**	**Survival**	**Notes**
Disease Assessment/Imaging	X									X	X	X		Screening: within 28 days before the first dose Treatment: every 6 weeks for the first 24 weeks, then every 12 weeks until disease progression confirmed by iRECIST (see Section 9.2.4 and Section 12.9.2) ; disease assessment (Section 9.2) must be performed after biopsy (See Section 9.1.2 for visit windows); EOT: required if the last disease assessment did not show progressive disease & was performed ≥6 weeks before EOT. Follow-up: every 12 weeks in the absence of progression or starting another anticancer therapy.
Fresh tumor tissue	X[1]								X[1]	X[2]	X[3]	X[3]		[1] Two fresh tumor biopsy samples are required in Part 1, the first during screening and the second after 5 weeks of study treatment. Please refer to Section 9.7.2. [2] With participant consent & agreement by the PI & GSK Medical Monitor, additional optional fresh biopsies may be obtained during the study. See Section 9.7.2. [3] Optional fresh tumor biopsy should be attempted at disease progression (EOT or during follow-up). PK & PD blood samples should be obtained within approximately 1h of tumor biopsy.

Monotherapy Schedule													
Visit Week		**1**		**2**	**3**		**4**	**5**	**6**	**7+**		**Follow Up**		
Visit Day	**SCR**	**1**	**2**	**8**	**15**	**16**	**22**	**29**	**36**	**43+**	**EOT**	**Response**	**Survival**	**Notes**
Blood PD		X[1]					X[2]		X[2,3]	X[4,5,6]	X	X[7]		[1] Pre-dose, 1.5h, and 8h after dosing [2] Pre-dose [3] After 5 weeks of study treatment, on the day of the fresh tumor biopsy collection. If no on-treatment biopsy, the blood PD sample must still be taken. [4] Obtain sample on day of first tumor imaging, before administration of any IV contrast [5] If participant consents to additional biopsies, the blood PD sample must be taken at the time of collection of the additional biopsy. [6] With participant consent & agreement by the PI & GSK Medical Monitor, additional optional blood samples may be obtained during the study. See Section 9.7.1. [7] If a tumor biopsy is taken at the time of disease progression at EOT or during follow-up, then a PD blood sample must be taken within approximately 1h of tumor biopsy.

Monotherapy Schedule													
Visit Week		**1**		**2**	**3**		**4**	**5**	**6**	**7+**		**Follow Up**		
Visit Day	**SCR**	**1**	**2**	**8**	**15**	**16**	**22**	**29**	**36**	**43+**	**EOT**	**Response**	**Survival**	**Notes**
Plasma PK		X[1]	X[1]	X[2]	X[3]	X[3]	X[2]		X[2]		X[4]	X[4]		[1] Day 1 (single dose PK): Pre-dose (within 1h prior to dosing) & 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h, and 24h (before Day 2 morning dose). The 10-hour collection is optional [2] Pre-dose and 1.5h post dose (morning dose only). [3] Day 15: Pre-dose & 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h (before evening dose), & 24h (before Day 16 morning dose). The 10-hour collection is optional. If possible after the Day 15 evening dose: 0.5h, 1h, 2h, 3h, 6h, & 8h (in addition to the pre-dose sample on Day 16). [4] If a tumor biopsy is taken at the time of disease progression at EOT or during followup, then a PK blood sample should be taken within approximately 1h of tumor biopsy. The number and sampling times may be adjusted based on the emerging PK data available. Refer to SRM for additional details.
4β-HC/Cholesterol Plasma		X			X				X					Part 1 only, all dose levels. Day 1 predose, Day 15 predose and Day 36 predose
Metabolite Plasma		X	X		X	X								Part 1 only, all dose levels. Day 1 to coincide with all PK timepoints. Day 2 predose, Day 15 to coincide with all PK timepoints, Day 16 predose. See SRM for additional details.

Monotherapy Schedule														
Visit Week		**1**		**2**	**3**		**4**	**5**	**6**	**7+**		**Follow Up**		
Visit Day	**SCR**	**1**	**2**	**8**	**15**	**16**	**22**	**29**	**36**	**43+**	**EOT**	**Response**	**Survival**	**Notes**
Urine Metabolite		X			X									Part 1 only, all dose levels. To be taken pre-dose, 0-24h on Day 1 and 0-24h on Day 15. The 024h urine volume will be measured, and 200 mL will be aliquoted for metabolite identification purposes.
Genetics (PGx) sample		X												See Appendix 7 for more details
Follow-up telephone call													X	Survival status: See Section 9.1 for more details regarding follow-up visit types. Participants should be contacted every 12±2 weeks after documented disease progression (or after initiation of another anticancer treatment) until death.

Abbreviations: AE=adverse event; AESI=AE of special interest; BID=twice daily; CBC=complete blood count; Con Meds=concomitant medications; CrCl=calculated creatinine clearance; ECG=electrocardiogram; EOT=end of treatment; HBVAb=hepatitis B virus antibody; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IC=informed consent; I/E=inclusion/exclusion; iRECIST = modified RECIST 1.1 for immune-based therapeutics; LFT=liver function test; MHx=medical history; PD=pharmacodynamics (or progressive disease, depending on context); PE=physical examination; PK=pharmacokinetic(s); PS=performance status; q#wks=every # weeks; SAE=serious AE; SRM=study reference manual; TFT=thyroid function test; UA=urinalysis; VS=vital signs; wks=weeks.

Combination Therapy Schedule

Visit Week / Visit Day (if applicable)	SCR	1		2	3		4	5	6	7+	EOT	Follow-Up		Notes
		1	2	8	15	16	22	29	36	43+		Response	Survival	
Office Visit	X	X[1]	X	X	X	X	X	X	X	X[2]	X	X		Visit Types/Windows – see Section 9.1 [1] On Week 1, Day 3, sites will call participants to assess AEs. [2] After the first 6 weeks, office visits to occur every 3 weeks.
Inclusion/Exclusion	X	X												I/E checked prior to first dose on Day 1 See Section 6.1 and Section 6.2 re: I/E criteria
Screening	X													Participant Registration, IC, Demographics, MHx, Prior Medications Refer to the Study Reference Manual (SRM)
Anti-Cancer Treatment	X											X	X	Any anti-cancer treatments administered prior to signing consent and/or during study followup periods will be collected.
Administer Pembrolizumab		See notes												See Section 7.1 for dosing schedule. Dosing may be delayed due to toxicity (Section 7.2). See Section 8 for treatment discontinuation criteria. GSK3145095 alone or in combination with pembrolizumab will be dosed for a maximum of 2 years. For GSK3145095, BID from Day 1. If the half-life is found to be more than 5 hours in monotherapy, the Day 1 evening dose will be omitted.
Administer GSK3145095		See notes												
Con Meds		See notes												Concomitant medications to be collected at all office visits (Day 1 through Response Follow-up). See Section 9.1 and Section 9.3 for more details.

Combination Therapy Schedule

Visit Week Visit Day (if applicable)	SCR	1		2	3		4	5	6	7+	EOT	Follow-Up		Notes
		1	2	8	15	16	22	29	36	43+		Response	Survival	
AE/SAE Assessment	See notes													On Week 1, Day 3, sites will call participants to assess AEs. All other AE assessments will be done at office visits (weekly for the first 6 weeks and then q3wks). AEs: Dose 1 – EOT. SAEs: Consent - 90d post last dose AESIs: Dose 1 – 90d post last dose. See Section 9.1 and Section 9.3 for more details
PS, PE, VS, Weight	X	X		X	X		X	X	X	X	X			Weekly for first 6 wks, then every 3 wks and at EOT visit; see Section 9.5.1 and Section 9.5.2 for more details.
12-lead ECG	X	X	X	X	X	X	X		X	X	X	X		Days 1, 2, 8, 15, 16, 22, and 36: triplicate 12-lead ECGs to coincide with PK timepoints (GSK3145095 and pembrolizumab). Other days: single 12-lead ECGs. PK samples will be collected directly after ECG, not during the recordings
HIV, HCV, HBVAb, UA	X													

Combination Therapy Schedule

Visit Week Visit Day (if applicable)	SCR	1		2	3		4	5	6	7+	EOT	Follow-Up		Notes
		1	2	8	15	16	22	29	36	43+		Response	Survival	
Pregnancy Test	X	X					X			X	X			Women of child bearing potential only. Serum test is required at screening & EOT visits. Urine pregnancy test is adequate at other visits. Day 1 test should be done within 24 hours before the first dose of any study drug. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. After starting study treatment, participants will undergo urine pregnancy testing every 3 weeks and whenever a menstrual cycle is missed or when pregnancy is otherwise suspected. If the participant hasn't been on an acceptable method of contraception for at least 2 weeks prior to start of therapy, pregnancy testing must be done weekly for the first month of treatment.
CBC, Chemistry, LFT	X	X		X	X		X	X	X	X	X			Weekly for the first 6 weeks, then q3wks, and at the EOT visit. See Table 9 for more details regarding Clinical Safety Laboratory Assessments.
TFT, Cortisol	X[1]	X[2]							X[1]	X[1]				[1]TFTs at screening, q6wks, and as clinically indicated. [2]Day 1: baseline a.m. cortisol only (no TFTs); to be collected before 1st dose, and then as clinically indicated. See Table 9 for more details regarding Clinical Safety Laboratory Assessments.

Combination Therapy Schedule

Visit Week / Visit Day (if applicable)	SCR	1		2	3		4	5	6	7+	EOT	Follow-Up		Notes
		1	2	8	15	16	22	29	36	43+		Response	Survival	
Disease Assessment and Tumor Imaging	X									X	X	X		Screening: within 28 days before the first dose Treatment: every 6 weeks for the first 24 weeks, then every 12 weeks until disease progression confirmed by iRECIST; disease assessment must be performed after biopsy; see Section 9.2. EOT: required if the last disease assessment did not show progressive disease and was performed ≥6 weeks before EOT. Follow-up: every 12 weeks in the absence of progression or starting another anticancer therapy.
Fresh Tumor Tissue	X[1]								X[1]	X[2]	X[3]	X[3]		[1] Two fresh tumor biopsy samples are required in Part 2, the first during screening and the second after 5 weeks of study treatment. Disease assessment must be performed after biopsy. Please refer to Section 9.7.2. [2] With participant consent & agreement by the PI & GSK Medical Monitor, additional optional fresh biopsies may be obtained during the study. See Section 9.7.2. [3] Optional fresh tumor biopsy should be attempted at disease progression (EOT or during follow-up). PK & PD blood samples must be obtained within approximately 1h of tumor biopsy.

Combination Therapy Schedule

Visit Week		1		2	3		4	5	6	7+		Follow-Up		
Visit Day (if applicable)	SCR	1	2	8	15	16	22	29	36	43+	EOT	Response	Survival	Notes
Blood PD		X[1]					X[2]		X[2,3]	X[4,5,6]	X	X[7]		[1] Pre-dose, 1.5h, and 8h after dosing GSK3145095 [2] Pre-dose relative to GSK3145095 [3] After 5 weeks of study treatment, on the day of the fresh tumor biopsy collection. If no on-treatment biopsy, the blood PD sample must still be taken. [4] Obtain sample on day of first tumor imaging, before administration of any IV contrast [5] If participant consents to a tional biopsies, the blood PD sample should be taken at the time of collection of the additional biopsy. [6] With participant consent & agreement by the PI & GSK Medical Monitor, additional optional blood samples may be obtained during the study. See Section 9.7.1. [7] If a tumor biopsy is taken at the time of disease progression at EOT or during follow-up, then a PD blood sample must be taken within approximately 1h of tumor biopsy.

Combination Therapy Schedule														
Visit Week		**1**		**2**	**3**		**4**	**5**	**6**	**7+**		**Follow-Up**		
Visit Day (if applicable)	**SCR**	**1**	**2**	**8**	**15**	**16**	**22**	**29**	**36**	**43+**	**EOT**	**Response**	**Survival**	**Notes**
Plasma PK for GSK3145095		X[1]	X[1]	X[2]	X[3]	X[3]	X[2]		X[2]		X[4]	X[4]		[1] Day 1 (single dose PK): pre-dose (within 1h prior to dosing) & 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h, and 24h (before Day 2 morning dose). The 10 hour collection is optional. [2] Pre-dose and 1.5h post dose (morning dose only, relative to GSK3145095 dose). [3] Day 15: pre-dose & 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h (before evening dose), & 24h (before Day 16 morning dose). The 10 hour collection is optional. If possible after the Day 15 evening dose: 0.5h, 1h, 2h, 3h, 6h, & 8h (in addition to the pre-dose sample on Day 16). [4] If a tumor biopsy is taken at the time of disease progression at EOT or during follow-up, then a PK blood sample must be taken within approximately 1h of tumor biopsy. The number and sampling times may be adjusted based on the emerging PK data available. Refer to SRM for additional details.

Combination Therapy Schedule

Visit Week / Visit Day (if applicable)	SCR	1		2	3		4	5	6	7+	EOT	Follow-Up		Notes
		1	2	8	15	16	22	29	36	43+		Response	Survival	
Pembrolizumab PK		X[1]		X[2]	X[2]		X[3]			X[3]	X[2]			[1] Cycle 1 Day 1: pre-dose (within 1 hour before the start of infusion) and 0.5 h (within 30 minutes after the end of infusion) and 24h (±4h) after the end of infusion. [2] Anytime during visit [3] Day 1 of all subsequent cycles: pre-dose (within 1 hour before the start of infusion) The number and sampling times may be adjusted based on the emerging PK data available. Refer to SRM for additional details. Refer to SRM for additional details.
Genetics (PGx) sample		X												See Appendix 7 for more details
Follow-up telephone call													X	Survival status: See Section 9.1 for more details regarding followup- visit types. Participants should be contacted every 12±2 weeks after documented disease progression (or after initiation of another anticancer treatment) until death.

Abbreviations: AE=adverse event; AESI=AE of special interest; BID=twice daily; CBC=complete blood count; Con Meds=concomitant medications; CrCl=calculated creatinine clearance; ECG=electrocardiogram; EOT=end of treatment; HBVAb=hepatitis B virus antibody; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IC=informed consent; I/E=inclusion/exclusion; iRECIST = Modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; LFT=liver function test; MHx=medical history; PD=pharmacodynamics (or progressive disease, depending on context); PE=physical examination; PK=pharmacokinetic(s); PS=performance status; q#wks=every # weeks; SAE=serious AE; SRM=study reference manual; TFT=thyroid function test; UA=urinalysis; VS=vital signs; wks=weeks.

3. INTRODUCTION

3.1. Study Rationale

Pancreatic ductal adenocarcinoma (PDAC) is the 4th leading cause of cancer deaths worldwide with a 5-year survival rate of less than 5%. A major therapeutic barrier for PDAC is the highly immunosuppressive myeloid infiltrate that is a hallmark of the pancreatic tumor microenvironment (TME). This immunosuppressive innate infiltrate is largely responsible for PDAC resistance to current immunotherapies that target the adaptive immune system. To overcome this barrier, the next generation of immunotherapies for pancreatic cancer and other tumors with a similar cellular phenotype will need to modulate the innate infiltrate to increase sensitivity to T cell checkpoint inhibitors.

Nonclinical evidence suggests that there is therapeutic potential for inhibition of receptor interacting protein 1 (RIP1), encoded by the RIPK1 gene, across multiple therapeutic areas, including oncology. Increased RIPK1 protein expression has been reported in human pancreatic (Seifert, 2016), hepatocellular (Wang, 2016), melanoma (Liu, 2015), and gallbladder (Zhu, 2014) cancer biopsies, as well as gliomas from resected brain tumors (Park, 2009). In each of these studies, RIPK1 expression correlated with a worse patient prognosis. In murine models, RIP1 kinase activity has been reported to drive pancreatic oncogenesis. Inhibition of kinase activity in the pancreatic TME leads to the replacement of tumor-permissive myeloid infiltrates with innate cells that promote an effective anti-tumor response by the adaptive immune system (Seifert, 2016). Furthermore, in an unbiased screen, RIPK1 was identified as a top gene contributing to resistance to immunotherapy (Manguso, 2017). These data suggest that the small molecule RIP1 inhibitor GSK3145095 may have therapeutic potential in multiple tumor types.

Study 205013 is a Phase 1 first-time-in-human (FTIH) study of GSK3145095 alone and in combination with other anticancer agents including pembrolizumab, in participants with PDAC, non-small cell lung cancer, triple-negative breast cancer, or melanoma. These tumor types were chosen based on preclinical evidence supporting a role for RIP1 kinase activity promoting oncogenesis and/or their phenotypic similarity to PDAC characterized by high infiltrates of immunosuppressive innate infiltrates (Seifert 2016; Manguso, 2017; Santoni, 2018; Liu, 2015; Lievense, 2013; Hartwig, 2017). The study includes up to 4 parts: Parts 1 and 2 (Dose Escalation) and Parts 3 and 4 (Dose Expansion) The hypothesis being tested in this study is that GSK3145095 can be safely administered to participants with selected advanced or recurrent solid tumors at doses at which target engagement and pharmacodynamic effects can be demonstrated. No formal statistical hypotheses will be tested; analyses will be descriptive and exploratory.

3.2. Background

Inflammation and cell death are intimately linked, and an appropriate balance between the two is essential for maintaining tissue homeostasis. Tumorigenesis represents one of

the best examples of the pathological consequences of a disruption in this balance, as dysregulated cross-talk between cell death and immune signaling in the tumor promotes immunosuppression and tissue-regeneration. To circumvent this miscommunication, much work has been done to develop immuno-therapies that directly activate the adaptive immune system to induce cytotoxicity and tumor regression. However, therapeutics that block immune checkpoints in T cells are only able to eradicate malignant cells if the T cells can infiltrate the tumor and effectively interact with proinflammatory innate immune cells (Garrido-Laguna, 2015).

The lack of efficacy of T cell based immuno-therapies in pancreatic ductal adenocarcinoma (Garrido-Laguna, 2015) underscores the importance of targeting additional immunoregulatory pathways. Hallmarks of PDAC that contribute to this therapeutic barrier include the vast infiltrate of myeloid cells, and impenetrable desmoplasia (Scarlett, 2013, Garrido-Laguna, 2015, Engblom, 2016). Tumor infiltrated myeloid cells often correlate with a worse patient prognosis and are increasingly recognized as key drivers of an immunosuppressive tumor microenvironment contributing to therapeutic resistance. For these reasons, immunomodulation of the myeloid cell population within tumors is an attractive target for next-generation therapeutics in PDAC (Scarlett, 2013).

Recent work demonstrates a novel role for RIP1 kinase activity in recruiting immunosuppressive myeloid cells in PDAC (Seifert, 2016). RIP1 is a ubiquitous kinase but is only active upon homeostatic disruptions. In its ubiquinated form, RIP1 provides a scaffolding function essential to pro-survival NF-κB signaling that is required for vitality. Inhibition of cIAP proteins prevent RIP1 ubiquitination, and in the absence of pro-apoptotic caspase activity, will lead to a RIP1 kinase dependent, pro-inflammatory programmed cell death termed necroptosis (Ofengeim, 2013). Initially it was thought that inducing necroptosis in tumor cells could serve as a novel treatment for tumors resistant to apoptosis. However, increasing evidence reveals a detrimental effect of danger associated molecular patterns (DAMPs) released following necrosis or necroptosis within solid tumors (Lofti, 2016), and necroptosis in endothelial cells promotes metastasis (Strilic, 2016).

It is increasingly clear that there are a variety of RIP1 driven processes that are independent of cell death including cytokine secretion (Najjar, 2016), cell differentiation (Xin, 2017), DNA stability (Chen, 2014, Park, 2009), extravasation (Hänggi, 2018), and anchorage independent cell growth (Liu, 2016). Given these additional roles for RIP1 kinase activity, combined with the negative effects of necroptosis in solid tumors, it is not surprising that recent in vivo work shows a role for RIP1 in promoting oncogenesis that contradicts earlier in vitro studies. Recent work from the Miller lab, for example, showed that RIP1 kinase activity leads to the recruitment of myeloid derived suppressor cells (MDSCs), tumor associated macrophages (TAMs) and IL-10 expressing T cells in a CXCL1 and SAP130 dependent manner to promote pancreatic oncogenesis (Seifert, 2016). This work has been expanded internally to show that therapeutic blockade of RIP1 kinase activity retarded tumor progression and decreased fibrosis within the remaining

pancreatic tumor. Preclinical PDAC models support the clinical hypothesis. The first models tested were the orthotopic KPC and transgenic KC models. In the former model, tumors are derived from a mouse harboring the same Kras and p53 mutations present in >90% of pancreatic cancer cases. In the latter, pancreatic intraepithelial (PanIN) lesions develop spontaneously due to a Kras mutation. Similar to human tumors, these tumors are fibrotic in nature and resistant to anti-PD1. In both models, maintenance of >90% inhibition of RIP1 in the periphery led to an approximate 50% decrease in tumor size. Concomitant with this efficacy, there was a significant decrease in the number of M2-like TAMS. Macrophages present in the tumor after RIP1 inhibition were polarized to a more M1-like anti-tumor phenotype (Seifert, 2016, and unpublished data). Furthermore, RIP1 inhibition markedly upregulated T-cell infiltration and PD-1 expression on the T cells in the TME. Functionally, this sensitized tumors to checkpoint blockade with anti-PD1. In a third subcutaneous model using pan02 cells, inhibiting RIP1 >90% in the periphery also led to an approximate 50% reduction in tumor size. Similarly, the addition of anti-PD1 increased the efficacy in this model.

3.2.1. GSK3145095

GSK3145095 is a compound which is structurally similar to the lead RIP1 inhibitor GSK2982772, which is currently in Phase 2 clinical development. Results from healthy volunteer study with GSK2982772 have been published (Weisel, 2017). GSK3145095 demonstrates consistent pharmacology across all the assays in the RIP1 critical path. GSK3145095 is a high-quality candidate with desirable physiochemical properties which result in excellent pharmacokinetic and safety profiles. Please refer to Section 5.7 for details on selection of the starting dose, and the Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2017N334332_00] for additional details.

In vivo efficacy for GSK3145095 could not be evaluated because it is not selective for non-primate RIP1. This necessitated the use of the tool compound GSK3540547A, a potent mouse RIP1 inhibitor for evaluation of anti-tumor activity in the pancreatic tumor model. One dose was evaluated in the form of food-based dosing which resulted in approximately 50% tumor growth inhibition with blood concentration maintained above 90% RIP1 inhibition during the entire dosing period. A dose of 100 mg when administered as 50 mg BID is anticipated to provide 97.4% RIP1 inhibition in the blood over the dosing interval in 50% of participants. The actual level of RIP1 inhibition required for anti-tumor activity in humans is not known.

GSK3145095 has not yet been studied in humans.

3.2.2. Pembrolizumab

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.

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 participants 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].

The dose of pembrolizumab planned to be studied in this trial is 200 mg Q3W.

3.2.3. Rationale for Combining GSK3145095 and Pembrolizumab

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.

Current immunotherapies such as the anti-PD1 checkpoint inhibitor pembrolizumab target the latter of these processes to release pathways negatively regulating T-cell activation. While these therapies have revolutionized cancer patient care in certain indications, they are not approved for pancreatic cancer. In order to complement T-cell checkpoint inhibitors and sensitize resistant tumors, one approach for the next generation of immuno-therapeutics is to target the innate immune system. This clinical study aims to release the immuno-suppressive mechanisms imposed on the adaptive system from M2-

like TAMs to sensitize tumors to checkpoint blockade. The preclinical data described above supports this hypothesis

RIP1 has also been implicated in promoting oncogenesis in hepatocellular, melanoma, and breast tumor models. Furthermore, in an unbiased screen, RIP1 was identified as a top gene contributing to resistance to immunotherapy (Manguso, 2017). These data suggest that the small molecule RIP1 inhibitor GSK3145095 may have therapeutic potential when combined with immunotherapy such as pembrolizumab in multiple tumor types.

3.3. Benefit/Risk Assessment

To date, GSK3145095 has not been administered to human participants; therefore, no clinical data are available. Th is is the first dose escalation study proposed in human participants with GSK3145095. GlaxoSmithKline is not aware of any compound targeting RIP1 for oncology having previously been administered in humans. The risk assessment of GSK3145095 is based on the nonclinical studies conducted to date. Summaries of findings from nonclinical studies conducted with GSK3145095 can be found in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2017N334332_00].

Details of these risks and the proposed strategy to mitigate/monitor these risks are detailed in Section 3.3.1. The proposed risk assessment and management plan for the study has been developed in accordance with the tenets of European Medicines Agency (EMA) guideline on strategies to identify and mitigate risks for first time in human (FTiH) clinical trials with investigational medicinal products [European Medicines Evaluation Agency **(**EMEA)/ Committee for Medicinal Products for Human Use (CHMP)/SWP/28367/07]. GlaxoSmithKline (GSK) has assessed this study for any risks that may be posed to participants taking part.

3.3.1. Risk Assessment

3.3.1.1. GSK314095 Risk Assessment

<table>
<tr><th colspan="3">GSK314095 Risk Assessment</th></tr>
<tr><th>Potential Risk of Clinical Significance</th><th>Summary of Data/Rationale for Risk</th><th>Mitigation Strategy</th></tr>
<tr><td>Hepatotoxicity</td><td>Non-clinical data:

<u>In vitro</u>
• BSEP inhibition in vitro (IC_{50}=25 uM). BSEP risk prediction (i.e., C_{max}/BSEP $IC_{50} \geq 0.05$) suggests GSK3145095 could be a BSEP inhibitor in vivo at ≥150 mg per day dose (C_{max} = 0.75 µg/mL; 1.8 µM)
• Glutathione adduct formation: A trace oxidative, defluorinated glutathione conjugate was detected in human liver microsomal incubates as well as at trace levels in rat and monkey hepatocytes, but not in human hepatocytes (however cryopreserved human hepatocytes might express low glutathione-S-transferase).
• CYP3A induction – In vitro human pregnane X receptor (hPxr) activation.
<u>In vivo</u>
• There was no evidence of hepatotoxicity in the 4-week rat or monkey studies. There was a small increase in liver weight and serum cholesterol after 1 month at high dose (300 mg/kg/day) in female rats and a small increase in liver weight and 4beta-hydroxycholesterol for 1 female monkey after 1 month of dosing at high dose (60 mg/kg/day), suggesting CYP3A induction.</td><td>Inclusion criteria:
<table><tr><th>Hepatic</th><th></th></tr><tr><td>Total bilirubin
For participants with Gilbert's Syndrome (only if direct bilirubin ≤35%)</td><td>≤1.5xULN
≤3.0xULN</td></tr><tr><td>AST
ALT</td><td>≤2.5xULN
≤2.5xULN</td></tr></table>Exclusion criteria:
• Current active liver or biliary disease (except for Gilbert's syndrome or asymptomatic gallstones, liver metastasis, 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.
• Known current drug or alcohol abuse.
Permitted Medications:
• Acetaminophen: Due to potential risk of liver toxicity when combining acetaminophen with GSK3145095, acetaminophen dosage is restricted to no more than 2g per day.
Participant Monitoring:
• Chemistry laboratory tests reflecting liver function are readily obtainable in the clinic and will be monitored weekly for the first 6 weeks, then q3wk and at the EOT visit.
• Plasma and urine will be screened for reactive metabolite formation.
• Liver Chemistry Stopping Criteria are included in the clinical protocol.</td></tr>
</table>

GSK314095 Risk Assessment		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Increases in Heart rate, Decreases in blood pressure and effects on QT interval	Nonclinical data: • Increases in heart rate observed in both the 4-week toxicology study and the single dose safety pharmacology monkey study were transient and reversible and seem to correlate with systemic drug exposure levels • There were apparent increases in QTc in both sexes given 60 mg/kg/day GSK3145095 during Week 4; however, the relationship to test item cannot be determined due to the test item related changes in heart rate. • In a cardiovascular study in monkeys, a single oral dose of 60 mg/kg produced a reversible increase in HR (up to 59 beats per minute or 45%), and a reversible decrease in mean arterial pressure (up to 22 mmHg or 24%), systolic blood pressure (up to 21 mmHg or 20%), diastolic blood pressure (up to 20 mmHg or 27%), and QT interval (up to 38 milliseconds or 16%). Since the effects of QT were inconsistent between the single dose CV study and the 4-week study, there was an uncertain relationship to drug,	Inclusion criteria: • QTcF >450 msec (or QTcF >480 msec for participants with bundle branch block) Exclusion Criteria: 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 electrocardiogram (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 beginning screening. • Documented congestive heart failure (Class II, III, or IV) as defined by the New York Heart Association functional classification system. • Recent (within the past 6 months) history of symptomatic pericarditis. Participant Monitoring: • Standard ECG monitoring for QT effect (i.e., intermittent PK matched timepoints to assess QTc)

<table>
<tr><th colspan="3">GSK314095 Risk Assessment</th></tr>
<tr><th>Potential Risk of Clinical Significance</th><th>Summary of Data/Rationale for Risk</th><th>Mitigation Strategy</th></tr>
<tr><td>Bone marrow effects/lymph node enlargement</td><td>Nonclinical data:
Sternal bone marrow necrosis or lymph node necrosis was present in 2 female monkeys given 60 mg/kg/day. Test item-related clinical pathology findings at 60 mg/kg/day were characterized by decreased reticulocyte (up to 0.23X Pretest) and platelet counts (up to 0.55X Pretest), and red cell mass (up to 0.64X Pretest) as measured by hemoglobin, hematocrit, and RBC counts in males and females, increased total white blood cells (up to 2.39X Pretest). GSK3145095-related microscopic changes were increased generalized cellularity or increased inflammatory cell infiltrates in various organs including the spleen (minimal to moderate), lymph nodes (minimal to marked) and bone marrow (slight to marked) in animals given ≥20 mg/kg/day, most notably at 60 mg/kg/day</td><td>Inclusion criteria:<table><tr><th>Hematologic</th><th></th></tr><tr><td>ANC</td><td>≥1.5x10^9/L</td></tr><tr><td>Lymphocyte count</td><td>>1000/mm^3</td></tr><tr><td>Hemoglobin</td><td>≥9 g/dL</td></tr><tr><td>Platelets</td><td>≥100x10^9/L</td></tr></table>Participant Monitoring:
CBC weekly for the first 6 weeks, then q3wks and at the EOT visit
Physical exams (weekly for first 6 wks, then q3wks and at the EOT visit) and imaging (see Schedules of Activities, Section 2) to include monitoring for lymphadenopathy</td></tr>
<tr><td>Immunomodulation and/or risk of infection</td><td>Although there were no signs of infections observed preclinically, the possibility of immune modulation including an increase in the frequency and/or severity of infections may result from the intended pharmacologic effect of GSK3145095.
Immune-compromised conditions such as malignancies and immunosuppressive cancer treatment may compound this risk.
Infections may include, but are not limited to, Herpes Zoster. Herpes Zoster is relatively common, with a</td><td>Exclusion criteria:
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 participant is on a stable dose.
Active infection (including active herpes zoster infection), known human immunodeficiency virus infection, or positive test for hepatitis B surface antigen or hepatitis C.</td></tr>
</table>

GSK314095 Risk Assessment		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
	lifetime risk between 25% and 30% and overall incidence between 3 to 5 cases per 1000 person-years in the general population.	Participant Monitoring: • Participants will undergo routine physical examinations at regular intervals while on study.
Vaccinations	There is a theoretical risk that GSK3145095 could alter an individual's immune response to vaccines or allow symptoms to develop following vaccination with a live vaccine when administered while on therapy.	Exclusion criteria: • Receipt of any live vaccine within 4 weeks before starting study treatment. Study Restriction: • Receipt of any live vaccine within 5 half-lives of GSK3145095 plus 30 days after discontinuation of GSK3145095. Participant management: • Attenuated or live vaccines should not be administered to participants from 30 days prior to the first dose of GSK3145095, during the study and for 5 half-lives plus 30 days (total 32 days) after GSK3145095 is discontinued. • If indicated, non-live vaccines (e.g. inactivated influenza vaccines) may be administered while receiving GSK3145095 based on a treating physician's assessment of the benefit:risk (e.g., risk of theoretical decreased responsiveness). Investigators will be expected to have followed local and/or national guidelines with respect to vaccinations, including against influenza and pneumococcus.
Drug-drug Interactions: Victim Interaction: with potent inhibitors of Pgp, resulting in potential increased exposure of GSK3145095 if fraction absorbed (Fa) is low (<50%) Perpetrator Interaction: with narrow therapeutic index (NTI) CYP3A4 substrates such as the anti-rejection drugs cyclosporine, sirolimus,	Nonclinical data: GSK3145095 was a P-gp substrate in vitro with an efflux ratio of >100. In vivo bioavailability (F) was high (≥78%) in all species tested except mouse, for which F= 26%, suggesting it may be high in human. In vitro human pregnane X receptor (hPxr) activation suggests potential for CYP3A4 induction in vivo; however in monkey 4 week study, no observed increase in 4β-hydroxycholesterol (4β-HC; biomarker for CYP3A activity) at NOAEL (20 mg/kg/day; Cmax =	Subject Selections: • Subjects who are taking concomitant medications known to inhibit Pgp or are CYP3A4 narrow therapeutic index (NTI) substrates or are sensitive substrates of OATP1B1 or OATP1B3 transporters will be excluded from the study. Subject Monitoring: • Subjects' concomitant medication usage will be reviewed prior to inclusion and monitored throughout the study. • Subjects should be monitored throughout the study for potential effects of interaction between GSK3145095 and other concomitant medications.

GSK314095 Risk Assessment		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
and tacrolimus, resulting in potential loss of exposure and thus efficacy. Via weak inhibition of CYP2C9, perpetrator risk for NTI CYP2C9 substrates (i.e., warfarin and phenytoin) only at highest dose of 800 mg BID. Via weak inhibition of uptake transporters, OATP1B1 and OATP1B3, perpetrator risk for sensitive OATP substrates, including but not limited to Grazoprevir, Eluxadoline, Paritaprevir, Rosuvastatin, Pitavastatin and Pravastatin No DDI risk is predicted for co-administration of GSK3145095 with pembrolizumab	9.58 μg/mL) and <2-fold increase in 4β-HC at highest dose (60 mg/kg/day; Cmax = 24 μg/mL). In vitro CYP2C9 inhibition in human liver microsomes IC50 = 78 μM In vitro inhibition of uptake transporters, OATP1B1 and OATP1B3 [IC50 = 38.0 and 43.9 μM, respectively, corrected for nonspecific binding] Literature review: Clearance of mAbs is through lysosomal degradation or endocytosis. Absorption is dependent on physiological parameters not related to enzymes or transporters and distribution is dependent on extravasation in tissue and distribution in the interstitial space. Thus no known mechanistic opportunity for a DDI with an NCE such as GSK3145095.	Patient urine will be pooled and analyzed for parent and metabolites to provide information on fraction absorbed. The 4β-HC to cholesterol ratio will be measured in patient plasma pre-dose and after repeat dosing to assess potential changes in hepatic CYP3A4 activity. Advise caution at GSK2982772 plasma Cmax ≥ 8 μg/mL, predicted for 1600 mg daily (800 mg BID), only with NTI CYP2C9 substrates.
Reproductive toxicity	Since EFD studies have not been completed, the reproductive toxicity is not known. GSK3145095 was not mutagenic. Induction of CYP3A4 in humans could lead to a potential DDI with oral contraceptives; as substrates, their exposure and thus effectiveness could decrease.	Participant Selection: • Male and female participants of childbearing potential will be included in this study only if they agree to use highly effective methods of contraception and avoid conception for defined periods of time before first administration of study drug until 15 days (males/females – Part 1) and 120 days (males/females – Parts 2-4) after the last administration of study drug • Females of childbearing potential will undergo serum pregnancy test at screening. After starting study treatment, participants will undergo urine pregnancy testing every 3 weeks and whenever a menstrual cycle is missed or when pregnancy is otherwise suspected. If the participant hasn't been on an acceptable method of contraception for at least 2

GSK314095 Risk Assessment		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
		weeks prior to start of therapy, pregnancy testing must be done weekly for the first month of treatment. • Pregnant and lactating females are not eligible for inclusion in the study. Withdrawal Criteria: If a female participant should become pregnant during the study, study medication should be discontinued. The participant will be followed to determine the outcome of the pregnancy. Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.

3.3.1.2. Pembrolizumab Risk Assessment

Pembrolizumab Risk Assessment		
Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Immune related reactions • Pneumonitis • Colitis • Nephritis • Neuritis • Hepatitis • Skin inflammation • Endocrinopathies	Identified risks caused by an excessive T-cell immune activation and potential expansion and activation of T-cell clones against normal tissues	Please refer to the KEYTRUDA prescribing information and Section 7.2 (Management of Immune Related SAEs)
Infusion reaction (pembrolizumab)	Identified risk associated with pembrolizumab infusion	Please refer to the KEYTRUDA prescribing information
Reproductive toxicity		Participant Selection: • Male and female participants of childbearing potential will be included in this study only if they agree to use highly effective methods of contraception and avoid conception for defined periods of time before first administration of study drug until 15 days (Part 1) for males/females, and 120 days (Parts 2-4) for males/females after the last administration of study drug • Females of childbearing potential will undergo serum pregnancy test at screening and then urine pregnancy testing at regular intervals during the study. • Pregnant and lactating females are not eligible for inclusion in the study. Withdrawal Criteria: If a female participant should become pregnant during the study, study medication should be discontinued. The participant will be followed to determine the outcome of the pregnancy. Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
No DDI risk is predicted for co-administration of GSK3145095 with pembrolizumab		

3.3.2. Benefit Assessment

In vivo efficacy for GSK3145095 could not be evaluated because it is not selective for non-primate RIP1. This necessitated the use of the tool compound GSK3540547A, a potent mouse RIP1 inhibitor for evaluation of anti-tumor activity in the pancreatic tumor model. Only one dose was evaluated in the form of food-based dosing which resulted in approximately 50% tumor growth inhibition with blood concentration maintained above the IC90 for RIP1 inhibition during the entire dosing period. A dose of 100 mg when administered as 50 mg BID is anticipated to provide 97.4% RIP1 inhibition in the blood over the dosing interval in 50% of participants. The actual level of RIP1 inhibition which would translate into efficacy in humans is not known.

3.3.3. Overall Benefit:Risk Conclusion

This is an open-label, dose escalation study and the FTIH study of this agent to be conducted in participants with relapsed/refractory solid tumors for which no standard therapies are anticipated to result in a durable remission. GSK3145095 has nonclinical activity in vivo, however it is unknown whether GSK3145095 will have clinical activity, thus any potential beneficial effect for an individual participant attributable to GSK3145095 is unknown. Data obtained in this study may help identify individuals more likely to benefit or have side effects from GSK3145095. Study participants may benefit from the medical tests and screening performed during the study.

4. OBJECTIVES AND ENDPOINTS

In the following tables, primary and secondary objectives are presented separately for Parts 1 & 2 (monotherapy and combination escalation) and Parts 3 & 4 (expansion), while exploratory objectives are presented together for all parts.

Parts 1 & 2: Dose Escalation		
	Objectives	**Endpoints**
Primary	To evaluate the safety and tolerability and identify the maximum tolerated dose (MTD) or the maximum administered dose (MAD) of GSK3145095 administered orally alone and in combination with other agents such as pembrolizumab to participants with selected advanced or recurrent solid tumors.	Frequency and severity of adverse events including frequency of DLTs.
Secondary	To evaluate the antitumor activity of GSK3145095 alone and in combination with other agents such as pembrolizumab in participants with selected advanced or recurrent solid tumors.	Best overall response based on RECIST 1.1 criteria

Parts 1 & 2: Dose Escalation		
	Objectives	**Endpoints**
	To characterize the pharmacokinetics (PK) of GSK3145095 alone and in combination with other agents such as pembrolizumab in participants with selected advanced or recurrent solid tumors.	Derived PK parameters for GSK3145095 including area under the plasma drug concentration versus time curve ($AUC_{(0-t)}$, $AUC_{(0-\tau)}$), maximum observed plasma drug concentration (C_{max}), minimum observed plasma drug concentration (C_{min}), time to maximum observed plasma drug concentration (t_{max}), clearance (CL/F), volume of distribution (V/F) and terminal half-life ($t_{1/2}$) following single and repeat doses, and evaluation of dose proportionality, accumulation ratio and time invariance where data allow
	To characterize the pharmacokinetics (PK) of pembrolizumab when administered in combination with GSK3145095.	Serum pembrolizumab concentrations and PK parameters including C_{max}, $AUC_{(0-\tau)}$, and C_{min}.
Parts 3 & 4: Dose Expansion		
	Objectives	**Endpoints**
Primary	To evaluate the antitumor activity of GSK3145095 in combination with other agents such as pembrolizumab in participants with selected advanced or recurrent solid tumors.	ORR (% of participants achieving CR or PR) based on RECIST 1.1 criteria.
Secondary	To further evaluate the safety and tolerability of GSK3145095 administered orally in combination with other agents such as pembrolizumab to participants with selected advanced or recurrent solid tumors.	Frequency and severity of adverse events.
	To further evaluate the antitumor activity of GSK3145095 in combination with other agents such as pembrolizumab in participants with selected advanced or recurrent solid tumors.	Progression-Free Survival and Overall Survival.
	To characterize the PK of GSK3145095 in combination with other agents such as pembrolizumab in participants with selected advanced or recurrent solid tumors.	Derived PK parameters for GSK3145095 and combination agent including $AUC_{(0-t)}$, $AUC_{(0-\tau)}$, C_{max}, t_{max}, and $t_{1/2}$ following single and repeat doses, and evaluation of dose proportionality, accumulation ratio and time invariance where data allow

Parts 1, 2, 3, & 4: Exploratory Objectives	
Objectives	**Endpoints**
To explore the inter-relationship between antitumor activity, PK parameters, pharmacodynamic activity, and other participant characteristics	Assessment of antitumor activity (CR, PR, SD, progressive disease [PD]), tumor kinetic/PK parameters, pharmacodynamic activity, and other participant characteristics
To evaluate the pharmacokinetic and pharmacodynamic activity of GSK3145095 in the periphery and the tumor microenvironment	Assessment of GSK3145095 tumor penetration, RIP1 target engagement, activation, and pathway inhibition may be explored.
To evaluate the relationship between GSK3145095 and safety parameters, including QTcF following single and repeated administration.	Relationship between GSK3145095 exposure (e.g. concentration, Cmax, AUC) and safety parameters including change from baseline QTcF.
To explore the effect of RIP1 inhibition on the tumor microenvironment and the immune response within the tumor and periphery	May include assessment of: • Tumor biopsies via immunohistochemistry (IHC) • Changes in gene expression (ribonucleic acid [RNA] and protein), T cell receptor [TCR] diversity, tumor microenvironment or mutational load (genomic deoxyribonucleic acid [DNA]) • Measures of immune function in peripheral blood mononuclear cells (PBMCs) • Expression of circulating soluble factors
To investigate the mechanism of action and indicators of sensitivity and resistance to GSK3145095 alone or in combination with other agents such as pembrolizumab	Assessment of DNA, RNA, and/or protein markers in tumor or periphery and their association with anti-tumor activity for potential use in the development of a predictive biomarker and/or diagnostic test
To characterize the metabolite profile of GSK3145095 after single or repeated oral dosing in some participants	Identification and quantitative estimates of parent GSK3145095 and metabolites in plasma and/or urine following single or repeat doses
To assess potential effect of repeat doses of GSK3145095 on Cytochrome P450 3A4 (CYP3A4) enzyme activity in some participants	Plasma 4βhydroxycholesterol to cholesterol ratio pretreatment and following repeat dosing of GSK3145095
To evaluate disease and treatment related symptoms and impact on function and health-related quality-of-life (Parts 3 & 4 only)	Qualitative telephone interview(s)
To investigate the relationship between genetic variants in candidate genes, PK, and safety profile of GSK3145095 alone or in combination with other agents such as pembrolizumab	Pharmacogenomic (PGx) study using blood samples

5. STUDY DESIGN

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Schedule of Activities (Section 2) are essential.

5.1. 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 GSK3145095 orally administered twice daily (BID) to participants with selected advanced or recurrent solid tumors.

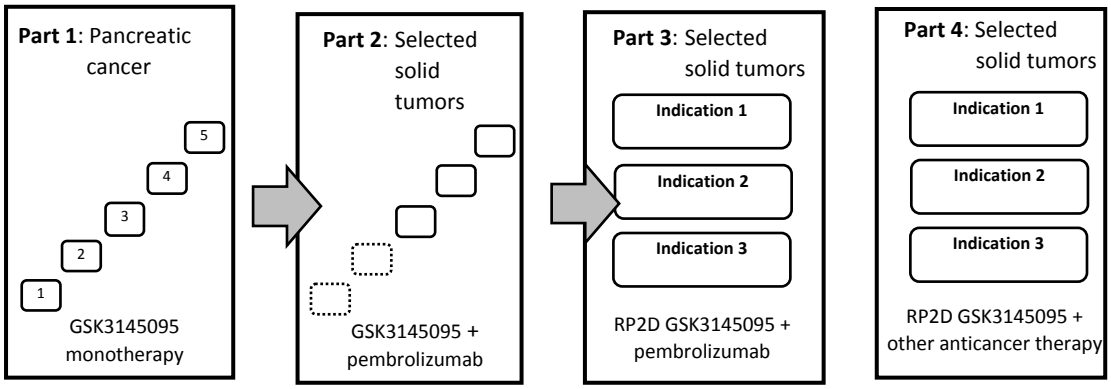
The study will be conducted in a staged approach consisting of at least 4 parts, as shown in Figure 1. Parts 1 and 2 represent dose escalation while Parts 3 and 4 represent dose expansion. Parts 2, 3, and 4 will be opened via protocol amendment. Part 1 dose escalation will be conducted in approximately 30 adult participants with advanced or metastatic pancreatic ductal adenocarcinoma (PDAC) using escalating doses of GSK3145095 as monotherapy only. The protocol may be amended to include one or more biomarker cohorts.

Part 2 will combine escalating doses of GSK3145095 with 200 mg pembrolizumab. Dose escalation of GSK3145095 will begin at least one level below the highest dose shown to have an acceptable toxicity profile in at least 3 participants in Part 1. Part 2 may be conducted in a broader population of selected solid tumors, including but not limited to, PDAC, NSCLC, triple-negative breast cancer (TNBC), and/or melanoma using a combination of escalating doses of GSK3145095 and 200 mg pembrolizumab.

Part 3 may enroll participants treated with one or more dose levels of GSK3145095 in combination with 200 mg pembrolizumab. Cohorts in Part 3 may be defined by indication or biomarker.

Part 4 may investigate the combination of additional anticancer agent(s) with one or more doses of GSK3145095 identified as safe in Part 1.

Figure 1 Study Design



5.1.1. Dose Escalation

5.1.1.1. Monotherapy Dose Escalation

In Part 1, dose level 1, a single 50 mg dose of GSK3145095 will be administered to each participant in that cohort on the first day of treatment. Blood samples will be taken before and after the first dose to assess PK parameters (see Schedules of Activities, Section 2). On study Day 2, participants will then continue to receive 50 mg of GSK3145095 BID. The first 3 participants treated at Part 1 dose level 1 will begin treatment at least 1 week apart to allow assessment of initial safety data between the enrolment of each participant.

Evaluation of the available PK and safety data over the first 4 weeks of treatment (DLT period) is required from at least 3 participants before a decision is made regarding whether to enroll additional participants at the same or the next higher dose level. Participants who do not experience a DLT and withdraw from the study before the completion of the DLT period may be replaced if they have not received at least 80% of GSK3145095 (all participants) and/or 2 doses of pembrolizumab (for combination therapy participants). All data from the replaced subjects who received less than 80% of GSK3145095 because of low grade toxicity not constituting a DLT will still be taken into consideration for dose-escalation and determination of the recommended Phase 2 dose (RP2D).

After a minimum of 3 participants in Part 1 dose level 1 have completed the DLT evaluation period (i.e., first 28 days), subsequent dose levels may initially enroll up to 4 participants with participants beginning treatment at least one calendar day apart. A minimum of 3 participants will be enrolled in each subsequent cohort until the maximum tolerated dose (MTD) or maximum administered dose (MAD) is defined.

The Neuenschwander Continual Reassessment Method (NCRM) (Neuenschwander, 2008) will be used to guide dose escalation decisions for monotherapy. At the time of each dose escalation decision, the Fixed and Adaptive Clinical Trial Simulator (FACTS) will be used to obtain, for each potential dose, the posterior probabilities that the DLT rate for that dose lies in each of four toxicity intervals (underdosing, target toxicity range,

excessive toxicity, and unacceptable toxicity). The four DLT toxicity intervals are defined as follows:

- [0%,16%)=Underdosing;
- [16%,33%)=Target toxicity range;
- [33%,60%)=Excessive toxicity;
- [60%,100%)=Unacceptable toxicity.

The recommended dose will be the dose with the highest posterior probability of lying in the target toxicity range with the additional requirement that the sum of the posterior probabilities of the DLT rate lying in the excessive toxicity range or unacceptable toxicity range is less than 25%. An updated estimate of the toxicity curve will be provided at the time of each dose escalation meeting. Statistical properties of NCRM are described in Section 10.

Exploration of lower dose levels than the NCRM-recommended dose (or expansion of a previously tested dose level) will be allowed if agreed upon by the Medical Monitor and treating investigators. The progression from one dose level to another will be made based on the assessment of all the available data from previous dose levels. This includes the NCRM-recommended dose as described earlier in this section, Section 5.1.1.6 and Section 10.4.1, and all safety and PK data. Safety data includes, but is not limited to, dose limiting toxicities and toxicities regardless of grade that result in dose reductions or delays. All dose escalation decisions will be assessed by the Dose Escalation Committee (DEC, see Section 12.2.3). The DEC is comprised of study investigators and the GSK study team (GSK Medical Monitor, pharmacokineticist, biomarker scientist, and statisticians).

Criteria that may be considered in the determination of which dose level(s) to expand and which tumor types to enroll in Parts 3 and 4 may include safety, target engagement, pharmacodynamic activity, and clinical activity.

5.1.1.2. Combination Therapy Dose Escalation

The DEC will make the decision of whether to start Part 2 as described in Section 12.2.3:

Dose escalation of GSK3145095 in combination with 200 mg pembrolizumab (Part 2) will target 3 participants up to a target maximum of 6 at each dose level and will begin with a GSK3145095 dose below the highest Part 1 (monotherapy) dose shown to have an acceptable toxicity profile in at least 3 participants. GSK3145095 dose levels used in combination therapy may be the same dose levels as for monotherapy. The dose of pembrolizumab will remain fixed at 200 mg administered IV once every three weeks (Q3W).

Fewer doses in combination therapy (compared to monotherapy) are expected to be studied for dose escalation; therefore, the modified Toxicity Probability Interval (mTPI) procedure (Ji, 2013) (and not NCRM) will be used to identify the MTD or the MAD of

GSK3145095 in combination with pembrolizumab (or other anticancer therapy) and determine the recommended dose to be used in the dose expansion phase (Parts 3 and 4). Dose escalation will proceed until the MTD or MAD for GSK3145095 in combination with 200 mg Q3W pembrolizumab is determined. Dose escalation decisions will be based on all available PK, pharmacodynamic, and safety data of ongoing and prior cohorts. This data will be reviewed by the (DEC). 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.

The rules guiding dose escalation based on the mTPI procedure are provided in Figure 2. Columns provide the numbers of participants treated at the current dose level, and rows provide the corresponding numbers of participants experiencing toxicity. The recommended decision (E = escalate to next higher dose, S = stay at current dose, D = de-escalate, DU = unacceptably toxic dose) is determined by taking the row showing the total number of participants with DLT at the current dose and finding the cell that corresponds to the column showing total number of participants in the current dose level. For example, when one of three participants experiences DLT at the current dose, the decision can be located at row indicating 1 and column indicating 3, which is S (to stay at the current dose level). All dose escalation decisions will be assessed by the DEC (See Section 12.2.3).

Figure 2 Rules Guiding Dose Escalation (mTPI Procedure)

No. of Dose-Limiting Toxicities	No. of Participants Treated at Current Dose														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	S	S	S	S	E	E	E	E	E	E	E	E	E	E
2		DU	D	S	S	S	S	S	S	S	E	E	E	E	E
3			DU	DU	D	S	S	S	S	S	S	S	S	S	S
4				DU	DU	DU	D	D	S	S	S	S	S	S	S
5					DU	DU	DU	DU	DU	D	S	S	S	S	S
6						DU	DU	DU	DU	DU	DU	D	S	S	S
7							DU	DU	DU	DU	DU	DU	DU	D	S
8								DU	DU	DU	DU	DU	DU	DU	DU
9									DU	DU	DU	DU	DU	DU	DU
10	E = Escalate to the next higher dose									DU	DU	DU	DU	DU	DU
11	S = Stay at the current dose										DU	DU	DU	DU	DU
12	D = De-escalate to the next lower dose											DU	DU	DU	DU
13	DU = Unacceptably toxic dose												DU	DU	DU
14	Target Toxicity Rate (Interval):													DU	DU
15	30% (25%, 35%)														DU

The spreadsheet was generated based on a beta/binomial model and precalculated before trial initiation. The letters in different colors are computed based on the decision rules under the mTPI method and represent different dose-finding actions. In addition to actions de-escalate the dose (D), stay at the same dose (S), and escalate the dose (E), the

table includes action unacceptable toxicity (DU), which is defined as the execution of the dose-exclusion rule in mTPI.

5.1.1.3. Dose-Limiting Toxicity

All toxicities will be graded using National Cancer Institute - Common Toxicity Criteria for Adverse Events (NCI-CTCAE) (version 5.0).

An AE is considered a DLT if it occurs during the first 28 days of treatment, is considered by the investigator to be clinically relevant, and meets one of the following criteria listed in Table 1, unless it can be clearly established that the event is unrelated to treatment. As described in Section 5.1.1.1, participants unable to receive at least 80% of scheduled doses for reasons other than toxicity (e.g., acute illness, disease progression) will not be evaluable for DLT purposes and will be replaced in the cohort. If an AE is considered related to the underlying disease, it is not a DLT. For Part 2 and Part 3, ≥Grade 3 toxicities that are known to occur with pembrolizumab and are controlled within 2 weeks using the recommended supportive measures (see Section 7.2) may not be considered dose-limiting.

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

Table 1 Dose-Limiting Toxicity Criteria

Toxicity	DLT Definition
Hematologic	• Febrile neutropenia of any duration • 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 GSK3145095 or GSK3145095 and pembrolizumab during the first 4 weeks of treatment • Toxicity attributed to treatment resulting in administration of <80% of scheduled GSK3145095 doses. • 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 a DLT

a. Suggested management guidelines are described in Section 7.2 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

Table 1 provides a list of protocol-defined DLTs; it does not provide guidelines for management of these toxicities. In appropriate clinical circumstances, resumed dosing after a DLT (at a reduced dose level) may be considered after discussion between the investigator, medical monitor, and GSK medical governance (as necessary). For management of liver toxicity, please refer to Section 8.1.1. For management of cardiac toxicity, see Section 8.1.2. For management of all other toxicities, see Section 7.2.

5.1.1.4. Maximum Dose Increment

Built-in safety constraints are in place to prevent exposing participants to undue risk of toxicity. The dose levels described in Section 5.1.1.5 represent protocol-defined maximum dose increments; investigators and the GSK medical monitor will include the data from all prior dose levels (Section 5.1.1.6) in the selection of the next dose level, and a smaller increment may be used based on the totality of the available data.

For each individual dose escalation step, if no grade ≥ 2 non-hematologic non-disease-related toxicity is observed at the current dose, the dose increment will be no more than 100% of the current dose.

5.1.1.5. Planned Dose Levels

Projected total daily dose levels of GSK3145095 are 100 mg, 200 mg, 400 mg, 800 mg, and 1600 mg. These doses will be administered twice daily in equally divided doses. For example, participants in the 100 mg dose level will receive 50 mg GSK3145095 by mouth twice daily. Please refer to Table 3 at the beginning of Section 7.1 for additional details of GSK3145095 administration. Doses intermediate to these or alternate schedules may be explored based on emerging safety, PK, and PD data. See Section 5.1.1.7 for discussion of alternate schedules.

5.1.1.6. Dose Escalation Decisions

The DEC will be responsible for determining whether dose escalation should continue as recommended by NCRM (Part 1) or mTPI procedure (Part 2). Prior to the dose escalation decision, the DEC will review critical safety data defined in the Dose Escalation Plan, including data on all adverse events including non-DLT toxicities, laboratory assessments and other safety evaluations, as well as PK and PD data. The quality review of critical safety data will be described in the Dose Escalation Plan, which includes ongoing study monitoring visits along with data review of the clinical database. See Section 12.2.3 for more details.

The dose-escalation decision and rationale for each cohort will be discussed with investigators during teleconference(s) and documented in writing with copies maintained at each study site and in the master study files at GlaxoSmithKline (GSK).

5.1.1.7. Alternative Dosing Schedules for GSK3145095

Alterations may be made to the schedule of GSK3145095 administration and/or PK/PD sampling schedule based on the results of emerging PK and safety data. Schedules of GSK3145095 administration that incorporate a recovery period may be explored (e.g., 3 weeks on, 1 week off). This approach will be considered if the safety and PK data suggest that a therapeutic exposure of GSK3145095 cannot be achieved using the initial schedule without excessive toxicity. Escalation of GSK3145095 using an alternate schedule will begin at or below the highest dose level with the initial schedule shown to be safe in at least 3 participants (and not to exceed the MTD, if identified). Escalation of GSK3145095 using the alternate schedule will then proceed as described in Section 5.1.1.1 through Section 5.1.1.6.

Schedules of GSK3145095 that use a different daily regimen (e.g., once daily [QD] or three times daily [TID] dosing) may also be explored. This approach will be considered if the safety, PK, and PD data suggest that a sufficient therapeutic exposure of GSK3145095 cannot be achieved using the initial schedule. If an alternate schedule of GSK3145095 with a shorter recovery period (for example, TID dosing) is used, escalation of GSK3145095 will begin with a dose that is ≤50% of the highest dose level shown to be safe in at least 3 participants with the initial schedule (and not to exceed the MTD, if identified). Escalation of GSK3145095 using the alternate schedule will then proceed as described in Section 5.1.1.1 through Section 5.1.1.6. If TID dosing is to be utilized, a study events table specific for TID dosing will be distributed to all sites.

The dosing schedule of GSK3145095 may also be adjusted to expand a prior dose cohort to further evaluate safety, pharmacokinetic and/or pharmacodynamic findings at a given dose level, or to add cohorts to evaluate additional dose levels. The study procedures for these additional participant(s) or cohort(s) will be the same as that described for other study participants.

Any changes to the dosing schedule may be made only after review of all available data and clearance by the GSK medical monitor. Any planned changes will apply to a cohort of participants and not an individual participant. Changes will be communicated to the site in writing along with justification and data supporting the change. A modified SRM, including updated Schedules of Activities, will be provided to the sites prior to initiation of the alternative regimen.

5.1.2. Dose Expansion

Any dose level(s) established as safe in Parts 1 or 2 may be selected for cohort expansion in Parts 3 or 4 to collect additional data on safety, PK, pharmacodynamic activity, and clinical activity. Each expansion cohort will enroll up to approximately 30 participants with the same tumor type.

Additional expansion cohorts may enroll up to approximately 20 participants per cohort to further explore pharmacodynamic activity.

Part 3 will evaluate GSK3145095 in combination with 200 mg pembrolizumab. Selection of tumor indications will be based in part on data generated in Parts 1 and 2, respectively. The GSK study team will review the available preliminary safety, PK, pharmacodynamic, and clinical activity data with investigators and site staff before selecting the dose level indications for all expansion cohorts. Criteria that may be considered in the determination of which dose level(s) to expand and which tumor types to select for cohort expansion may include:

- Target engagement and pharmacodynamic activity
- Tolerability: The frequency and severity of AEs and DLT.
- Clinical activity: Evidence of clinical response, including SD of at least 12 weeks and/or minor responses.

After 10 participants have been enrolled at a given dose level, continued accrual in the expansion cohort up to a total of approximately 20 to 30 participants may occur based on emerging anti-tumor and pharmacodynamic data. While it is anticipated that the additional 10 to 20 participants in each cohort will be treated at the same dose level as the initial 10 participants, exploration of a different dose level based on emerging data is also possible.

The selection of dose level(s) and tumor types selected for Part 3 will be communicated to the sites in writing.

The protocol may be amended to include investigation of additional anticancer agent combinations with GSK3145095 in Part 4.

5.1.3. Intra-Participant Dose Escalation and/or Therapy Switch

There will be no intra-participant dose escalation.

Participants in Part 1 may be eligible for crossover into Parts 3 or 4 (once these Parts have been opened at a dose of GSK3145095 previously shown to be safe in Part 1) upon disease progression and with discussion and approval from the GSK Medical Monitor.

5.1.4. Treatment Duration

The study includes a screening period, a treatment period, and a follow-up period (visit windows for these periods are in Section 9.1.2). Participants will be screened for eligibility beginning approximately 4 weeks before the start of treatment. The maximum duration of treatment with GSK3145095 with or without pembrolizumab will be 2 years (Table 2) or 35 cycles (each cycle is 21 days), whichever comes first. The follow-up period for safety assessments will be a minimum of 3 months from the date of the last dose of any study drug. The post-treatment follow-up period includes disease assessments every 12 weeks until documented progressive disease (PD), initiation of other anticancer therapy, or death. Following PD or initiation of other anticancer therapy, participants will be contacted every 12 weeks to assess survival status.

Participants with confirmed partial response (PR) or complete response (CR) will be followed for response duration and may be eligible for additional treatment with GSK3145095 with or without pembrolizumab at the time of relapse/progression. The decision whether a participant will receive additional treatment beyond two years will be discussed and agreed upon by the treating investigator and the Sponsor/Medical Monitor on a case-by-case basis.

Table 2 Study Treatments

Part 1: Dose Escalation – GSK3145095 monotherapy GSK3145095 PO BID[a] for up to 2 years
Part 2: Dose Escalation – GSK3145095 + pembrolizumab GSK3145095 PO BID[b] for up to 2 years Pembrolizumab 200 mg IV Q3W for up to 2 years
Part 3: Dose Expansion – GSK3145095 + pembrolizumab GSK3145095 PO BID[c] for up to 2 years Pembrolizumab 200 mg IV Q3W for up to 2 years
Part 4: Dose Expansion – GSK3145095 + anticancer agent GSK3145095 PO BID[c] for up to 2 years Combination Partner to be communicated by amendment

Note: Participants will receive a single dose of GSK3145095 on Day 1 with the BID schedule starting on Day 2.
a: For dose levels, see Section 5.1.1.5.
b: Combination escalation to start at least one dose level below the highest dose of GSK3145095 shown to be safe in Part 1.
c: At one or two dose levels shown to be tolerable in Part 2.
PO = by mouth; BID = twice daily; IV = Intravenous; Q3W = Every 3 weeks

5.2. Number of Participants

Up to approximately 220 participants will be treated in the study. Parts 1 and 2 will each treat up to approximately 30 participants will be treated. Parts 3 and 4 may treat up to approximately 160 participants (up to 80 participants in each Part).

5.3. Participant and Study Completion

Because participants will be followed for survival in this study, only when a participant 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 overall survival (OS) is desired. If a participant 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 participant's last visit/contact.

5.4. Scientific Rationale for Study Design

The study will utilize a staged approach consisting of at least four parts. In Part 1, GSK3145095 monotherapy will be assessed in escalating doses in participants with advanced or metastatic pancreatic cancer. Part 2 will assess escalating doses of GSK3145095 in combination with a fixed dose of pembrolizumab in participants with selected solid tumors that may include PDAC, NSCLC, triple-negative breast cancer, and/or melanoma. Initiation of Part 2 will occur after emerging data from Part 1 demonstrates the safety and pharmacodynamic activity of GSK3145095 monotherapy.

Part 2 will begin with a GSK3145095 dose below the highest Part 1 dose shown to be safe in at least 3 participants. Part 3 may evaluate the combination one or more doses of GSK3145095 and pembrolizumab in disease-specific expansion cohorts via protocol amendment. All available safety, pharmacodynamic, PK, and efficacy data will be used to select 1 or more doses of GSK3145095 to evaluate in Part 3. The population of participants selected for Part 3 will also be determined by data emerging from Part 2. The protocol may be amended to include investigation of additional anticancer agent combinations with GSK3145095 in Part 4.

To ensure sufficient safety and pharmacodynamic data are available before beginning enrollment in Part 2 of the study, available clinical data from Part 1 of the study, including safety, PK, pharmacodynamics, and efficacy, will be reviewed. The decision to initiate Part 2 will be documented and reported to all participating PIs and IRBs/IECs.

In the dose escalation phase (Parts 1 and 2), participants will be enrolled with selected solid tumors that are likely to respond to RIP1 inhibition therapy (e.g., indications previously reported to have a response to immunotherapies, predicted immunogenicity, and/or expression of RIP1). The tumor types to be evaluated in dose escalation may include the following: PDAC, NSCLC, triple negative breast cancer, and/or melanoma.

The inclusion of the combination with pembrolizumab is based on the preference to identify potential transformational activity early in development. GSK3145095 is not expected to have significant clinical activity as a monotherapy, and the full potential of the molecule is likely to be discovered in combination with other agents, particularly immunotherapies because RIP1 was identified as a top gene contributing to resistance to immunotherapy (Manguso, 2017). Pembrolizumab is an ideal combination partner for GSK3145095 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 show that within the pancreatic TME, RIP1 inhibition leads to the replacement of tumor-permissive myeloid infiltrates with innate cells that promote an effective anti-tumor response by the adaptive immune system (Seifert, 2016). To better understand dose-response and variables that may influence clinical response to treatment with GSK3145095 alone or in combination with pembrolizumab, it is critical that immune biomarkers in the TME are assessed in this study across a range of doses and, if feasible, correlated with clinical response. Thus, pharmacodynamic markers will be evaluated in Parts 1 and 2 to aid dose selection.

5.5. Human PK Prediction

Several methods were used to predict the PK of GSK3145095 in humans based on nonclinical PK data from various species (mouse, rat, dog, and cynomolgus monkey) and in vitro studies conducted with human liver microsomes and hepatocytes. Population PK analysis using data delivered from Dedrick transformation allowed prediction of compartmental IV PK parameters with predicted human blood clearance of 14.3 L/h/70 kg, central volume of distribution of 46.6 L/70 kg, peripheral volume of distribution of

66.4 L/70 kg and intercompartmental clearance of 7.76 L/h/70 kg. Oral bioavailability is calculated as 79% based on average in nonclinical species. Linear PK of GSK3145095 is assumed for human PK prediction.

5.6. Potential Efficacious Dose

In vivo efficacy for GSK3145095 could not be evaluated because it is not selective for nonprimate RIP1 (IC_{90} range from 4503 -14239 ng/mL). This necessitated the use of tool compound GSK3540547A, a potent mouse RIP1 inhibitor for evaluation of anti-tumor activity in the pancreatic tumor model. One dose level of the tool molecule (administered in the diet) was evaluated which resulted in approximately 50% tumor growth inhibition, with blood concentrations maintained at approximately IC98 for RIP1 inhibition during the entire dosing period. A dose of 140 mg GSK3145095 (when administered as 70 mg BID) is anticipated to provide 98% RIP1 inhibition in the blood over the dosing interval in 50% of participants. When between-subject variability in PK parameters and IC50 are accounted for, assuming the variability between subjects with respect to PK parameters and IC50 is similar for GSK3145095 and the RIP1 inhibitor lead (GSK2982772), a dose of 400 mg GSK3145095 administered as 200 mg BID is anticipated to provide 98% RIP1 inhibition in the blood over the dosing interval in 90% of participants. The level of RIP1 inhibition which would translate into efficacy in humans is not known and the anticipated efficacious dose could be greater than a total daily dose of 400 mg and higher.

5.7. Justification for Starting Dose

The proposed starting dose of GSK3145095 is 100 mg (50 mg twice daily) based on the ICH S9 guidance which allows for the human starting dose in advanced cancer patients to be 1/6 of the HNSTD (highest non-severely toxic dose) in non-rodent or 1/10 the STD10 (severely toxic dose to 10%) in rodents based on body surface area scaling of dose. Monkey was considered as the more relevant species for determining the starting dose based on RIP1 potency in monkeys being similar to human for GSK3145095. The NOAEL in monkeys was 20 mg/kg/day (240 mg/m^2) and the HNSTD was determined to be 60 mg/kg/day (720 mg/m^2) While a 194-mg total daily starting dose of GSK3145095 is the human equivalent dose of 1/6 of the HNSTD in the monkey GLP toxicity study, the actual total daily starting dose for this study is 100 mg. Details of the rat and monkey studies are summarized below.

GSK3145095 was given to rats at once daily oral doses of 20, 60, and 300 mg/kg/day for up to 4 weeks. The no observed adverse effect level (NOAEL) in this study was 300 mg/kg (1800 mg/m^2) (AUC of 349 µg.h/mL and C_{max} of 37.8 µg.h/mL). As an STD_{10} was not determined in the 4-week rat study, the NOAEL was used to conservatively define the STD_{10}. A starting dose based on 1/10 of the rat NOAEL translates to a starting dose in a human of 292 mg, assuming a 60-kg adult with a surface area of 1.62 m^2.

GSK3145095 was given to monkeys at once daily oral doses of 6, 20, and 60 mg/kg/day for up to 4 weeks. The NOAEL in this study was 20 mg/kg (240 mg/m^2) (AUC of 52.2 µg.h/mL and C_{max} of 9.58 µg.h/mL). The HNSTD was determined to be 60 mg/kg/day (720 mg/m^2) based on the nature and demonstrated, or predicted, reversibility of the

hematologic, inflammatory and heart rate findings. A 194-mg (approximately 200 mg) total daily starting dose is the human equivalent dose of 1/6 of the HNSTD in the monkey GLP toxicity study.

MABEL (Minimum Anticipated Biological Effect Level) approach was also considered similar to what was used for the healthy volunteer FTIH study of GSK2982772, a RIP1 inhibitor which shares similar chemical structure and selectivity profile compared to GSK3145095. For GSK2982772, the MABEL dose was estimated to be provide approximately 30% RIP1 inhibition in the blood at Cmax. Based on this approach, a total daily starting dose of 0.15 mg (0.075 mg twice daily) of GSK3145095 is estimated to provide approximately 30% RIP1 inhibition in the blood at C_{max} in 50% of participants. GSK2982772 has demonstrated safety and tolerability in Phase I healthy volunteer study with single and repeated doses having RIP1 inhibition in blood greater than 90% over a 24-hour period. Although the starting dose for GSK3145095 is predicted to have a high level of target engagement in the blood, this measure may not directly translate to predicting anti-tumor activity. It is unclear what level of exposure in the blood is required to achieve changes in the tumor, which is especially hard to penetrate due to its fibrous outer layer. Since participants with pancreatic cancer have a short life expectancy, an initial dose of 100 mg (50 mg twice daily) was selected with the goal of administering a therapeutically relevant dose that is also anticipated to be safe to use, in accordance with ICH S9.

The starting dose of 100 mg (50 mg twice daily) has a predicted total exposure AUC of 5.52 µg.h/mL with a C_{max} of 0.5 µg/mL and provides mean 97.4% inhibition of target engagement at predicted trough concentration (C_{trough}; 74.6 ng/mL). These human predicted exposures are 19.2- and 9.45-fold lower than the monkey plasma C_{max} and $AUC_{(0-t)}$ values at the NOAEL providing sufficient safety margin.

6. STUDY POPULATION

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

6.1. Inclusion Criteria

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

1. Participant must provide signed, written informed consent.
2. Male and female participants, age ≥18 years (at the time consent is obtained).
    a. Male participants are eligible to participate if they agree to the following during the study treatment period and for at least 15 days (Part 1) and 120 days (Parts 2-4) after the last dose of study treatment:
        - Refrain from donating sperm

          PLUS either:

- Be abstinent from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception/barrier: male condom and female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year as described in Appendix 6.

b. Female Participants are eligible to participate if they are not either pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a woman of childbearing potential (WOCBP)

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, as described in Appendix 6 during the study treatment period and for at least 15 days (Part 1) and 120 days (Parts 2-4) after the last dose of study treatment and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Therefore, a barrier method is also required for participants using a hormonal option (including hormonal IUD, oral contraceptive pills/ patch/ vaginal inserts, and hormonal implants) and both highly effective methods of contraception should be utilized during the treatment period and for at least 15 days (Part 1) and 120 days (Parts 2-4) after the last dose of study treatment. If a highly effective non-hormonal method is used, then only one method of contraception is required during the treatment period and for at least 15 days (Part 1) and 120 days (Parts 2-4) after the last dose of study treatment.

A WOCBP must have a negative highly sensitive pregnancy test (urine or serum) as required by local regulations) within 24 hours before the first dose of study intervention. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. If the participant hasn't been on an acceptable method of contraception for at least 2 weeks prior to start of therapy, pregnancy testing must be done weekly for the first month of treatment.

Additional requirements for pregnancy testing during and after study treatment are described in Appendix 6.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

3. Histological documentation of locally advanced, recurrent or metastatic pancreatic ductal adenocarcinoma (PDAC) (Part 1), non-small cell lung cancer (NSCLC), triple-negative breast cancer, or melanoma (Part 2) 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. Participants should have received at least one, but not more than 2 prior lines of therapy for advanced disease including both standards of care and investigational therapies. Participants 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. All participants in Parts 1 and 2 must consent to provide a fresh biopsy during screening of a primary tumor lesion or from other metastases (e.g. liver, lung, etc.), and a second biopsy after approximately 5 weeks of treatment. Please refer to Section 9.7.2.
5. Measurable disease per RECIST version 1.1. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilized as the only measurable lesion. Participants are encouraged to provide a pre-baseline scan (within 24 weeks before the baseline scan) to support exploratory investigation of tumor growth kinetics.
6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 1.
7. Life expectancy of at least 12 weeks.
8. Adequate organ function (see Table below):

System **Laboratory Test**	**Laboratory Values**
Hematologic	
ANC	≥1.5x10^9/L
Lymphocyte count	≥1000/mm^3
Hemoglobin	≥9 g/dL
Platelets	≥100x10^9/L
Hepatic	
Total bilirubin *For participants with Gilbert's Syndrome (only if direct bilirubin ≤35%)*	≤1.5xULN ≤3.0xULN
AST ALT	≤2.5xULN ≤2.5xULN
Serum Albumin	≥ 3.0 g/dL
Renal	
Serum Creatinine OR Calculated CrCl[a]	≤1.5xULN >50 mL/min

NC = 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 or per institutional standard.

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

9. QTcF <450 msec (or QTcF <480 msec for participants with bundle branch block)*

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

6.2. Exclusion Criteria

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

1. Prior treatment with the following agents:
   - Agents affecting tumor associated macrophage function or number, including but not limited to inhibitors of RIP1, RIP3, CSFR-1, CCR2, and CD40.

     NOTE: Participants treated in monotherapy with GSK3145095 may be eligible for crossover into combination therapy upon disease progression and upon discussion and approval from the GSK Medical Monitor.

   - Other anticancer therapy, including chemotherapy, targeted therapy, and biological therapy, within 14 days or 5 half-lives (from last dose of prior treatment to first dose of GSK3145095), whichever is shorter. Prior radiation therapy is permissible if at least one non-irradiated measurable lesion is available for assessment via RECIST version 1.1. No washout after palliative radiation is required.
   - Subjects who are currently taking concomitant medications known to inhibit Pgp, CYP3A4 narrow therapeutic index (NTI) substrates, or sensitive substrates of OATP1B1 and OATP1B3 transporters within 14 days or 5 half-lives (from last dose of prior treatment to first dose of GSK3145095), whichever is shorter.
   - Investigational therapy within 14 days or 5 half-lives (from last dose of prior treatment to first dose of GSK3145095), whichever is shorter.
2. Prior allogeneic or autologous bone marrow transplantation or other solid organ transplantation.
3. Toxicity from previous treatment:
   - Participants 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:
    - Participant with any other malignancy from which the participant 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. Major surgery ≤4 weeks before the first dose of study treatment. Participants must have also fully recovered from any surgery (major or minor) and/or its complications before initiating study treatment.
6. Active autoimmune disease 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.
7. 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 participant is on a stable dose.
8. Active infection (including active herpes zoster infection), known human immunodeficiency virus infection, or positive test for hepatitis B surface antigen or hepatitis C.
9. Current active liver or biliary disease (except for 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.
10. Known current drug or alcohol abuse.
11. Recent history (within the past 6 months) of acute diverticulitis, inflammatory bowel disease, intra-abdominal abscess, or gastrointestinal obstruction.
12. Receipt of any live vaccine within 4 weeks before starting study treatment.
13. Recent history of allergen desensitization therapy within 4 weeks before starting study treatment (applies to participants enrolled in Parts 2 and 3 only)
14. 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 electrocardiogram (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 beginning screening.
- Documented congestive heart failure (Class II, III, or IV) as defined by the New York Heart Association functional classification system.
- Recent (within the past 6 months) history of symptomatic pericarditis.

15. 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 GSK Medical Monitor.
16. History of (non-infectious) pneumonitis that required steroids or current pneumonitis.
17. Recent history (within 14 days) of ascites or pleural effusions requiring drainage.
18. Any serious and/or unstable pre-existing medical, psychiatric disorder, or other condition that could interfere with the participant's safety, obtaining informed consent, or compliance to the study procedures.
19. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial, unless prospective Institutional Review Board (IRB) approval (by chair or designee) is given allowing exception to this criterion for a specific participant.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

GSK3145095 will be administered under fasting conditions, with no food or antacids for 1 hour before and 2 hours after each dose. Fasting will consist of avoiding the oral ingestion of calorie-containing products; however, ingestion of water is permitted. Participants will be instructed to record the time and date of study treatments and meals in relation to dosing in the supplied GSK dosing diary.

On serial PK sampling days, participants should fast overnight (i.e., nothing by mouth apart from water and other medications for at least 8 hours) and should continue fasting until at least 2 hours after administration of the morning dose. Fasting is required for 1 hour before and 2 hours after administration of the evening dose. Also, participants will abstain from ingesting alcohol, tobacco products, caffeine- or xanthine-containing products (e.g. coffee, tea, cola drinks, chocolate) for 24 hours prior to the start of dosing until collection of the final pharmacokinetic and/or pharmacodynamic sample during each serial PK/PD session.

If a participant vomits after taking study medication, the participant should be instructed not to retake the dose and should take the next scheduled dose. Requirements for fasting before and after dosing may be modified based on emerging PK, pharmacodynamic, and

safety data. Any change in fasting requirements will be communicated to each investigator and site staff in a future protocol amendment.

Participants should abstain from consumption of Seville oranges, grapefruit, grapefruit hybrids or grapefruit juice and/or pomelos, exotic citrus fruits, from one day prior to the first dose of study treatment through the last dose of study drug.

6.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants will be assigned a new screening number.

7. TREATMENTS

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

7.1. Treatments Administered

Table 3 Study Drug Characteristics

Characteristic	Study Treatments	
Product name:	GSK3145095	Pembrolizumab
Dosage form:	Capsule or Tablet	Solution for infusion
Unit dose strength(s)	• GSK3145095 Size '1' capsule: Opaque white HPMC capsule containing 5 mg – 25 mg GSK3145095. • GSK3145095 Size '00' capsule: Opaque white HPMC capsule containing above 25 mg – 75 mg GSK3154095. • 25 mg GSK3145095 tablet: White to slightly colored round coated tablet. • 50 mg GSK3145095 tablet: White to slightly colored round coated tablet. • 200 mg GSK3145095 tablet: White to slightly colored oval-shaped coated tablet	100 mg/4 mL solution Dose: 200 mg
Route of Administration	Oral	IV infusion – 30 min[a]

Characteristic	Study Treatments	
Treatment Schedule	Day 1 – single dose only. Participants will start receiving twice daily (BID) in two equal doses starting on Day 2.	Q3W
Dosing instructions:	Participants must take their doses fasted (i.e. with no food or antacids for 1 hour before and 2 hours after each dose.) with approximately 200 mL of water. On extensive PK sampling days, participants must fast overnight and 2 hours post dose.	Make every effort to target infusion duration 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 25 to 40 min).
Manufacturer/ source of procurement	GSK	Merck

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

7.1.1. Transition of Study Treatment from Capsules to Tablets

Participants will initially receive API capsules (size "00/1", 5 mg to 75 mg) until the tablet formulation (25 mg/50 mg/200 mg) of the study treatment is manufactured and ready for distribution. The dose level at which this transition will occur will be designated the "transition" dose level. At the transition dose level, the safety of capsules compared with tablets will be assessed as follows. Three subjects will be dosed with capsules and evaluated for DLT, as described in Section 5.1.1.3. After the transition dose has met criteria for dose escalation with capsules as per the N-CRM method, an additional three participants will receive the same transition dose with tablets and will be evaluated for DLT. Once the safety of the transition dose has been established in tablets as per the N-CRM method, all participants still receiving capsules (including those receiving capsules at lower dose levels) will begin receiving tablets.

7.2. Toxicity Management Guidelines

Distinct safety management guidelines, including dose modification algorithms, are provided in Section 7.2.1 for the management of AEs associated with pembrolizumab exposure; these AEs are defined as immune-related AEs (irAEs) as the etiology may be immune mediated. General safety management guidelines for GSK3145095 are provided in Section 7.2.2. Refer to Section 3.3.1.1 for the Risk/Benefit Assessment for GSK3145095 based on preclinical data with GSK3145095, and Section 8.1 for a discussion of criteria for discontinuation of study treatment(s). Please note that in instances where the investigator is directed to permanently discontinue study treatment (single agent or combination), these instructions are mandatory as described in the sections mentioned above.

All AEs will be graded according to NCI-CTCAE (version 5.0) (http://ctep.cancer.gov). All dose modifications and the reason(s) for the dose modification must be documented in the eCRF.

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

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

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

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

Organs most frequently affected by irAEs include the skin and the colon due to their rapid regeneration rate. Less frequently affected tissues are lung, liver, and the pituitary and thyroid glands. Mild irAEs are usually treated symptomatically and do not require dosing delays or discontinuation. Higher grade and persistent lower grade irAEs typically necessitate interrupting or discontinuing treatment and administration of systemic steroids or other immunosuppressive agents (such as TNF blockers) when systemic steroids are not effective. Dose modification and toxicity management guidelines for irAEs associated with study drug(s) are provided in Table 4 .

7.2.1.1. Overview of Management of irAEs

Please refer to Table 4 for details.

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 study drug(s) has been withheld, study drug(s) can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Study drug(s) 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.

The decision to withhold or permanently discontinue study drug(s) is at the discretion of the investigator or treating physician. However, study treatment should be permanently discontinued for life-threatening adverse events. In cases where discontinuation of study treatment is not mandated in Section 8.1, continuation of study treatment may be considered on a case by case basis after discussion between the GSK medical monitor and treating physician, and after a participant has recovered to baseline from the event.

For participants with Grade 3 or 4 immune-related endocrinopathy where withholding study drug(s) is required, study drug(s) may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of Type 1 diabetes mellitus [T1DM]).

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

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

AESI (See Appendix 5) are a subset of irAEs. Such events recently reported after treatment with other immune modulatory therapy include, but are not limited to ≥Grade 2 colitis, uveitis, hepatitis, pneumonitis, ≥Grade 3 diarrhea, endocrine disorders, and specific cutaneous toxicities, as well as other events that may be immune mediated, including but not limited to demyelinating polyneuropathy, myasthenia gravis-like syndrome, non-infectious myocarditis, or non-infectious pericarditis.

For participants who experience signs or symptoms that may be consistent with an AESI, sites are strongly encouraged to immediately notify the GSK Medical Monitor of the event via email and/or phone. Documentation of events potentially qualifying for AESI should occur after discussion between the investigator and the Sponsor/Medical Monitor. Even events without clear confirmation of their immunologic etiology may qualify for AESI. Many of these events may also qualify as an SAE. See the SRM for details.

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-related AEs

Event	Grade (CTCAE v5.0)	Action: study drug(s)	Management	Follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg methylprednisolone or equivalent) followed by taper	Monitor participants for signs and symptoms of pneumonitis Evaluate participants 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 participants 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). Participants with ≥Grade 2 diarrhea suspecting colitis should consider gastrointestinal (GI) consultation and performing endoscopy to rule out colitis. Participants 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		
Aspartate and/or alanine transaminase (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)	

Event	Grade (CTCAE v5.0)	Action: study drug(s)	Management	Follow-up
			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 participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
	Grade 3 or 4	Withhold or permanently discontinue		
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)
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 to 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 1-2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

Event	Grade (CTCAE v5.0)	Action: study drug(s)	Management	Follow-up
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		

7.2.2. General Guidelines for Clinically Significant Toxicities Not Otherwise Specified

While specific guidance is provided for AESI, it is possible that other clinically significant drug-related toxicities that are not specifically described may occur and warrant dose modification. Table 5 provides general guidance for the management of clinically significant toxicities that are not otherwise specifically described in Table 4 or in subsections of Section 8.1.

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

In case toxicity does not resolve to Grade 0 to 1 within 12 weeks after the last infusion, study treatment should be permanently discontinued after consultation with the Sponsor. With investigator and Sponsor agreement, participants with a laboratory AE still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled.

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

The decision to withhold or permanently discontinue study drug(s) is at the discretion of the investigator or treating physician. However, study treatment should be permanently discontinued for life-threatening adverse events. In cases where discontinuation of study treatment is not mandated in Section 8.1, continuation of study treatment may be considered on a case by case basis after discussion between the GSK medical monitor and treating physician, and after a participant has recovered to baseline from the event.

Table 5 Dose Modification and Toxicity Management Guidelines for Other 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* • Interrupt study drug(s)[a] o Resume study drug(s) at the same dose if symptoms have improved to Grade 1 and, if applicable, steroid dose is 10 mg prednisone/day or less • Consider starting moderate dose systemic corticosteroids (e.g., 0.5 mg/kg/day of prednisone or equivalent) if clinically indicated OR if toxicity is considered pembrolizumab-related 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 study drug(s)[a] • Consult subspecialist • Administer 1-2 mg/kg/day IV methylprednisolone if clinically indicated OR if toxicity is pembrolizumab-related • Discuss with Sponsor/Medical Monitor	*Symptoms improve to ≤Grade 2:* • If applicable, continue steroids until improvement to ≤Grade 1 or baseline; taper steroids over at least 1 month, then if symptoms have improved to Grade 1 and steroid dose is 10 mg prednisone/day or less, consider resumption of study drug(s) at the next lower dose level *Symptoms ongoing:* • Discuss further management with consultant and Sponsor/Medical Monitor • Discontinue study drug permanently for Grade 3 or Grade 4 symptoms persisting for ≥ 21 days (see Section 8.1). • Consider alternative immunosuppressive therapy if indicated/applicable

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.

7.3. Method of Treatment Assignment

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

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

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

7.4. Blinding

Not applicable to this open-label study.

7.5. Preparation/Handling/Storage/Accountability

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

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

Further guidance and information for 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.

7.6. Treatment Compliance

For GSK3145095, compliance will be assessed by querying the participant at study visits and counting the number of tablets dispensed and returned. A record of the number of GSK3145095 tablets dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions, will also be recorded in the electronic case report form (eCRF).

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

7.7. Concomitant Therapy

Participants will be instructed to inform the investigator 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 will be recorded. Additionally, a complete list of all prior anticancer therapies will be recorded in the eCRF.

Medications or vaccinations specifically prohibited (see Section 7.7.2) 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 participant's primary physician. However, the decision to continue the participant on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor, and the participant.

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.

7.7.1. Permitted Medications and Non-Drug Therapies

Supportive Care: Participants 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 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.

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 while the participant is undergoing treatment on this study. Participants 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 participant has been on a stable dose for at least 4 weeks before enrollment.

Warfarin and Phenytoin: GSK3145095 at doses of ≥1600 mg daily (800 mg BID) may inhibit CYP2C9. A potential risk for drug-drug interaction (DDI) exists for CYP2C9 narrow therapeutic index (NTI) substrates such as warfarin and phenytoin. Therefore, caution is advised to monitor for higher levels of these agents when co-administered with GSK3145095 doses ≥1600 mg daily.

Acetaminophen: due to potential risk of liver toxicity when combining acetaminophen with GSK3145095, acetaminophen dosage is restricted to no more than 2g per day.

7.7.2. Prohibited Medications and Non-Drug Therapies

The following medications are prohibited before the first dose of study treatment (see Section 6.2 Exclusion Criteria for specific time requirements) and while on treatment in this study:

- Any investigational drug(s).
- Other non-study related anticancer therapy (chemotherapy, radiation therapy [unless administered palliatively], immunotherapy, biologic therapy, or hormone therapy other than for replacement).
- Live vaccines such as intra-nasal flu vaccine. Attenuated or live vaccines should not be administered to participants from 30 days prior to the first dose of GSK3145095, during the study, and for 5 half-lives plus 30 days (total 32 days) after GSK3145095 is discontinued.
    - If indicated, non-live vaccines (e.g., inactivated influenza vaccines) may be administered while receiving GSK3145095 based on a treating physician's assessment of the benefit:risk (e.g., risk of theoretical decreased responsiveness).
    - Investigators will be expected to have followed local and/or national guidelines with respect to vaccinations, including against influenza and pneumococcus.
- **Drugs that are CYP3A substrates:** Narrow therapeutic index (NTI) CYP3A4 substrates (examples include alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, and terfenadine) are prohibited. Please refer to the FDA website for more information: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm
    - **Drugs that are strong inducers of CYP3A4:** examples include avasimibe, carbamazepine, phenytoin, rifampin, and St. John's wort.
- **Drugs that are inhibitors of PgP:** examples include amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir,

propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, and verapamil. Please refer to the FDA website for more information:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table5-2

- **Drugs that are sensitive substrates of OATP1B1 and OATP1B3 transporters:** including but not limited to grazoprevir, eluxadoline, paritaprevir, rosuvastatin, pitavastatin and pravastatin

- Over the counter medications, including but not limited to, dietary supplements (such as biotin or St. John's Wort).

7.8. Treatment after the End of Study Therapy

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

Refer to Section 5.1.4 for follow-up assessments of participants for disease progression and/or survival after they permanently discontinue from study treatment.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Participants will receive study treatment for the scheduled time period (up to 2 years or 35 cycles, whichever occurs first), unless one of the following occurs earlier: disease progression (as determined by iRECIST), death, or unacceptable toxicity.

Events that may lead to permanent discontinuation of study treatment include, but are not limited to, the following:

- Major deviation(s) from the protocol
- Request of the participant or proxy (withdrawal of consent by participant or proxy)
- Investigator's discretion
- Participant is lost to follow-up
- Study is closed or terminated
- Toxicity attributed to study treatment and resulting in interruption of study treatment that does not resolve to Grade 0 to 1 within 12 weeks after the last dose of study treatment.
- Intercurrent illness that prevents further administration of study treatment(s)
- Criteria for discontinuation of study drug(s) as described in Section 7.2 have been met

- Criteria described in Section 8.1.1 (Liver Chemistry Stopping Criteria) have been met
- Criteria described in Section 8.1.2 (QTcF Stopping Criteria) have been met
- Criteria described in Section 8.1.3 (Clinical Deterioration Stopping Criteria) have been met
- Confirmed CR. A participant with a complete response (CR) requires confirmation of response via imaging at least 4 weeks after the first imaging showed a CR. Early discontinuation of GSK3145095 and/or pembrolizumab may be considered for participants 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 cycles beyond the date when the initial CR was declared.

The primary reason study treatment was permanently discontinued must be documented in the participant's medical records and eCRF.

Note: Participants who require permanent discontinuation of one of the study treatments due to toxicity in a given treatment combination must permanently discontinue both treatments (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 end-of-treatment (EOT) visit should be conducted within 30 days (+10 days) of the decision to discontinue study drug(s).

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

- New anticancer therapy is initiated
- Disease progression (as determined by iRECIST)
- Death

Participants permanently discontinuing study intervention after progression by RECIST 1.1 but prior to confirmed progression by iRECIST should be followed to confirm progression (see Table 11). Once progression has been confirmed by iRECIST, participants may continue study treatment(s) on a case by case basis if agreed by the treating investigator and Sponsor/Medical Monitor.

Once a participant has permanently discontinued from study treatment, the participant will not be allowed to be re-treated, except as described in Appendix 3 and in the following scenario. Re-treatment of participants 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 GSK3145095 ± pembrolizumab.

- The participant meets the safety parameters listed in the Inclusion/Exclusion criteria.
- The study is open.

Participants allowed to resume study therapy will do so at the same regimen, dose, and schedule that they were taking at the time of initial study treatment discontinuation. Response or progression in this Second Course Phase will not count towards the primary efficacy endpoint in this study.

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, initiation of other anticancer therapy, or death. Following PD or initiation of other anticancer therapy, participants will be contacted every 12 weeks to assess survival status.

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

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

8.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (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 criteria in this section (Table 6) are met, study treatment must be discontinued.

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

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

Please refer to Appendix 3 for guidelines on study treatment restart.

Please refer to Table 7 for liver chemistry monitoring criteria after restart.

Table 6 Liver Chemistry Stopping Criteria – Liver Stopping Event

Liver Chemistry Stopping Criteria –Liver Stopping Event	
ALT Absolute	ALT ≥5xULN
ALT Increase	ALT ≥3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1,2]	ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin)
INR[2]	ALT ≥3xULN and INR>1.5, if INR measured
Cannot Monitor	ALT ≥3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart** participant with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to Appendix 3) • If restart is **not allowed per protocol or not granted**, permanently discontinue study treatment and may continue participant in the study for any protocol specified follow up assessments **MONITORING:** **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Blood sample for pharmacokinetic (PK) analysis, obtained 24 hours after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications • Record alcohol use on the liver event alcohol intake case report form **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins) • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to

recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerized tomography [CT]) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms

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

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

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

4. Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody

5. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].

6. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Table 7 Liver Chemistry Monitoring Criteria after Study Treatment Restart

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3x ULN and ≥1.5x baseline value **but** ALT <5x ULN and <2x baseline value **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury, or hypersensitivity **and** who can be monitored weekly for 4 weeks	• Notify the medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment. • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize, or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above. • If, after 4 weeks of monitoring, ALT <3xULN and <1.5x baseline value, and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

8.1.2. QTc Stopping Criteria

The QT duration corrected for heart rate by Fridericia's formula (QTcF) *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.

The QTcF should be based on single or averaged QTcF values of triplicate ECGs obtained over a brief (e.g., 5 to 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 participant meets either of the following criteria, they must be discontinued.

- QTcF >500 msec

OR

- Change from baseline of QTcF >60 msec

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

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

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

8.1.3. Clinical Deterioration Stopping Criteria

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"). To adequately assess the antitumor effect of immunotherapeutic agents, it is reasonable to allow participants experiencing apparent progression as defined by RECIST 1.1 guidelines to continue to receive treatment until progression is confirmed at the next imaging assessment at least 4 weeks later as indicated by iRECIST guidelines. Please refer to Appendix 9 for additional details. These considerations should be balanced by clinical judgment as to whether the participant 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 participant 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 central nervous system (CNS) metastases
- Any setting where the initiation of new antineoplastic therapy has been deemed beneficial to the participant even in the absence of any such documented clinical events

8.2. Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

Refer to the Schedules of Activities (Section 2) for data to be collected at the time study discontinuation and any further evaluations that need to be completed.

8.3. Lost to Follow Up

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

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

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

9. STUDY ASSESSMENTS AND PROCEDURES

9.1. Study Visits

9.1.1. Visit Types

Screening: All screening assessments should be completed within 21 days prior to dosing start. Pregnancy testing must be completed 7 days prior to dosing start and checked again on Day 1 within 24 hours before the first dose of study drug. Screening assessments can be done over multiple office visits as needed.

Treatment: While on study drug(s), participants should have office visits per the Schedule of Activities (Section 2) and within the visit windows specified in Section 9.1.2. One cycle is 21 days in length.

End of Treatment (EOT): The end-of-treatment (EOT) visit should be conducted within 30 days (+10 days) of the decision to discontinue study drug(s).

Follow up (see also Section 8.1 and Schedules of Activities [Section 2]):

- Response Follow-up (RFU): If study treatment has been permanently discontinued in the absence of progressive disease, participants still in the study must have a RFU office visit every 12 weeks until disease progression, initiation of another anticancer treatment, or death.
- AEs and Concomitant Medications: All AEs and concurrent medications will be collected until at least 30 days after the last dose of study treatment (i.e., AEs and Concomitant Medications: All AEs and concurrent medications will be collected from study day 1 until at least 30 days after the last dose of study treatment (i.e., at least through the EOT visit). AESIs will be collected starting day 1, while SAEs will be recorded from the time a participant consents to participate in the study. 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 anticancer 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.
- Survival Follow-up (SFU): The SFU telephone call should be completed every 12 weeks after documented disease progression or after initiation of another anticancer treatment. All participants still in the study should be contacted every 12 weeks (±2 weeks) until death occurs.

9.1.2. Visit Windows

All screening assessments should be completed within 21 days prior to dosing start. Pregnancy testing for screening must be completed 7 days prior to dosing start and checked again on Day 1 within 24 hours before the first dose of study drug.

Week 1: Visits for Week 1 Days 1 and 2 must be performed on the day indicated. Telephone call on Week 1 Day 3 must be performed on the day indicated.

Week 2 through Week 7: Based on participant and clinic schedule, assessments can be ±3 days.

The Week 3 Day 1 PK collection is timed to permit evaluation of GSK3145095 PK at steady-state dosing. If a participant is not receiving drug on Week 3 Day 1 (either as a consequence of a planned drug holiday or due to toxicity), then this PK collection should be rescheduled for a later timepoint when the participant is again being dosed at steady state, and the alternate collection date noted in the eCRF.

Visits at Week 8 and beyond will be allowed to have a ±3-days window.

The EOT visit should be completed within 30 days (+10 days) after the last dose of study drug(s).

9.2. Assessments

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Schedules of Activities (Section 2).

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

The timing and number of planned study assessments may be altered during 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 Sponsor study 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.

Protocol waivers or exemptions are not allowed except for immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Schedules of Activities (Section 2), are essential and required for study conduct.

9.2.1. Screening and Critical Baseline Assessments

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

9.2.2. 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 6.

Procedures conducted as part of the participant's routine clinical management (e.g., blood counts, ECG, and scans) and obtained prior to signing of the ICF may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe specified by the Schedules of Activities (Section 2).

9.2.2.1. Critical Baseline Assessments

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

9.2.3. Baseline Documentation of Target and Non-Target Lesions

All baseline lesion assessments must be performed within 21 days before the first dose. Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected based on their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

- 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 short axis ≥10 mm but <15 mm are considered nonmeasurable-.
- Pathological lymph nodes with short axis ≥15 mm 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.
- 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.

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.

The following are required at baseline: A CT scan with contrast of the chest, abdomen, and pelvis, and other areas as indicated by the participant's underlying disease, and clinical disease assessment for palpable lesions. For participants 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 participants for whom a CT scan is contraindicated due to allergy to contrast agent, 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 were met initially 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).

9.2.4. Disease Assessments

A participant'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 (Eisenhauer, 2009) and iRECIST (Seymour, 2017). A decision to discontinue treatment due to disease progression will be based upon iRECIST and the primary endpoint analysis will use RECIST. Scans will be collected and stored to allow for the option of central radiologic audit or review. See Appendix 9 for more details.

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 21 days prior to the first dose of GSK3145095. Post-baseline disease assessments must be performed after the mandatory biopsies per the Schedule of Activities Section 2).

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.

Participants 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 first demonstrated.

Participants 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. See Appendix 9 for more details. If the last radiographic assessment was more than 12 weeks prior to the participant's withdrawal from study and PD has not been documented, a disease assessment should be obtained at the time of withdrawal from the study.

To ensure comparability between the baseline and subsequent assessments, the same method of assessment and the same technique will be used when assessing response throughout the study.

9.3. Adverse Events

The definitions of an adverse event (AE) or serious adverse event (SAE) can be found in Appendix 4.

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

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

All AEs and concurrent medications will be collected until at least 30 days after the last dose of study treatment (i.e., through the EOT visit). 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 anticancer 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.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF.

All AESIs and SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 4.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating, and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 4.

9.3.2. Method of Detecting AEs and SAEs

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

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

9.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AESIs (defined in Appendix 5), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.3.4. Regulatory Reporting Requirements for SAEs

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to all investigators as necessary.

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

9.3.5. Cardiovascular and Death Events

For any cardiovascular events (Table 8) 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 the 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.

Table 8 Definition of Cardiovascular Event

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

9.3.6. Pregnancy

Details of all pregnancies in female participants and female partners of male participants 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 must inform GSK within 24 hours of learning of the pregnancy and must follow the procedures outlined in Appendix 6.

9.4. Treatment of Overdose

9.4.1. GSK3145095 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 participant for AEs/SAEs and laboratory abnormalities for at least 130 days.

- Obtain a plasma sample for PK analysis within 24 hours 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 participant.

There is no specific antidote for overdose with GSK3145095. In the event of a suspected overdose, it is recommended that the appropriate supportive clinical care should be instituted, as dictated by the participant's clinical status.

9.4.2. Pembrolizumab Overdose

An overdose of pembrolizumab will be defined as ≥1000 mg (5 times the dose) of pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant 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, must be reported within 5 days to GSK as an AESI, either by electronic media or paper.

9.5. Other Safety Assessments

Planned time points for all other safety assessments are provided in the Schedules of Activities (Section 2).

9.5.1. Physical Examinations and Performance Status Evaluations

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.

All physical examinations should also include an evaluation of organ systems described in Section 3.3.1, including an assessment for lymphadenopathy.

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

For participants with melanoma, 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 all physical exams per the Schedules of Activities (Section 2) or more frequently as necessitated. Wherever possible, the same physician should perform these examinations. Follow-up skin examinations by a referral dermatologist should be conducted if clinically indicated.

Participant performance status will be assessed using the ECOG scale (Appendix 10) as specified in the Schedules of Activities (Section 2).

9.5.2. Vital Signs

Vital sign measurements to be measured in semi-supine position after 5 minutes rest will include temperature, systolic and diastolic blood pressure, and pulse rate.

Vital signs will be measured more frequently if warranted by the clinical condition of the participant. On days on which vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.

9.5.3. Electrocardiograms

The 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 8.1.2 for QTcF stopping criteria and additional QTcF readings that may be necessary.

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

The ECG measurements will be performed in triplicate at specified times (Section 2, including footnotes), and will coincide with PK assessments as specified in the Schedules of Activities.

9.5.4. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 9 , must be conducted in accordance with the SRM and the Schedule of Activities (Section 2). Laboratory requisition forms must be completed and samples must be clearly labeled with the participant number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the SRM. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

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

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

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

- Hematology
- Clinical Chemistry, including cortisol
- 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.

Table 9 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[b], free T4, free T3, cortisol[b]
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 8.1.1.

b. At screening only

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.

9.6. Pharmacokinetics

9.6.1. Blood Sample Collection

Blood samples for PK analysis of GSK3145095 and pembrolizumab will be collected at the time points described in Section 2, Schedule of Activities. 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.

The sampling scheme is based on a BID dosing regimen. The number and sampling times may be adjusted once the human PK data are available.

Blood samples (1 mL) for analysis of plasma GSK3145095 concentrations will be collected from all participants at the times indicated in Section 2. In Part 1, an additional blood sample (2 mL) will be collected for metabolite profiling at the timepoints described in Section 2, as well as an additional blood sample (1 mL) for analysis of 4β-hydroxycholesterol and cholesterol as a marker for CYP3A4 activity at the timepoints described in Section 2.

Blood samples (approximately 3 mL) for possible analysis of pembrolizumab concentrations (blood processing details to be included in the SRM) will be collected from all participants at the times indicated in Section 2.

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

Permissible time windows for PK sampling are as follows:

- Up to ≤1 hour post-dose: ±5 minutes
- More than 1 hour but <24 hours post-dose: ±15 minutes
- More than 24 hours post-dose: ±2 hour and before the next dose administration.

9.6.2. Blood Sample Processing for GSK3145095

Blood will be collected into EDTA tubes and processed to plasma for PK analysis of GSK3145095 at the time points indicated in Section 2. The actual date and time (24-hour clock time) of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Blood will be collected into EDTA tubes and processed to plasma for 4β-hydroxycholesterol and cholesterol. This will be collected at the time points indicated in Section 2. The actual date and time of each blood sample collection will be recorded.

Details of blood sample collection, processing, storage and shipping procedures are provided in the SRM.

9.6.3. Sample Analysis

Plasma analysis will be performed under the control of Platform Technology and Science In Vitro/In Vivo Translation (PTS IVIVT) and Third Party Resource, GlaxoSmithKline. Concentrations of GSK3145095 will be determined in plasma samples using the currently approved bioanalytical methodology. The original raw data, report and any amendments will be held under the control of the US/UK GSK R&D GLP archives, where they will be managed in accordance with the applicable GSK procedures, including GSK Global Records Retention Schedule.

Once the plasma sample has been analyzed for GSK3145095, any remaining plasma sample may be analyzed for any compound-related material and the results may be reported as part of this study or under a separate PTS GlaxoSmithKline protocol.

Serum bioanalysis for pembrolizumab will be performed under the control of Merck Sharp & Dohme Corp the details of which will be included in the SRM. Concentrations of pembrolizumab may be determined in select PK serum samples, using the currently approved bioanalytical methodology. The original raw data, report and any amendments will be held under the control of Merck Sharp & Dohme Corp. Once the serum has been analyzed for pembrolizumab, any remaining sample may be analyzed for other compound-related metabolites and the results reported under a separate Merck Sharp & Dohme protocol.

9.6.4. Tumor Tissue Biopsy for Pharmacokinetic Assay

See Section 9.7.2 for details on tumor tissue biopsies. Select tumor tissue biopsy samples may be analyzed to measure the concentration of GSK3145095 in the tumor tissue. Information on processing the biopsies for the tumor tissue pharmacokinetic assay will be provided in the SRM.

Once the tumor tissue has been analyzed for GSK3145095, any remaining tissue may be analyzed for other compound-related material and the results reported under a separate

Platform Technology and Science In Vitro/In Vivo Translation (PTS IVIVT), GlaxoSmithKline protocol.

9.6.5. Tissue Sample Analysis

Tumor tissue biopsy sample analysis will be performed under the control of PTS-IVIVT, GlaxoSmithKline. An exploratory analysis will be conducted to assess concentrations of GSK3145095 in tumor tissue if available.

9.6.6. Assessment of CYP3A4 Enzyme Activity

9.6.6.1. Plasma Analysis

Plasma derived from select PK blood samples in Part 1, will be analyzed for 4βhydroxycholesterol and cholesterol as a potential *in vivo* marker of CYP3A4 enzyme activity. Samples collected pre-treatment and at steady-state will be compared to evaluate this potential marker.

Details on CYP3A4 enzyme activity marker plasma sample collection, processing, storage and shipping procedures are provided in the SRM.

Baseline, Day 15, and Day 36 plasma samples will be analyzed using a validated, specific, and sensitive liquid chromatography–mass spectrometry (LC-MS/MS) method to determine concentrations of 4βhydroxycholesterol and total cholesterol. A comparison will be made between the ratio of 4βhydroxycholesterol: cholesterol at baseline and on Days 15 and 36 to assess potential changes in CYP3A4 enzyme activity following GSK3145095 treatment.

Analysis will be performed at a bioanalytical site (to be detailed in the SRM) under the control of PTS-IVIVT and Third Party Resource, GlaxoSmithKline.

9.6.6.2. Urine Sample Collection and Analysis

Urine samples for analysis of GSK3145095 and any metabolites will be collected at the time points listed in the Schedules of Activities in Section 2.

Prior to dosing on Day 1, each participant will be instructed to void their bladder and no more than 40 mL of this urine sample will be retained as a control. Urine samples will be collected during the first 24 hours after dosing (a list of time points may be found in the Schedule of Activities). Urine samples will be shipped to GSK and may be analyzed for GSK3145095 and any compound-related metabolites. Results will be reported under a separate PTS GlaxoSmithKline protocol. Processing, storage and shipping procedures are provided in the SRM. The original urine raw data, report and any amendments will be held under the control of GSK.

9.7. Pharmacodynamics

9.7.1. Blood Biomarkers

Blood samples will be collected to evaluate peripheral PD at the time points indicated in the Schedule of Assessment tables in Section 2.

Peripheral PD measurements may include, but are not limited to, target engagement of the RIP1 protein by compound, detection of circulating tumor DNA (ctDNA) using genetic analysis techniques, detection of circulating tumor antigens CA19-9 and CEA, and detection of circulating cytokines and chemokines in plasma or serum.

Blood samples and PBMCs may also be collected and used or stored for other exploratory analyses. These include, but are not limited to, flow cytometry to determine effects of GSK3145095 on peripheral immune cell numbers and phenotype or by using genetic analysis techniques to evaluate genomic or transcriptomic signatures (using isolated DNA or RNA). Plasma and serum samples may also be used for analysis of circulating factors including, but not limited to, tumor-derived exosomes or serum proteomic signature. Refer to SRM for full details on PD measurements.

With participant consent and agreement by the PI and GSK Medical Monitor, additional PD samples may be obtained during the study. Examples of when this may be considered is at subsequent tumor imaging scans or 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.

9.7.2. Tumor Tissue

Participants in Part 1 and Part 2 are required to provide at least two fresh biopsies from their primary tumor or from other metastases (e.g. liver, lung, etc). One fresh biopsy must be obtained before beginning study treatment, and a second must be obtained at the week 6 visit (i.e., after completion of 5 weeks of treatment), which must be collected 1 week prior to tumor imaging. Additional optional fresh biopsies may be obtained during the study, as described below. All participants will be encouraged to provide an archival tumor sample prior to starting study drug. Fresh biopsies will be evaluated by IHC for expression of phenotypic and functional immune cell markers on tumor infiltrating myeloid cells and lymphocytes 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. Inhibition of RIP-1 pathway activation by IHC may be assessed. Gene expression signatures in pre- and on-treatment biopsies will be evaluated for changes using genetic analysis techniques of RNA. Additionally, tumor tissue may be sequenced to assess T-cell receptor diversity or tumor mutation burden as well as evaluated for any DNA/RNA/protein changes correlating with response. Archival tissue may also be assessed as described above.

It is strongly encouraged that paired fresh pre- and on-treatment tumor biopsies are obtained from the same tumor lesion. If it is not possible to obtain the on-treatment biopsy from the same lesion the pre-treatment biopsy was obtained from, it is strongly

encouraged that the on-treatment biopsy is obtained from the same organ as the pre-treatment biopsy. The tumor site chosen for biopsy must not be the one used as an indicator lesion for assessment of disease unless otherwise discussed and agreed upon with the GSK medical monitor.

With participant 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, including but not limited to measurements of protein changes, genetic analysis techniques of DNA or RNA, or percent target engagement of RIP1 by compound. 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.

9.8. Genetics

Information regarding genetic research is included in Appendix 7.

9.9. Immunogenicity Assessments

Serum samples may be collected and tested for the presence of antibodies that bind to pembrolizumab, or other select anti-cancer agents administered in combination with GSK3145095, as described in the Schedule of Activities (Section 2). 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 participant withdrawing from the study, blood samples should be taken from the participant for immunogenicity testing at the time of the event and again 30 days, 12 weeks, and 24 weeks after. For participants who 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.

9.10. Health-Related Quality of Life

To further evaluate disease and treatment related symptoms and associated impacts on function and health-related quality of life, participants will participate in qualitative interviews (Parts 3 and 4) conducted via telephone. The interview will be conducted by a trained interviewer in the participant's native language and will be audio recorded for

transcription and analysis. Please refer to the SRM for further details on these assessments.

The telephone interview should be conducted within 21 days following completion of Weeks 12 and 52 and/or the EOT Visit, unless the participant has already completed an interview within the prior 30 days.

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Determination

The planned sample size for each part of the study was chosen to allow adequate characterization of safety, clinical activity, PK, and pharmacodynamic profile based on the objectives of each part of the study.

For dose escalation, the total sample size will depend on the number needed to adequately characterize the DLT profile and determine the MTD.

For the dose expansion phase, approximately 30 participants will be targeted for each tumor type and treatment combination.

10.2. Populations for Analyses

The All-Treated Population is defined as all participants who receive at least one dose of GSK3145095. Safety and anticancer activity will be evaluated based on this analysis population.

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

The Pharmacodynamic Population will consist of all participants from the All-Treated Population who contribute Pharmacodynamic/Biomarker sample(s).

10.3. Hypotheses

10.3.1. Dose Escalation (GSK3145095)

No formal statistical hypothesis will be tested in the dose escalation phase.

10.3.2. Dose Expansion (GSK3145095)

The antitumor activity of GSK3145095 in combination with pembrolizumab or another anticancer agent will be tested using the predictive probability design by Lee and Liu (Lee, 2008). The null and alternative hypotheses are as follows:

H_0: $p \leq P_0$

H_A: $p > P_A$.

The response rates to be tested, P_0 and P_A ($P_0 < P_A$) will depend on the tumor type chosen for the expansion part as well as the choice of anticancer agent used in combination with GSK3145095.

10.4. Statistical Considerations for Dose Escalation

The NCRM dose-escalation procedure will be implemented for monotherapy and the mTPI procedure will be used for combination therapy.

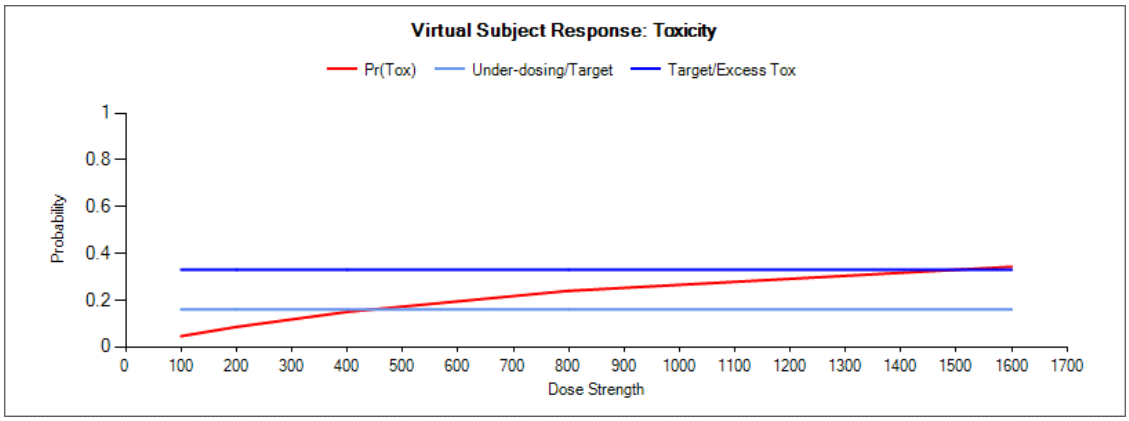
10.4.1. NCRM for Monotherapy Dose Escalation

Dose escalation for monotherapy will use NCRM. This method utilizes a 2-parameter logistic model, with parameters α and β, to describe the relationship between DLT and dose (100, 200, 400, 800, and 1600 mg per day). NCRM uses a Bayesian framework where the parameters α and β are assumed to have a bivariate normal prior distribution.

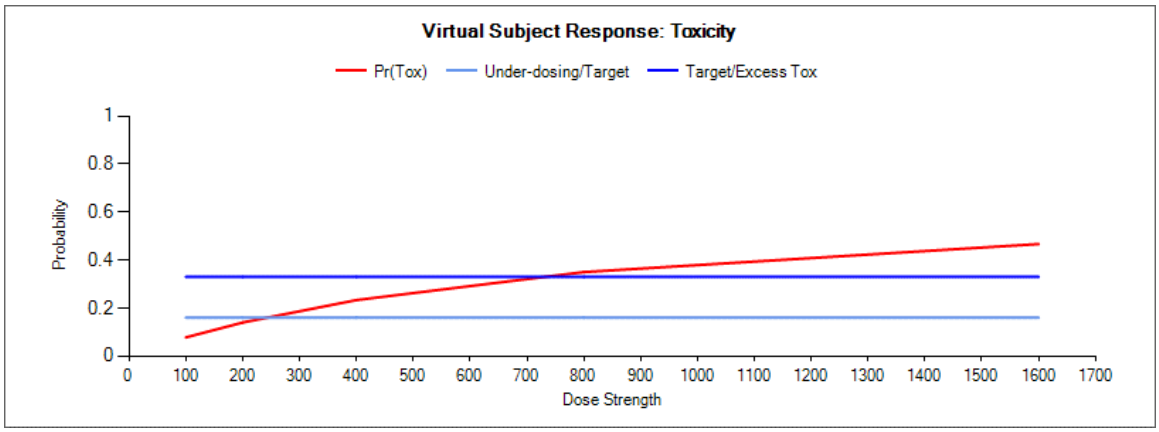
Using the FACTS software version 6.1, the parameters (mean[sd]) of the bivariate normal prior for (α, ln(β)) were derived, using the 'Scenarios' option, as: α = -1.7451[1.5665], ln(β) = -0.1671[0.2087], and correlation ρ = -0.969, with median dose as reference and independent variable as log(dose/reference dose)

Simulations were conducted to understand the statistical properties of NCRM in this study, including the average sample size and percentage of times each planned dose is selected as MTD. Three scenarios were considered for this simulation: scenario 1 representing toxicity at high dose has toxicity based on E_{max} with ED_{50}=1200 mg/day and maximum toxicity of 0.60; scenario 2 representing toxicity at middle dose has toxicity based on E_{max} with ED_{50}=800 mg/day and maximum toxicity of 0.70; scenario 3 representing toxicity at low dose has toxicity based on E_{max} with ED_{50}=200 mg/day and maximum toxicity of 0.75; scenario 4 representing no toxicity up to the high dose has toxicity based on logistic model with ED_{50}=1600 mg/day and maximum toxicity of 0.60. In scenario 1, the DLT rate exceeds 0.33 (the upper limit of the target) at high dose starting around 1500 mg/day. In scenario 2, the DLT rate exceeds 0.33 starting around 800 mg/day. In scenario 3, the DLT rate exceeds 0.33 at low dose starting around 150 mg/day. The toxicity curves for these 4 scenarios are shown below.

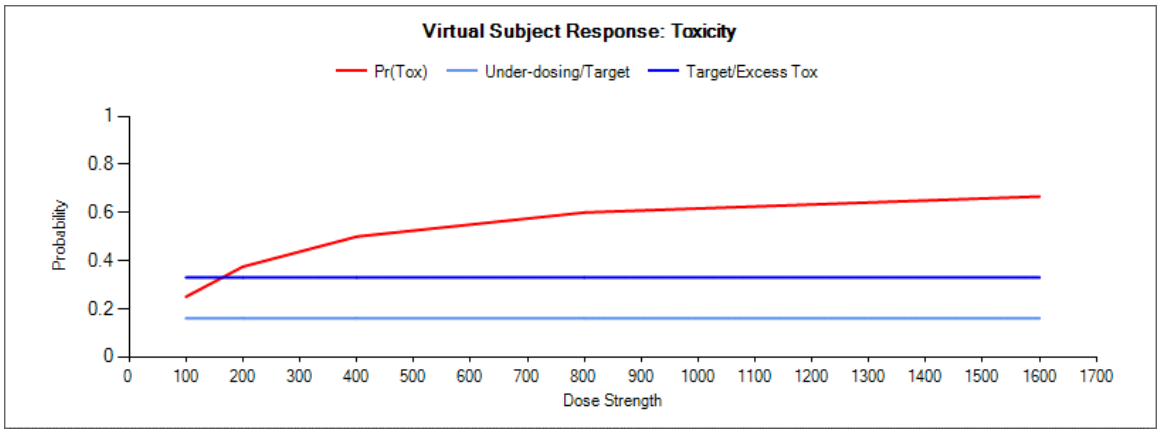
Scenario 1: Toxic at high dose.



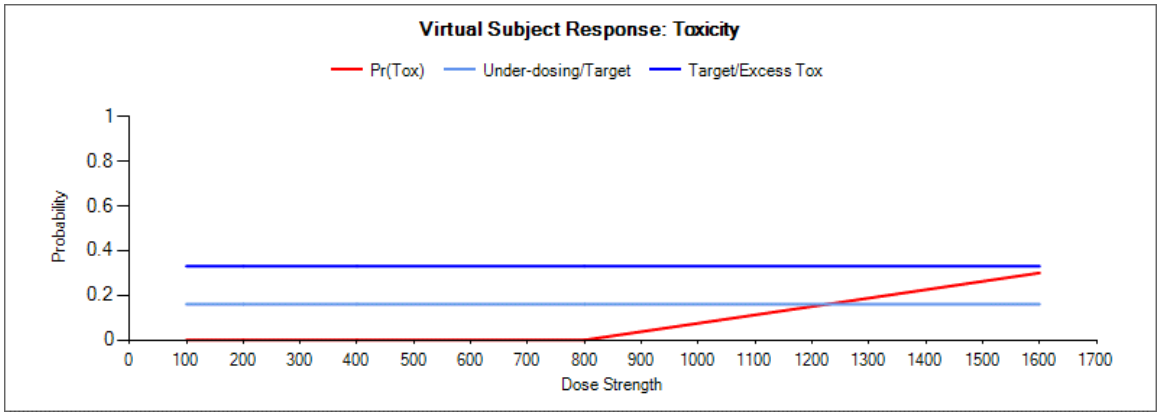
Scenario 2: Toxic at middle dose.



Scenario 3: Toxic at low dose.



Scenario 4: No toxicity up to high dose.



For each of these scenarios, 10,000 clinical trials were simulated and the table below shows the percent of times the various dose levels are selected as MTD in these simulations.

Simulation Results Under Various Scenarios:								
	Scenario 1 Toxic at high dose.		Scenario 2 Toxic at middle dose.		Scenario 3 Toxic at low dose.		Scenario 4 No toxicity up to the high dose.	
Dose (mg/day)	True DLT Rate	Percent of Trials Selecting Dose as MTD	True DLT Rate	Percent of Trials Selecting Dose as MTD	True DLT Rate	Percent of Trials Selecting Dose as MTD	True DLT Rate	Percent of Trials Selecting Dose as MTD
100	0.05	2.3%	0.08	8.7%	0.25	80.5%	0	0.0%
200	0.09	4.2%	0.14	19.2%	0.38	16.9%	0	0.0%
400	0.15	28.2%	0.23	45.8%	0.50	2.5%	0	0.0%
800	0.24	46.0%	0.35	23.4%	0.60	0.1%	0	19.6%
1600	0.34	19.3%	0.47	3.0%	0.67	0.0%	0.30	80.4%

Based on these simulations, the average sample sizes are 24, 23, 14, and 24 for scenarios 1, 2, 3, and 4, respectively, assuming the maximum number of cohorts is 8 and each cohort has 3 subjects.

10.4.2. mTPI for Combination Therapy Dose Escalation

The number of dose levels that will be used for dose escalation for combination therapy is expected to be fewer than the number of levels in monotherapy. This is the key rationale for the choice of mTPI rather than NCRM for dose escalation for combination therapy.

10.5. Statistical Considerations for Dose Expansion

Up to 30 participants per cohort (tumor type and treatment combination) will be targeted for the dose expansion phase. Futility assessment will be performed after approximately 10 participants and then with each additional participant, allowing the study to stop for futility but not efficacy. The type 1 error rate, power and other statistical properties will depend on the rates to be tested. Dose-escalation participants who took the same treatment (dose and anticancer agent combination) selected for the expansion phase will be included in the dose expansion analysis.

10.6. Statistical Analyses

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

(RAP). Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report.

10.6.1. Efficacy Analyses

The All Treated Population will be used for anticancer activity analyses. Since this is a Phase I/II 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.

RECIST v1.1 guidelines are used for disease measurements. iRECIST will be used by the Investigator to assess tumor response and progression and make treatment decisions.

A description of the adaptations and iRECIST process is provided in Appendix 9 and Seymour, 2017. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 11 and illustrated as a flowchart in Figure 3 in Appendix 9.

If the data warrant, ORR, PFS and OS will be calculated and listed for each participant.

ORR is defined as the percentage of participants with a best overall confirmed CR or PR at any time as per disease-specific criteria (refer to Appendix 9). DCR is defined as the percentage of participants with a confirmed CR + PR at any time, plus SD ≥12 weeks.

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 participant received subsequent anti-cancer therapy prior to the date of documented events, PFS will be censored at the last adequate assessment (e.g., assessment where visit level response is CR, PR, or SD) prior to the initiation of therapy. Otherwise, if the participant does not have a documented date of event, PFS will be censored at the date of the last adequate assessment.

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 participant 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.

10.6.2. Safety Analyses

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

10.6.2.1. Extent of Exposure

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

10.6.2.2. Adverse Events

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

Events will be summarized by frequency and proportion of total participants, by system organ class and preferred term. Separate summaries will be given for all AEs, treatment-related AEs, SAEs and AEs leading to discontinuation of study treatment. AEs, if listed in the NCI-CTCAE (version 5.0) will be summarized by the maximum grade. Otherwise, the AEs will be summarized by maximum intensity.

Characteristics (e.g., number of occurrences, action taken, grade, etc) of AESI will be summarized separately.

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

10.6.2.3. Clinical Laboratory Evaluations

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

10.6.2.4. 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.

10.6.3. Other Analyses

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

10.6.3.1. Pharmacokinetic Parameters and Analyses

Bioanalysis of GSK3145095 and pembrolizumab will be the responsibility of GSK and Merck Sharp and Dohme Corp respectively.

PK analysis of drug concentration-time data of both GSK3145095 and pembrolizumab 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:

- C_{max}
- time to C_{max} (t_{max})
- C_{min}
- area under the plasma concentration-time curve ($AUC_{(0-t)}$, $AUC_{(0-\tau)}$ [repeat dosing] and/or $AUC_{(0-\infty)}$ [single dose])

- apparent terminal phase elimination rate constant (λ_z) (single dose)
- apparent terminal phase half-life ($t_{½}$) (single dose)
- systemic clearance of parent drug (CL/F)
- volume of distribution (V/F)

- time invariance (TI) and accumulation ratio (AR) as calculated by the following equations:

$$TI = \frac{AUC(0-\tau), Day15}{AUC(0-\infty), Day1}$$

$$AR = \frac{AUC(0-\tau), Day15}{AUC(0-\tau), Day1}$$

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

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

Cmax and AUC (AUC(0-∞), single dose, and AUC(0-τ), steady state) will be plotted as a function of the dose administered and data from all available Parts may be combined. If more than 2 dose levels are evaluated, dose proportionality of AUC and Cmax for GSK3145095 following single dose administration and AUC(0-τ) and Cmax following repeat dose administration will be assessed graphically and using the power model as described below:

log (pharmacokinetic parameter) = a + b * log(dose)

where a is the intercept and b is the slope.

The power model will be fitted by restricted maximum likelihood (REML) using SAS Proc Mixed. Both the intercept and slope will be fitted as fixed effects. If there is sufficient data, the model may also be fit with the intercept and/or slope as random effects depending on the ability of the model to converge and on estimation of variance covariance matrix. The mean slope and corresponding 90% confidence interval will be estimated from the power model.

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

10.6.3.2. 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.

In addition, exposure-response relationship between GSK3145095 exposure (e.g. dose, concentration, Cmax or AUC) and clinical activity or safety including change from baseline QTcF may be explored.

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

10.6.3.3. Translational Research Analyses

The results of translational research investigations may be reported in 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.

10.6.3.4. 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.

10.6.3.5. Longitudinal Tumor Size Modeling

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 participant characteristics, such as dose group, GSK3145095 exposure, or biomarkers.

10.6.3.6. Pharmacogenetic Analyses

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

10.6.4. Interim Analyses

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 10.4.

For each dose expansion cohort, continuous assessment of futility and safety will be performed after approximately 10 participants with available unconfirmed Overall Response data. Safety and efficacy will be monitored by study investigators and staff, as well as GSK team members (including the GSK medical monitor, safety physician,

statistician, pharmacokineticist, biomarker scientist, and other staff) following the futility rules for expansion cohorts described in Section 10.4.1.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ACT	Adoptive cell transfer
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)
iRECIST	modified RECIST 1.1 for immune-based therapeutics
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
µg	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 microsatellite instability
MTD	Maximum tolerated dose
mTPI	modified Toxicity Probability Interval
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NK	Natural killer
NOAEL	No observed adverse effect level
NCRM	Neuenschwander Continual Reassessment Method
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
TCR	T-cell receptor
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
Keytruda

12.2. Appendix 2: Study Governance Considerations

12.2.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

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

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

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

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable.
- 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 participant 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 participants 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.

12.2.3. Dose Escalation Committee

The Dose Escalation Committee (DEC) will make the decision to proceed to the next dose level of GSK3358699 at the end of each monotherapy and combination therapy cohort in Parts 1 and 2; along with making the decision to move into Part 2 of the study.

The decision will be based on:

- All available data (including, but not limited to PK, PD, safety, dose reductions/delays) from a minimum of 3 participants who have received a dose of GSK3145095 at the current dose level and have been followed for at least 48 hours post dose.
- All available data accumulated from preceding dose levels.

Safety stopping criteria will be strictly applied. Details of these criteria are in Section 8.

Although the escalation of the GSK3145095 monotherapy dose will be guided by the NCRM and escalation of the GSK3145095 dose in combination with pembrolizumab will be guided by the mTPI, the DEC can override this recommendation.

DEC members and requirements are provided in the Dose Escalation Plan.

12.2.4. 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.

12.2.5. 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.

12.2.6. 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.

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

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

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

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

12.3. Appendix 3: Liver Safety and Study Treatment Restart Guidelines

If a participant meets liver chemistry stopping criteria detailed in Section 8.1.1, do not restart/ participant with study treatment unless:

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

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

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 participant must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.

- Participants approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.

- If after study treatment re-start, participant meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.

- GSK Medical Monitor, and the Ethics Committee or IRB as required, must be informed of the participant's outcome following study treatment restart.

- GSK to be notified of any AEs, as per Appendix 4.

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

Definition of AE

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

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

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

normal life functions.

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording AEs and SAEs

AE and SAE Recording

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

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator may be 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 CRF. • The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

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 v5.0.:

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

Reporting of SAEs to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable 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 participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information to the Medical Monitor by telephone. • Contacts for SAE reporting can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.5. Appendix 5: Adverse Events of Special Interest

The list of terms and reporting requirements for GSK AESI are provided below. These are selected SAEs and non-serious AEs that **must be reported to GSK within 24 hours** regardless of relationship to study treatment. Any event that meets the criteria described below must be reported within 24 hours 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.

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 9.4.2, 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.

12.6. Appendix 6: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

    Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male participants

Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following from first administration of study drug until 15 days (Part 1) and 120 days (Parts 2-4) after the last administration of study drug:

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

- Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 10 when having penile-vaginal intercourse with a WOCBP.

Also, men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration from first administration of study drug until 15 days (Part 1) and 120 days (Parts 2-4) after the last administration of study drug.

In addition, male participants must refrain from donating sperm for duration of study and for 15 days (Part 1) and 120 days (Parts 2-4) after the last dose.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 10. Female participants of childbearing potential must use highly effective methods of contraception and avoid conception for defined periods of time before first administration of study drug until 15 days (Part 1) and 120 days (Parts 2-4) after the last administration of study drug.

Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Therefore, a barrier method is also required for participants using a hormonal option (including hormonal IUD, oral contraceptive pills/ patch/ vaginal inserts, and hormonal implants) and both highly effective methods of contraception should be utilized during the treatment period and for at least 15 days (Part 1) and 120 days (Parts 2-4) after the last dose of study treatment. If a highly effective non-hormonal method is used, then only one method of contraception is required during the treatment period and for at least 15 days (Part 1) and 120 days (Parts 2-4) after the last dose of study treatment

In addition, women must agree not to donate eggs (ova, oocytes) for the purposes of reproduction during the treatment period and for at least 15 days (Part 1) and 120 days (Parts 2-4) after the last dose of study treatment.

Table 10 Highly Effective Contraceptive Methods

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

NOTES:

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

b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Therefore, a barrier method is also required for participants using a hormonal option and both highly effective methods of contraception should be utilized during the treatment period and for at least 15 days (Part 1) and 120 days (Parts 2-4) after the last dose of study treatment. If a highly effective non-hormonal method is used, then only one method of contraception is required during the treatment period and for at least 15 days (Part 1) and 120 days (Parts 2-4) after the last dose of study treatment.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive pregnancy test (urine or serum) as required by local regulations) within 24 hours before the first dose of study treatment. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

Additional pregnancy testing should be performed per Schedules of Activities (Section 2).

Pregnancy testing will be performed every 3 weeks and whenever a menstrual cycle is missed or when pregnancy is otherwise suspected. If the participant hasn't been on an

acceptable method of contraception for at least 2 weeks prior to start of therapy, pregnancy testing must be done weekly for the first month of treatment.

Pregnancy testing (serum and/or urine β-hCG) will be performed by the certified local laboratory.

Action to be taken if pregnancy occurs

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator will be reported to GSK. 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.

Action to be taken if pregnancy occurs in a female partner of a male study participant

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

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

12.7. Appendix 7: Genetics

Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.

Genetic Research Objectives and Analyses

The objectives of the genetic research are as follows:

- To investigate the relationship between genetic variants and:

  Response to medicine, including GSK3145095 or pembrolizumab or any concomitant medicines;

  PDAC or other selected solid tumors, susceptibility, severity, progression, and related conditions

- To develop tests/assays including diagnostic tests) related to GSK3145095 and PDAC and other selected solid tumors.

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.

Note that the analyses may be part of a multi-study assessment of genetic factors involved in the response of PDAC and other selected solid tumors to GSK3145095 or RIP1 inhibitors.

Study Population

Any participant who is enrolled in the study (except for those who have received an allogeneic bone marrow transplant) may participate in the genetic research component of the study.

Study Assessments and Procedures

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

- A 6 mL blood sample will be taken for deoxyribonucleic acid (DNA) extraction. A blood sample is collected at the baseline visit, after the participant has 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 participant by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

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

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

Informed Consent

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

Participant Withdrawal from Study

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

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

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

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

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

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the participant does not meet the entry criteria for participation in the study, then the investigator should instruct the participant that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Participant's Genetic Data

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

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the participant, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the participant's medical care at the time of the study, unless required by law. This is because 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: NYHA Functional Classification System for Heart Failure

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

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

12.9. Appendix 9: Guidelines for Assessment of Disease, Disease Progression and Response Criteria – adapted from RECIST version 1.1

12.9.1. Assessment Guidelines by RECIST 1.1

Please note the following:

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion. Contrast agents must be used in accordance with the Image Acquisition Guidelines.
- All measurements 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 5 mm 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.

Guidelines for Evaluation of Disease

Measurable and Non-measurable Definitions

Measurable lesion:

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

- ≥10 mm with MRI or CT when the scan slice thickness is no greater than 5 mm. If the slice thickness is greater than 5 mm, the minimum size of a measurable lesion must be at least double the slice thickness (e.g., if the slice thickness is 10 mm, a measurable lesion must be ≥20 mm).
- ≥10 mm caliper/ruler measurement by clinical exam or medical photography.
- ≥20 mm by chest X-ray.
- Additionally, lymph nodes can be considered pathologically enlarged and measurable if ≥15 mm in the short axis when assessed by CT or MRI (slice thickness recommended to be no more than 5 mm). At baseline and follow-up, only the short axis will be measured.

Non-measurable lesion:

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

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

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

12.9.2. Evaluation of Response by iRECIST

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

few months after the start of immunotherapy, and then experience subsequent disease response. These data will be captured in the clinical database.

Clinical stability is defined as meeting all of the following:

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

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

In a clinically unstable participant, if the Investigator decides to continue treatment, following consultation with the Sponsor medical monitor, the participant may continue to receive study intervention. The tumor assessment should be repeated at least 4 weeks and up to 8 weeks later to confirm PD by iRECIST.

If repeat imaging does not confirm PD per iRECIST and the participant continues to be clinically stable, study intervention may continue and follow the regular imaging schedule or as clinically indicated; see Section 2 SOA for more details. If PD is confirmed, participants will be discontinued from study intervention.

If a participant has confirmed radiographic progression (iCPD) as defined below, study intervention should be discontinued; however, if the participant is achieving a clinically meaningful benefit, continuation of study intervention may be considered following consultation with the Sponsor. In this case, if study intervention is continued, tumor imaging should follow the regular imaging schedule or as clinically indicated; see Section 2 SOA for more details.

Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

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

Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological PD by RECIST 1.1 the Investigator will decide whether to continue a participant on study intervention until repeat imaging is obtained (using iRECIST for participant management (see Table 11 and Figure 3). This decision should be based on the participant's overall clinical condition.

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

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir
    - Note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

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

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

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

Assessment at the Confirmatory Imaging

At the confirmatory imaging visit assessment, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR). Timing of confirmatory imaging is described in Section 9.2.4.

Confirmation of Progression

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

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

  - Visible growth of new non-target lesions
  - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

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

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

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

Resolution of iUPD

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

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

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

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

Management Following the Confirmatory Imaging

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

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, continuation of study intervention may be considered following consultation with the Sponsor. In this case, if study intervention is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 2.

Detection of Progression at Visits After Pseudo-Progression Resolves

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

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

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

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

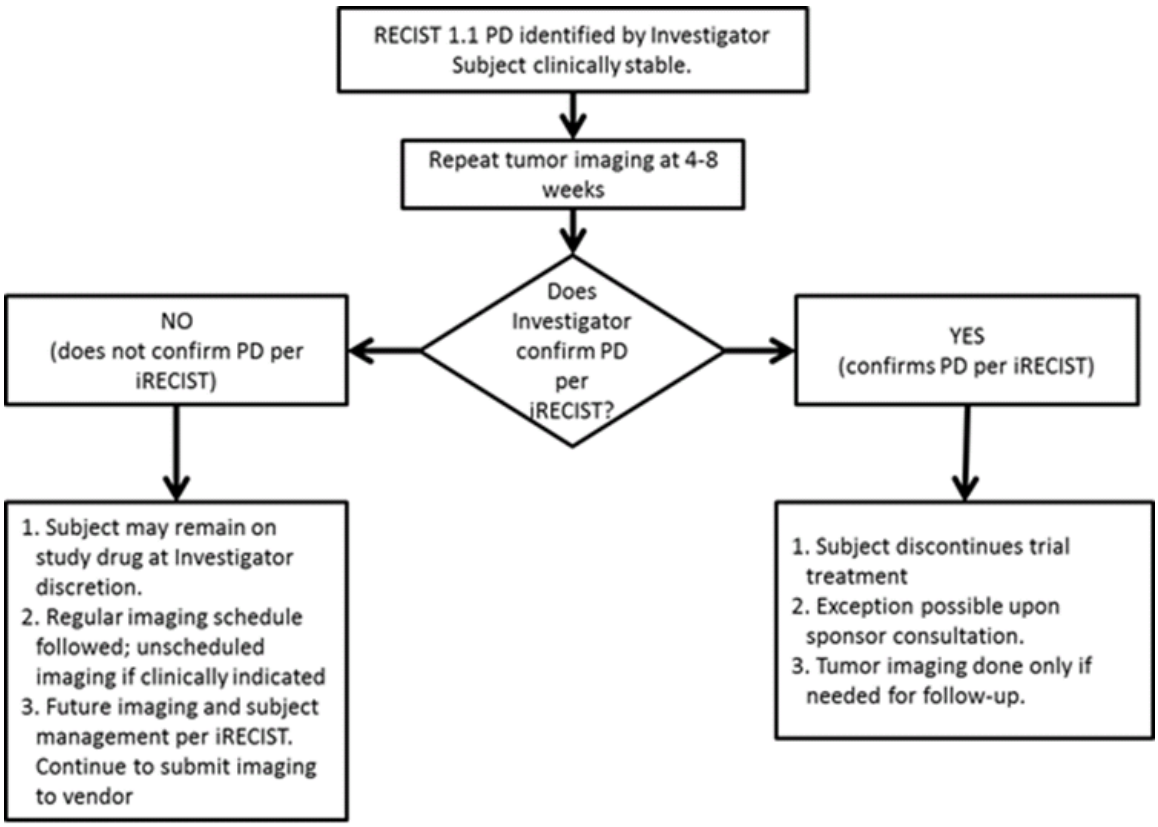
Additional details about iRECIST are provided in the iRECIST publication [Seymour, 2017].

Table 11 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

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

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

Figure 3 Imaging and Treatment for Clinically Stable Participants after First Radiologic Evidence of PD Assessed by the Investigator



12.10. Appendix 10: ECOG Performance Status

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

Oken, 1982.

12.11. Appendix 11: Protocol Amendment History

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