GEMMK

A phase I study to assess the safety and tolerability of pembrolizumab in combination with fixed rate gemcitabine chemotherapy in patients with leiomyosarcoma and undifferentiated pleomorphic sarcoma	
Short title:	GEMMK study
Sponsor:	Royal Marsden NHS Foundation Trust
Sponsor protocol number:	CCR 4541
EudraCT:	2016-004092-45
ClinicalTrials.gov ID:	NCT03123276
Protocol version and date:	V5.1, 16 May 2022
REC Reference:	17/LO/0767

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CONFIDENTIAL

Signature Page:

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trials regulations, GCP guidelines, the Sponsor's SOPs and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator / Principle Investigator

Name (Please print)

Signature

Date

Statistician

Name (Please print)

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABPI	Association of the British Pharmaceutical Industry
ADC	apparent diffusion coefficient
AE	adverse event
alk phos/ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukaemia
ANC	absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	aspartate aminotransferase
ATM	Ataxia telangectasia mutated
ATR	Ataxia telangectasia and Rad3-related
AUC	area under the curve
BP	blood pressure
Cmax	maximum observed plasma concentration
CPT	Cell Preparation Tube
CR	complete response
CRF	case report form
CR-UK	Cancer Research UK
CT	computed tomography
CTA	clinical trial authorisation
Day	calendar day
DDR	DNA damage response
DLT	dose limiting toxicity
DMR	Dose modification ratio
DNA-PK	DNA-dependent protein kinase
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediaminetetra-acetic acid
ELISA	Enzyme-linked immunosorbent assay
ESMO	European Society for Medical Oncology
FDR	Fixed Dose Rate
GGT	Gamma-glutamyl transpeptidase
GCLP	Good Clinical Laboratory Practice
GCP	Good Clinical Practice
gdL	gram(s) per decilitre
GFR	Glomerular Filtration Rate
GI50	Concentration for half-maximal growth inhibition
GMP	Good Manufacturing Practice
GSK3b	Glycogen synthase kinase 3 beta
Gy	Gray
Hb	Haemoglobin
HNSTD	Highest non-severely toxic dose
IC50	Half maximal inhibitory concentration
ICMJE	International Committee of Medical Journal Editors

IMP	Investigational medicinal product
INR	International normalised ratio
IR	Ionising radiation
ITF	Investigator Trial File
L/h	litres per hour
LDH	Lactate Dehydrogenase
MTD	Maximum tolerated dose
mg	Milligram
mg/m2	milligram per square metre
MHRA	Medicines and Healthcare products Regulations Agency
mmHg	Millimetres of mercury
MRI	magnetic resonance imaging
NTD	non-tolerated dose
PBMC	Peripheral blood mononuclear cells
PDc	pharmacodynamics
PD	progressive disease
P-gp	P-glycoprotein
PET	positron emission tomography
PFS	Progression free survival
PK	Pharmacokinetic
PR	partial response
PT	Prothrombin time
QC	quality control
QP	Qualified Person
QTc	Corrected Q-T interval
REC	Research Ethics Committee

RECIST	Response Evaluation Criteria in Solid Tumours
RPA	Replication protein A
SAE	serious adverse event
SD	stable disease
SDV	source data verification
SJS	Stevens Johnson syndrome
SOP	standard operating procedure
SPC	Summary of marketed Product Characteristics
SRC	safety review committee
STD10	Severely toxic dose for 10% of animals
STS	Soft Tissue Sarcomas
SUSAR	suspected unexpected serious adverse (drug) reaction
T1/2	terminal elimination half-life
TEN	toxic epidermal necrolysis
TSC	Trial Steering Committee
Tmax	Time to reach Cmax
TGI	Tumour growth inhibition
ULN	upper limit of normal
UPS	Undifferentiated pleomorphic sarcoma
USM	urgent safety measure
WBC	white blood cell

TABLE OF REVISIONS MADE TO THE PROTOCOL

Protocol v2.0			
Page/ Section	**Previous Wording**	**New Wording**	**Comments/Explanation/Rationale for Amendment**
Page 7	N/A	N/A	Updates to key trial contacts
Section 1	Subjects will receive treatment in repeated 3-week cycles. Subjects may remain on treatment until they experience disease progression or unacceptable toxicity, until they meet any of the withdrawal criteria or until the study is terminated by the sponsor	Subjects will receive treatment in repeated 3-week cycles. Subjects may remain on treatment until they experience disease progression or unacceptable toxicity, until they meet any of the withdrawal criteria or until the study is terminated by the sponsor. *Note*: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved.	Clarification of exception to withdrawal criteria which appears later in the protocol
Section 3	Primary Endpoint: To establish the maximum tolerated dose (MTD) of pembrolizumab that can be safely combined with Gemcitabine in the absence of dose limiting toxicities (DLTs). Exploratory Endpoint Immunophenotyping of pre- and post-treatment (9 weeks) biopsies (FFPE samples, density and phenotype of tumour infiltrating lymphocytes; CD3+, CD8+, CD45, FoxP3 and PD1,	Endpoint: To establish the maximum tolerated dose (MTD) of gemcitabine that can be safely combined with pembrolizumab in the absence of dose limiting toxicities (DLTs). Exploratory objective: "To explore the relationship between, T cell and myeloid compartments, immune checkpoints and response to Pembrolizumab and Gemcitabine in leiomyosarcoma and undifferentiated pleomorphic sarcoma" Exploratory Endpoint Immunophenotyping of pre- and post-treatment (9 weeks) biopsies (FFPE samples, density and phenotype of tumour infiltrating lymphocytes; CD3+, CD8+, CD45, FoxP3 and PD1 fresh biopsy samples for immunology studies to perform detailed phenotypic and functional analysis of T cell and myeloid compartments) .	Clarification of primary endpoint Additional tissue collection & analysis details for exploratory endpoint
Section 4	A mandatory tumour biopsy will be collected prior to the start of treatment for pre-treatment testing for PD-L1 expression, Immunophenotyping and extent and localization of tumour infiltrating lymphocytes and following 3 cycles of therapy for analysis of potential markers of tumour response on post-treatment tissue. Additional mandatory bloods will be collected for analysis of potential circulating immune markers. Patient genetic material will also be collected for analysis of potential markers of tumour response and future pharmacogenetic analyses. Provision of genetic material is not mandatory for	Up to four mandatory paired tumour biopsies will be collected prior to the start of treatment for genomic and proteomic analyses, pre-treatment testing PD-L1 expression, Immunophenotyping and extent and localization of tumour infiltrating lymphocytes, and following 3 cycles of therapy for analysis of potential markers of tumour response on post-treatment tissue. Immunogenicity of sarcomas including PD-L1 expression can change with previous treatment (Ref: Patel et al (39). It is essential that biopsies reflect	Clarification of the rationale for obtaining biopsies Treatment period time frame for first patient in a cohort removed-this was an error in the original protocol.

	participation in the main study. The first patient entered in a cohort will be treated over 72 hours and observed for 11 days (Day 14 of the treatment cycle).	the immunophenotype at the timepoint of starting the trial, and after treatment has been received. Archival tumour tissue can therefore not be used in this part of the study. Additional mandatory bloods will be collected for analysis of potential circulating immune markers.	
Section 5.2	2. Be able to provide archival tissue for pathology review and confirmation of a diagnosis of leiomyosarcoma or undifferentiated pleomorphic sarcoma 9. Demonstrate adequate organ function as defined in Table-1 (all screening labs should be performed within 10 days of treatment initiation).	1. Have a histologically confirmed case of undifferentiated pleomorphic sarcoma or leiomyosarcoma and be willing to consent for archival tumour material to be requested for transfer to The Royal Marsden for future review. 2. Have biopsiable disease and be willing to agree to a biopsy in order to permit acquisition of mandatory paired tumour biopsies done during screening and following 9 weeks of treatment for analysis of immunomodulation. 8. Demonstrate adequate organ function as defined in Table-1 (all screening labs should be performed within 28 days of treatment initiation).	Inclusion criteria number 1 amended and number 2 reworded Inclusion criteria-Timeframe for screening labs amended
Section 6.1 Visit Schedule	See protocol v1.3 (20 May 2017)	See protocol v2.0 for updated Visit Schedule and corresponding updates to text in Section 6.	Visit Schedule updated in order to support text
Table 2 Laboratory Tests	Blood Urea Nitrogen	Urea	Confirmation that Urea not blood urea nitrogen should be tested as part of biochemistry Labs.
Section 7.1.2 Dose Modification Table	See protocol v1.3 (20 May 2017)	See protocol v2.0	New Dose Modification Table from Funder
Section 4 & 7.1.2	Neutropenia <0.5 x 10^9/L for >5 days or with fever. Thrombocytopenia <25 x 10^9/L. Any non-haematological CTCAE Grade 3 or 4 toxicity that is, in the opinion of the investigator, clinically significant. Where, in the investigator's opinion, it is likely that administration of gemcitabine is causally linked with the toxicity or observed effect.	A dose limiting toxicity is defined as: • Neutropenia <0.5 x 109/L for >5 days. This must be confirmed with repeat blood tests at the Royal Marsden Hospital within 6 days of the diagnosis of neutropenia. • Febrile neutropaenia as per definition by ESMO (>38.3°C or two consecutive readings of >38.0°C for 2 hours and an absolute neutrophil count (ANC) of <0.5 x 109/L or expected to fall below <0.5 x 109/L) • Thrombocytopenia <25 x 109/L. • Any non-haematological CTCAE Grade 3 or 4 toxicity that is, in the opinion of the investigator, clinically significant. The toxicities listed above must be, in the investigator's opinion, likely to be causally linked with the administration of	Reworded DLT definition agreed at Safety Review Committee Meeting.

		Gemcitabine.	
Section 6	Correlative blood studies will be collected on Day 1 of cycle 1 and repeated every 2 cycles until cycle 6. Bloods will be performed according to local procedures, usually under ultrasound guidance, and handled in accordance with the procedures described in the Appendix.	30-40ml blood will be collected for correlative research studies at the timepoints specified in the Visit Schedule in Section 6.1. 18 mls of blood (2xEDTA tubes) will be collected at the time of pre-treatment biopsy and post-treatment biopsy following 3 cycles of treatment. In addition, 3 mls of blood will be collected in Tempus tubes to extract RNA.	Clarification of volume of blood to be collected for research purposes.
Section 7.1.1	See Table 3 in protocol v1.3 (20 May 2017)	See protocol v2.0 - Table 3 Cycles will be repeated every 21 days for 6-8 cycles depending on tolerability and response. Further cycles of Gemcitabine can be administered if clinically indicated.	Clarification of Gemcitabine Dosing
Section 7.1.1	N/A	The pembrolizumab infusion will be administered on day 1 and repeated every 21 days until disease progression or withdrawal criteria are met; for up to 24 months of uninterrupted treatment or 35 administrations, whatever is later.	Clarification of Pembrolizumab dosing
Section 7.1.2	N/A	Toxicities which are, in the Investigator's opinion, a consequence of treatment with Gemcitabine will be managed according the Royal Marsden Sarcoma Unit's standard procedures for managing Gemcitabine-related toxicity. Patients will be clinically assessed prior to the administration of every dose of Gemcitabine.	Clarification of the process for the management of Gemcitabine –related toxicity
Section 5.2 (Inclusion Criteria) & 7.7.2	Patients should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.	Patients should start using birth control from study Visit 1 throughout the study period up to 6 months after the last dose of study therapy.	Time frame for use of birth control increased from 120 days to 6 months after the last dose of study therapy as per Gemcitabine SmPC.
Section 8.2	N/A	In case of grade 3 and grade 4 toxicity, blood and samples from affected tissue can be used for immune analysis, genomic and proteomic studies. Tissue will only be collected if it can be obtained as part of a clinically indicated investigation or a therapeutic procedure to treat the toxicity. This is optional.	Clarification that optional additional research samples pose no additional risk.
Section 10.1	See Table 8 in Protocol v1.3 (20 May 2017)	See protocol v2.0 – Table 8	Details of IMP-Gemcitabine supply added
Section 12.8.2	*Trial Steering Committee (TSC)* A trial steering committee (TSC) will be established at the start of the trial. The TSC will be chaired by an independent chair and include the chief investigators (Dr Jones). Other	*Safety Review Committee (SRC)* The SRC will include the Chief investigator for the trial (Dr Robin Jones), a Representative from RM-Clinical Trials Unit, a Statistician and be chaired by a	Safety Review Meetings are conducted by the SRC not TSC.

	independent members (1-2 including a sarcoma expert and statistician) will be appointed prior to the start of the study. The TSC will also take on the role of IDMC as part of a closed session without Dr Jones. The role of the TSC is to monitor trial progress and to ensure the protocol and GCP principles are adhered to. The TSC's terms of reference, roles and responsibilities will be defined in a charter. Further internal or external experts may be consulted by the TSC as necessary.	clinician independent of study investigators. The SRC will meet at every dose escalation point. The role of the SRC is: • Review relevant safety data and make dose escalation decisions • Reviews all SAEs and emerging safety data both from RM Sponsored studies and external SUSARS received from MSD • Monitor progress of the trials and ensure emerging safety information is evaluated and protocol and GCP principles are adhered to. The SRC terms of reference, roles and responsibilities will be defined in a charter. Further internal or external experts may be consulted as necessary.	
Section 12	12.6.1.3 Participating Sites Responsibilities are defined in an agreement between an individual participating sites and the sponsor, which must be signed and in place prior to recruitment commencement. Also (but not limited to);-putting and keeping in place arrangements to adhere to the principles of GCP keeping a copy of all 'essential documents' (as defined under the principles of GCP) in an Investigator Site and Pharmacy File and ensuring appropriate archiving of all essential documentation once the trial has ended -taking appropriate urgent safety measures -Sites wishing to participate in this study will be required to provide evidence that they can are equipped to deliver the protocol treatment for the duration of the study.	12.6.1.3.Sarcoma Research Fund A grant from the Sarcoma Research Fund will fund the translational research.	This is a single centre study therefore 'participating sites' section not required. Confirmation of source of funding for translational research.
Section 4.2	Trial Diagram (Flowchart)		Flowchart removed as no longer required. Details included in amended Visit Schedule in Section 6.
Protocol v3.0			
Page/ Section	**Previous Wording**	**New Wording**	**Comments/Explanation/Rationale for Amendment**
Section 4.1 Part A: Dose escalation cohort	N/A	Three patients must complete one full cycle of treatment (to day 21 of cycle 1) without the need for a dose reduction, for a dose-escalation decision to be made. Treatment delays of up to 14 days within the first cycle are acceptable. Patients who undergo treatment delays will still be considered evaluable.	Clarification regarding the definition of an evaluable patient added to the protocol on the recommendation of the Safety Review Committee. Clarification regarding the maximum delay to treatment permitted during cycle 1, defined in days.

Section 6.1 Visit Schedule	Please see Visit Schedule (Protocol v2.0, dated 27.03.2019)	Please see Visit Schedule (Protocol v3.0)	Visit Schedule updated in order to support text
Section 6.4 Laboratory Procedures/Assessments	Please see Table 2 (Protocol v2.0, dated 27.03.2019)	See Protocol v3.0 – Table 2 Additional blood test results can be collected at the clinician's discretion….but blood tests can be performed at additional time-points if deemed necessary by a clinician.	Amylase, bicarbonate and GGT added as routine chemistry test. Clarification that additional blood test results may be collected if considered necessary by a clinician.
Section 7	Please see Table 3 (Protocol v2.0, dated 27.03.2019)	See Protocol v3.0 – Table 3	The table has been updated to provide clarification of the treatment period and dosing for both Pembrolizumab and Gemcitabine at study visits.
Section 7.1.2 Dose Modification	N/A	Patients requiring dose reductions during the first cycle of treatment will be considered non-evaluable.	Clarification of the definition of an evaluable patient as per recommendations from the trial's Safety Review Committee.
Section 8.4.1	Assessment of expectedness will be made by the Chief Investigator (CI) ~~against the current version of the Investigator Brochure (Pembrolizumab IB, Section 7.3) or Summary of Product Characteristics (Gemcitabine SmPC, Section 4.8). If updated versions of the investigator brochure are released during the course of the trial then assessment of expectedness will be made against the current regulatory approved version.~~	The Investigator Brochure for Pembrolizumab and Summary of Product Characteristics for Gemcitabine as last amended and approved by the national competent authority serve as the reference safety information for the assessment of the expectedness of any adverse reaction that might occur during the clinical trial.	Specific location of RSI removed from Protocol.
Key Trial Contacts	~~Bodil Engelmann~~ ~~Bodil.engelmann@rmh.nhs.uk~~ ~~Victoria Pittordou~~ Tel: 02088642 6011 Ext: ~~4297~~	Alannah Smrke Alannah.Smrke@rmh.nhs.uk Marta Vergnano Tel: 02088642 6011 Ext: 6767	Update to the key trial contacts
Section 1 Trial Summary	Subjects may remain on treatment until they experience disease progression or unacceptable toxicity, until they meet any of the withdrawal criteria or until the study is terminated by the sponsor.	Subjects may remain on treatment until they experience disease progression or unacceptable toxicity, until they meet any of the withdrawal criteria or until the study is terminated by the sponsor, for up to 24 months of uninterrupted treatment or 35 administrations whichever is later.	Clarification of Pembrolizumab period and dosing.

Section 7.7.2. Contraception	Non-pregnant, non-breast- feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive.	Non-pregnant, non-breast- feeding women may be enrolled if they are willing to use 2 methods of birth control (1 effective form of contraception from the list provided below and a condom) or are considered highly unlikely to conceive.	Accepted methods of contraception to be used have been clarified.
Protocol v4.0			
Page/ Section	**Previous Wording**	**New Wording**	**Comments/Explanation/Rationale for Amendment**
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Section 5.5 Registration	When the patient signs the consent form, they will be allocated a trial ID that will be used to identify the patient for all future assessments. If eligible, the patient will begin on the trial ~~and~~ keep the same trial ID assigned at consent. Treatment will begin within ~~3~~ days from the date ~~of registration~~.	When the patient signs the consent form, they will be registered onto the study and allocated a trial ID that will be used to identify the patient for all future assessments, before entering screening. If eligible, the patient will be enrolled and begin on the trial, keeping the same trial ID assigned at consent. Treatment will begin within 7 days from the date eligibility is confirmed by a member of RM-CTU.	The stepwise process of trial id assignment and registration, screening assessment, eligibility confirmation and patient enrolment, and finally treatment start, has been clarified. The time between eligibility confirmation and treatment start has been updated, to account for public holidays and patient commitments.
Section 6 Study Plan and procedures	See visit schedule in protocol v3.0 (10 September 2020)	See protocol v4.0 for updated Visit Schedule and keys, and corresponding updates to text in Section 6.6.2, 6.6.3 and 6.6.4	The possibility of telephone consultations has been introduced to account for the impact of a pandemic on the study. Visit Schedule has been updated in order to support text.
Section 13 List of References	~~38. Tawbi HA, Burgess MA, Crowley J, van Tine BA, Hu J, Schuetze S, et al. Safety an defficacy of PD- 1 blockade using pembrolizumab in patienst with advanced soft issue and bone sarcomas: Results of SARC028, a multicentre Phase II study. Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting 2016.~~	38. Tawbi HA, Burgess M, Bolejack V, Van Tine BA, Schuetze SM, Hu J, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. Lancet Oncol. 2017; 18(11): 1493-1501.	Reference 38 has been updated from a conference presentation to the correspondent journal article, published in the following year.

Protocol v5.0			
Page/ Section	**Previous Wording**	**New Wording**	**Comments/Explanation/Rationale for Amendment**
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Multiple instances	neutropaenia	neutropenia	Spelling update
Multiple instances	Laboratory Manual	Study Sample Manual	Wording update to reflect reference document.
5.3 Subject Exclusion Criteria	10. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis. 18. Has received a live vaccine within 30 days of planned start of study therapy.	10. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or current pneumonitis /interstitial lung disease. 18. Has received a live vaccine or live-attenuated vaccine within 30 days of planned start of study therapy. Administration of killed vaccines is allowed	Wording update in line with new IB.

6.1 Visit Schedule	n/a	Table updated, AD-HOC column added. Key point m added: Optional bloods for germline sequencing can be taken at any point in the trial. These bloods should only be collected once. Consent must be given for the bloods to be taken.	Amendments made to include new optional blood collection.
6.3.6	n/a	Mandatory tumour biopsies will be examined by a pathologist to identify parts of the specimen needed for routine histopathological examination. Any remaining material will be used to generate FFPE tissue, fresh frozen samples (snap frozen); and cellular material will be transferred on ice or viably frozen for xenograft implantation into mice.	Added summary of how mandatory biopsies are processed.
6.3.6	In addition, 3mls of blood will be collected in Tempus tubes to extract RNA.	In addition, 2.5mls of blood will be collected in PAXgene tubes to extract RNA.	Update to type of tubes available to the trial
6.3.7	n/a	**Optional blood and tissue collection at significant toxicity** When a patient suffers a significant toxicity blood and tissue samples may be collected; if considered safe and the patient has consented to do so. Tissue will only be collected if it can be obtained as part of a clinically indicated investigation or a therapeutic procedure to treat the toxicity (i.e. colonoscopy for colitis).	Added new section 6.3.7 to clarify optional blood and tissue collection at significant toxicity.
6.3.8	n/a	**6.3.8. Optional research blood collection** Optional research bloods for germline analysis can be taken at any point in the trial and should be taken at the most appropriate timepoint/visit to allow for the collection. Five tubes of bloods will be taken; EDTA 3ml, two EDTA 9ml vacutainer blood and two PAXgene® 2.5mL Blood RNA tubes. Optional research bloods will be collected once. Consent must be given prior to sample collection. Sample collection will be performed according to local procedures and handled in accordance with the procedures described in the Study Sample Manual. The results of the	Added new section 6.3.7 to for new optional research blood collection.

		germline analysis will not be distributed to trial participants.	
7.1.2 Dose Modification (escalation/titration/other)	n/a If an SAE is thought to be related to pembrolizumab (see the investigator's brochure for more details), pembrolizumab will be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per Table 3 below. Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. See Section 7.6.1 for supportive care guidelines, including use of corticosteroids. n/a	Interventions administered in combination can be difficult to attribute of an adverse event to a single component. The investigator may attribute a toxicity event to the combination, to gemcitabine alone or to pembrolizumab alone, for adverse events listed in [Table 4]. Both interventions must be held according to the criteria in Table 6 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Pembrolizumab. If the AE is considered immune-related, both interventions should be held according to recommended dose modifications. If an SAE is thought to be related to pembrolizumab (see the investigator's brochure for more details), pembrolizumab will be withheld for drug-related Grade 4 hematologic toxicities, non-haematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per Table 4 below. Adverse events (both non-serious and serious) associated with pembrolizumab exposure, including coadministration with additional compounds may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. See Section 7.6.1 for supportive care guidelines, including use of corticosteroids. Participants may not have any dose modifications (no change in dose or schedule, as described in Table 4) of pembrolizumab in this study. If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be	Wording update in line with new IB.

		discontinued from all study interventions. If the toxicities do resolve and conditions are aligned with what is defined in Table 4, the combination of gemcitabine and pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to gemcitabine alone, re-initiation of pembrolizumab as a monotherapy may be considered at the investigator's discretion.	
Table 4	Table 4 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab New Table	Table 4 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab monotherapy and IO Combinations New Table	Table update in line with new IB.

1. TRIAL SUMMARY

Title	Phase I trial gemcitabine + pembrolizumab in leiomyosarcoma and undifferentiated pleomorphic sarcoma (GEMMK study)
Trial Phase	Phase 1
Clinical Indication	Metastatic or inoperable leiomyosarcoma and undifferentiated pleomorphic sarcoma
Trial Type	Open-label
Type of Control	None
Route of Administration	Intravenous
Trial Blinding	None
Treatment Groups	Part A: Dose-escalation cohort Part B: Expansion cohort
Number of trial subjects	Up to a total of 30 patients. Part A (Dose-escalation cohort): Max of 18 patients Part B (Expansion cohort): Total of 12 patients
Estimated enrolment period	24 months
Estimated duration of trial	36 months
Duration of participation	Subjects will receive treatment in repeated 3-week cycles. Subjects may remain on treatment until they experience disease progression or unacceptable toxicity, until they meet any of the withdrawal criteria or until the study is terminated by the sponsor, for up to 24 months of uninterrupted treatment or 35 administrations whichever is later. *Note*: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved.
Objectives	<u>Primary</u> • To evaluate the safety and tolerability of a fixed dose rate of gemcitabine when administered in combination with pembrolizumab. <u>Secondary</u> • To establish the appropriate dose of gemcitabine for use in combination with pembrolizumab the expansion cohort • To obtain efficacy evidences of the anti-tumour activity of gemcitabine in combination with pembrolizumab in patients with advanced leiomyosarcoma and undifferentiated pleomorphic sarcoma, according to RECIST

Exploratory

- To explore the relationship between PD-L1 tumour expression and immune response

- To explore the relationship between, T cell and myeloid compartments, immune checkpoints and response to Pembrolizumab and Gemcitabine in leiomyosarcoma and undifferentiated pleomorphic sarcoma.

- To complement other work aimed at generating a sarcoma "immunoscore" created from Immunophenotyping samples from the Royal Marsden Sarcoma Unit tissue bank correlated with progression-free and overall survival

- To explore other predictive biomarkers of immune response to PD-L1 inhibition in leiomyosarcoma and undifferentiated pleomorphic sarcoma.

Endpoints

Primary

- To establish the maximum tolerated dose (MTD) of gemcitabine that can be safely combined with pembrolizumab in the absence of dose limiting toxicities (DLTs)

Secondary

- To make a preliminary evaluation of response by using RECIST v1.1 to document best response rate, best reduction in tumour size and progression free survival, assessed 9 weeks after start of therapy

Exploratory

- Immunophenotyping of pre- and post-treatment (9 weeks) biopsies (FFPE samples, density and phenotype of tumour infiltrating lymphocytes; CD3+, CD8+, CD45, FoxP3 and PD1 fresh biopsy samples for immunology studies to perform detailed phenotypic and functional analysis of T cell and myeloid compartments).
- to perform detailed phenotypic and functional analysis of T cell and myeloid compartments.
- Location of tumour infiltrating lymphocytes (proximity to tumour cells and location relative to the microvasculature; Prototype analysis software at ICR)
- Response stratification according to tumour PD-L1 expression
- Exploratory analyses to research other potential immune response biomarkers in collected tissue and potential circulating immune markers in additional collected bloods.

2. BACKGROUND & RATIONALE

2.1 Background

Refer to the Summary of Product Characteristics (SPC) for detailed background information on pembrolizumab.

2.1.1. Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades(1). Accumulating evidence shows a correlation between tumour- infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies (2-6). In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumours.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumours to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (7, 8). The structure of murine PD-1 has been resolved (9). PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade (10-12). The mechanism by which PD- 1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins (13, 14). PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells (15, 16). Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells (17). The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumours (18-20). Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumour-specific T-cell expansion in subjects with melanoma (MEL)(21). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumour immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if *BRAF V600* mutation positive, a BRAF inhibitor.

2.1.2. Preclinical and Clinical Trial Data

Refer to the Summary of Product Characteristics for the data.

2.2 Rationale

2.2.1. Rationale for the Trial and Selected Subject Population

Soft tissue sarcomas (STS) are a group of rare mesenchymal neoplasms affecting all ages. STS most commonly present as localised disease but despite surgery and adjuvant treatment more than half of patients will develop recurrent or metastatic disease. Leiomyosarcoma (LMS), a malignancy of smooth muscle, is one of the most common STS and when advanced is typically treated with chemotherapy. Undifferentiated pleomorphic sarcoma (UPS) is also a common sarcoma subtype with an aggressive behavior. Recent studies have demonstrated reasonable sensitivity of LMS and UPS to gemcitabine monotherapy with an objective response rate of 8-19% (22, 23). In addition, the SARC 28 trial demonstrated that pembrolizumab has single agent activity in UPS with a response rate of 44% (4 out of 9 patients) (38). However, the overall survival is still only about 12 months which illustrates the critical clinical need for improved therapies for advanced UPS and LMS as well as sarcomas in general.

Immunotherapy has shown great promise for advanced solid tumour malignancies including sarcoma. Immune checkpoint blockade with the antibodies ipilimumab and nivolumab, targeting CTLA4 and programmed cell death 1 (PD-1), has led to rapid, deep and durable objective responses in 53% of patients with advanced melanoma (24). Some sarcoma subtypes (synovial and myxoid/ round cell liposarcoma) express high levels of NY-ESO-1, one of the most immunogenic cancer testis antigens (CTA), and by augmenting the natural immune response, significant anti-tumour response would be anticipated. Studies of adoptive T cell therapy have shown some activity in synovial sarcoma.(25) However, in a pilot study of a CTLA4 inhibitor in synovial sarcoma, no clinical responses were seen in 6 synovial sarcoma patients despite high CTA expression (26).

The inhibitory interaction between PD1 on T lymphocytes and PD-L1 or PD-L2 on tumour cell surface attenuates the immune response by decreasing cytokine production and inducing T-lymphocyte anergy and apotosis. Expression of PD-L1 on sarcoma cells is prognostic (27) and, at least in NSCLC, pretreatment tumour PD-L1 expression was a significant predictor of response to pembrolizumab (RECIST response rate according to PD-L1 above/below significant expression = 57% vs 9%)(28

Leiomyosarcoma patient samples express PD-L1 protein in approximately 70% of cases indicating that anti-PD-L1 is a rationale strategy for this histological subgroup of sarcoma (27).

Gemcitabine becomes di and tri phosphorylated in cells and has a number of actions including inhibition of ribonucleotide reductase and, because of false incorporation into DNA, causing chain termination during DNA replication, resulting in impaired cell replication and apoptosis (29). In addition, gemcitabine is suggested to augment the anti-tumour T-cell response in at least 4 different ways. 1) The gemcitabine related apoptosis causes increased dendritic cell dependent antigen presentation to T-cells (30). 2) In BALB-C mice bearing mesothelioma, gemcitabine leads to depletion of B-cells causing a relative increase in the T-cells (31). 3) Patients with NSCLC treated with a 30min infusion of gemcitabine have increased tumour necrosis factor (TNF), increased interleukin (IL)-2 production, and significant decreases in total white blood cell and lymphocyte counts (CD3+, CD8+, and CD16+ lymphocytes) (32). 4) Partial restoration of immune-visibility of tumour cells to T cells by an upregulation of HLA1 expression (33). The anticancer activity of gemcitabine, previously thought to be purely cytotoxic, may in fact be due, in part, to an altered immune tumour microenvironment. In addition to the immune modulation of gemcitabine monotherapy, gemcitabine combinations may have even more pronounced immune effects. Gemcitabine treatments been shown to augment cellular CD40 monoclonal antibody induced CD8 T-cell anti-tumour activity in a mouse model (34), and in patients with pre-treated renal

cancer, gemcitabine enhances the activity of TNF-α (29).

In this study we propose to combine the immune synapse checkpoint inhibitor with the cytotoxic and immune modulating agent, gemcitabine. It is hoped that this dual immunomodulatory approach will enhance the effect of pembrolizumab on PD-L1 expressing undifferentiated pleomorphic sarcoma and leiomyosarcomas, leading to a safe treatment with improved patient outcomes.

2.2.2. Rationale for Dose Selection/Regimen/Modification

Pembrolizumab Dose Selection

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumours. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumour size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumour activity. Recent data from other clinical studies within the pembrolizumab program has shown that a lower dose of pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication.

The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumour burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumours is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumour burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumour type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3

weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

Gemcitabine Dose Selection

Fixed Dose Rate Infusion

Initial pharmacokinetic data from pancreatic adenocarcinoma studies documented an increase in intracellular gemcitabine triphosphate concentration when gemcitabine was administered at a fixed dosed rate.(35) Subsequently, a phase II trial in soft tissue sarcoma compared single agent gemcitabine administered as a fixed dose rate (FDR) of 10 mg/m^2/min during a 120-minute intravenous infusion, at 1,200 mg/m^2 days 1 and 8, every 21 days to a combination therapy where gemcitabine dose was administered at a fixed dose rate 900 mg/m^2 intravenous infusion during 90 minutes on days 1 and 8, with docetaxel 100 mg/m^2 intravenously during 60 minutes day 8, every 21 days. In the 9 LMS patients treated with single agent gemcitabine, there was 1 PR and 7 SD over a period of 6 months. One dose reduction was necessary in 26% of STS patients treated with single agent gemcitabine with 94% overall dose intensity.

A second phase II trial randomly assigned LMS (uterine and non- uterine) patients to single agent gemcitabine (1,000 mg/m^2 administered at a fixed-dose rate of 10 mg/m^2 per minute via a 100-minute i.v. infusion on days 1, 8, and 15 every 28 days) compared to gemcitabine plus docetaxel arm (gemcitabine was administered at a fixed-dose rate of 900 mg/m^2 in a 90-minute infusion on days 1 and 8, with docetaxel at 100 mg/m^2 in a 60-minute infusion on day 8 after gemcitabine, every 21 days).(23) In the single agent arm, among 43 LMS patients, there was 1 CR, 6 PR and 21 SD. Dose intensity was 85% and 96% respectively for the non-uterine and uterine subgroups.

Immunomodulatory Role of Gemcitabine

The immunomodulatory role of FDR gemcitabine was explored in a prospective study in patients with advanced refractory renal cell carcinoma.(36) Twelve patients received 800 mg/m^2 FDR gemcitabine (i.v. infusion of 10 mg/m^2/min) on days 1 and 8 every 3 weeks, combined with 3.0 x106 U s.c. IFN-α on days 1, 3, and 5 of each week. A disease control rate (PR+SD) of 64% and time to progression of 7.1 months was significantly better than historical controls. A dose reduction of gemcitabine was necessary in 25% of patients.

Treatment Sequencing in Mouse Models

Treatment protocols were initiated 9 days after tumour inoculation in BALB/c mice. 120ug/g gemcitabine i.p. D1, 4, 7, 10 & 13 and 100ug FGK45 (anti-CD40 antibody) 3x over 6 days were administered. The combination and sequence of gemcitabine followed by FGK45 led to the greatest tumour kill.(37)

Dose Selection

With the previous described pre-clinical and clinical data, a starting dose of single agent gemcitabine administered as a fixed dose rate (FDR) of 10 mg/m^2/min during a 120-minute intravenous infusion, at 800 mg/m^2 days 1 and 8, every 21 days was selected with subsequent incremental doses to 1000 mg/m^2 and 1200 mg/m^2 depending on dose limiting toxicity.

3. OBJECTIVES & ENDPOINTS

3.1 Primary Objective & Endpoint

Objective:

To evaluate the safety and tolerability of a fixed dose rate of gemcitabine when administered in combination with pembrolizumab

Hypothesis:

Administration of gemcitabine with pembrolizumab is safe.

Endpoint:

To establish the maximum tolerated dose (MTD) of gemcitabine that can be safely combined with pembrolizumab in the absence of dose limiting toxicities (DLTs).

3.2 Secondary Objective & Endpoint

Objective:

1. To establish the appropriate dose of gemcitabine for use in combination with pembrolizumab the expansion cohort

2. To obtain evidence of the anti-tumour activity of gemcitabine in combination with pembrolizumab in patients with advanced leiomyosarcoma and undifferentiated pleomorphic sarcoma, according to RECIST

Hypothesis:

Gemcitabine acts in synergy with PD-L1 inhibition as an anti-cancer strategy

Endpoint:

To make a preliminary evaluation of response by using RECIST v1.1 to document best response rate, best reduction in tumour size and progression free survival, assessed 9 weeks after start of therapy

3.3 Exploratory Objective (Biomarker research)

Objective:

1. To explore the relationship between PD-L1 tumour expression and immune response

2. To explore the relationship between T cell and myeloid compartments, immune checkpoints and response to Pembrolizumab and Gemcitabine in leiomyosarcoma and undifferentiated pleomorphic sarcoma.

3. To complement other work aimed at generating a sarcoma “immunoscore” created from Immunophenotyping samples from the Royal Marsden Sarcoma Unit tissue bank correlated with progression-free and overall survival

4. To explore other predictive biomarkers of immune response to PD-L1 inhibition in leiomyosarcoma and undifferentiated pleomorphic sarcoma.

Endpoints:

1. Immunophenotyping of pre- and post-treatment (9 weeks) biopsies (FFPE samples, density and phenotype of tumour infiltrating lymphocytes; CD3+, CD8+, CD45, FoxP3 and PD1 fresh biopsy samples for immunology studies to perform detailed phenotypic and functional analysis of T cell and myeloid compartments).
2. Location of tumour infiltrating lymphocytes (proximity to tumour cells and location relative to the microvasculature; Prototype analysis software at ICR)
3. Response stratification according to tumour PD-L1 expression
4. Exploratory analyses to research other potential immune response biomarkers in collected tissue and potential circulating immune markers in additional collected bloods

4. TRIAL DESIGN

4.1 Trial Design

This is a two part, phase I, single centre dose escalation and dose expansion study to establish the safety, tolerability and pharmacokinetics of pembrolizumab in combination with different dose levels of fixed dose rate gemcitabine in patients with newly diagnosed metastatic or inoperable leiomyosarcoma and undifferentiated pleomorphic sarcoma (UPS), for whom gemcitabine monotherapy is deemed appropriate, or in patients with previously treated leiomyosarcoma and undifferentiated pleomorphic sarcoma, not including gemcitabine, with disease progression documented in the 12 weeks prior to enrolment.

There will be a maximum of 18 patients in the dose-escalation cohort (part A) and the starting dose will be a fixed dose rate (FDR) gemcitabine of 800 mg/m^2 on day 1 and 8 of 21 days cycles in combination of 200 mg of pembrolizumab given as an infusion on day 1 every 3 weeks. There will be a minimum of three and a maximum of six evaluable patients entered per dose cohort and each patient will continue to receive treatment cycles of gemcitabine in combination with pembrolizumab for as long as he/she is, in the opinion of the investigator, deriving clinical benefit and continues to meet re-treatment criteria. Treatment will continue until disease progression or is stopped because of toxicity. There will be an option to continue pembrolizumab alone in patients with SD or response who stop gemcitabine for toxicity before completing 6 cycles of combination therapy. During the dose-escalation phase, safety, tolerability, biological and clinical activity will be assessed and the maximum tolerated dose (MTD) will be established.

The MTD cohort (part B) will then be expanded to a total of 12 patients in order to further evaluate the safety and tolerability of that dose as well as to preliminarily assess response to therapy

Up to four mandatory tumour biopsies will be collected prior to the start of treatment for genomic and proteomic analyses, pre-treatment testing PD-L1 expression, Immunophenotyping and extent and localization of tumour infiltrating lymphocytes and following 3 cycles of therapy for analysis of potential markers of tumour response on post-treatment tissue. Immunogenicity of sarcomas including PD-L1 expression can change with previous treatment (39). It is essential that biopsies reflect the immunophenotype at the timepoint of starting the trial, and after treatment has been received. Archival tumour tissue can therefore not be used in this part of the study. Additional mandatory bloods will be collected for analysis of potential circulating immune markers.

Part A: Dose escalation cohort

Part A will be the dose escalation phase. Gemcitabine doses will be escalated (or de-escalated) until the non-tolerated dose (NTD) is attained and a maximum tolerated dose (MTD) is defined. A maximum of 18 patients will be recruited in cohorts of 3 to 6 patients as part of a toxicity rule-based 3+3 design. The total number of patients will depend upon the number of dose escalations and toxicities observed.

The starting dose (dose level 1) will be 800 mg/m^2 of FDR gemcitabine given by 120 min IV infusion on Day 1 and Day 8 of each 3 week cycle (see Rationale for choice of starting doses). Pembrolizumab will be administered as a 200 mg IV infusion on Day 1 following the infusion of FDR gemcitabine. Pembrolizumab infusions will be

repeated every 3 weeks. Each dose escalation cohort will consist of a minimum of three and a maximum of six patients.

A dose limiting toxicity is defined as:

- Neutropenia <0.5 x 109/L for >5 days. This must be confirmed with repeat blood tests at the Royal Marsden Hospital within 6 days of the diagnosis of neutropenia.
- Febrile neutropenia as per definition by ESMO (>38.3°C or two consecutive readings of >38.0°C for 2 hours and an absolute neutrophil count (ANC) of <0.5 x 109/L or expected to fall below <0.5 x 109/L)
- Thrombocytopenia <25 x 109/L.
- Any non-haematological CTCAE Grade 3 or 4 toxicity that is, in the opinion of the investigator, clinically significant.

The toxicities listed above must be, in the investigator's opinion, likely to be causally linked with the administration of Gemcitabine.

In the unlikely event that dose-limiting toxicity (DLT) occurs at the proposed starting dose and that dose is deemed intolerable, a second cohort of patients will be recruited and a dose of 600 mg/m^2 (dose level –1). If no dose limiting toxicity (DLT) is documented, the FDR gemcitabine dose will be escalated to 1000 mg/m^2 and subsequently to 1200 mg/m^2 unless 2 or more patients in a single cohort have experienced DLT.

If the first patient does not experience dose-limiting toxicity by Day 14 of the first treatment cycle, two additional patients may be entered. Three patients must complete one full cycle of treatment (to day 21 of cycle 1) without the need for a dose reduction, for a dose-escalation decision to be made. Treatment delays of up to 14 days within the first cycle are acceptable. Patients who undergo treatment delays will still be considered evaluable.

If one of the first three patients in a cohort experiences a DLT during the first cycle, the cohort will be expanded to six patients. If 2/3 or 2/6 patients in a cohort experience DLT during the first cycle, that dose will be considered intolerable, no further dose-escalations will occur and cohort expansion of the next lowest dose (the presumed maximum tolerated dose – MTD) will commence. Only toxicities occurring during the first treatment cycle will be taken into account for dose escalation decisions.

If a patient withdraws or is withdrawn for reasons other than DLT prior to completing Cycle 1, the patient will be replaced.

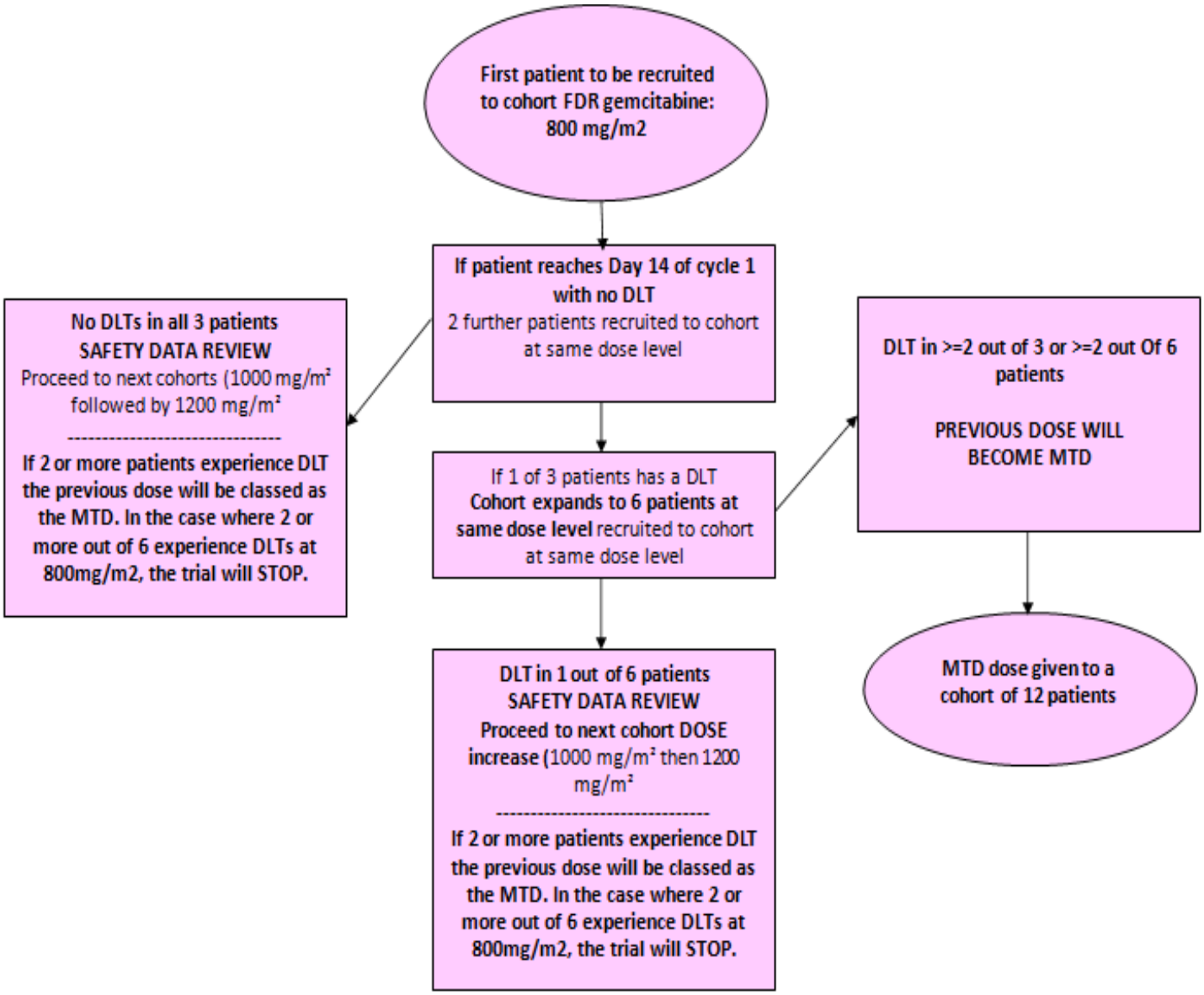
Part B: Maximum tolerated dose cohort

A total of 12 additional patients will be recruited and dosed at the MTD identified in Part A in order to ensure the tolerability and biological activity of gemcitabine in combination with pembrolizumab as well to preliminarily assess response to therapy.

Evaluation of tumour response will be according to RECIST v1.1 (Response Evaluation Criteria in Solid Tumours) criteria. The RECIST v1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria (complete response, partial response, stable disease or progression of disease) are presented in the Appendix.

All patients will have imaging performed at the end of the 3rd and the 6th cycle. After cycle 6, RECIST evaluation will be performed at the end of every third cycle for the duration of the entire study, or more frequently if it deemed necessary by the Investigator.

4.2 Study flow chart



5. SELECTION OF PATIENTS

5.1 Entry Criteria

Patients with newly diagnosed metastatic or inoperable leiomyosarcoma, for whom gemcitabine monotherapy is deemed appropriate or previously treated leiomyosarcoma, not including gemcitabine, with disease progression documented in the 12 weeks prior to enrolment.

5.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Have a histologically confirmed case of undifferentiated pleomorphic sarcoma or leiomyosarcoma and be willing to consent for archival tumour material to be requested for transfer to The Royal Marsden for future review.

2. Have biopsiable disease and be willing to agree to a biopsy in order to permit acquisition of mandatory paired tumour biopsies done during screening and following 9 weeks of treatment for analysis of immunomodulation.

3. Be willing and able to provide written informed consent/assent for the trial

4. Be $\geq$ 18 years of age on day of signing informed consent

5. Have a performance status of 0 or 1 on the ECOG Performance Scale.

6. Have measurable disease based on RECIST 1.1.

7. Have a life expectancy of >12 weeks (investigator to record this in patient's medical notes)

8. Demonstrate adequate organ function as defined in Table-1 (all screening labs should be performed within 28 days of treatment initiation).

Table 1- Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1.5 and 10^9/L
Platelets	≥100 x 10^9/L
Hemoglobin	≥9 g/dL without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR** Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** **≤** 5 X ULN for subjects with liver metastases
Albumin	≥25 g/L
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

9. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

10. Female subjects of childbearing potential (Section 7.7.2) must be willing to use an adequate method of contraception as outlined in Section 7.7.2 – Contraception, for the course of the study through 6 months after the last dose of study medication.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

11. Male subjects of childbearing potential (Section 7.7.2) must agree to use an adequate method of contraception as outlined in Section 7.7.2 - Contraception, starting with the first dose of study therapy through 6 months after the last dose of study therapy.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

5.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

3. Has a known history of active TB (Bacillus Tuberculosis)

4. Hypersensitivity to either Pembrolizumab or Gemcitabine or any of their excipients.

5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

6. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study if considered appropriate after undergoing a baseline neurological examination.

Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

9. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

10. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or current pneumonitis/interstitial lung disease.

11. Has an active infection requiring systemic therapy.

12. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

14. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 6 months after the last dose of trial treatment.

15. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

16. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

17. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

18. Has received a live vaccine or live-attenuated vaccine within 30 days of planned start of study therapy. Administration of killed vaccines is allowed

Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

5.4 Screening and enrolment

The Investigator at site should keep a record of all patients screened for entry into this study. Copies of the screening logs should be filed in the Site File. For each patient the primary reason for exclusion should be recorded. Diagnostic data obtained as part of the patient's standard care can be used to determine eligibility provided they fall within the protocol defined timelines. Written informed consent must be obtained prior to the patient undergoing any study specific procedures.

5.5 Registration

When the patient signs the consent form, they will be registered onto the study and allocated a trial ID that will be used to identify the patient for all future assessments, before entering screening. Once all the screening assessments have been completed and the data entered in the CRFs, the patient will be assessed for eligibility. This eligibility assessment will also be confirmed by a member of RM-CTU. If eligible, the patient will be enrolled and begin on the trial, keeping the same trial ID assigned at consent. If the patient is not eligible then the local investigator will make alternative arrangements for the treatment of the patient.

The trial ID will be a unique number that once assigned will become the permanent study identifier for that patient. In the event a patient is registered onto the study but does not begin

treatment, then that patient's trial ID will not be reassigned. Treatment will begin within 7 days from the date eligibility is confirmed by a member of RM-CTU. To ensure patient confidentiality, patients will only be identified on CRFs, other trial specific forms and all communication to RM-CTU using their assigned trial ID. It is the PI's responsibility to maintain a confidential record of the identity i.e. full name, date of birth and hospital number for the patients enrolled in this study and their assigned trial ID. At the end of the study this record should be archived along with the Site File.

6. STUDY PLAN AND PROCEDURES

6.1 Visit Schedule

Trial Period:		Treatment Cycles																		End of Treatment		Post-Treatment			Ad-Hoc
Treatment Cycle/Title:	Main screening	1		2		3[l]		4[l]		5[l]		6[l]		7[l]		8[l]		Cn D1[l]	Cn D8[l]	Discon	Safety Follow-up	Safety Follow-up	Follow-up visits[j,k]	Survival F/up	
Scheduling Window (Days):	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3						
		D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	At time of Discon	Within 30 days post discon	135 days post discon	Every 6-8 weeks post	Every 12 weeks	Once at any timepoint / visit
Administrative Procedures																									
Informed Consent	x[a]																								
Inclusion/Exclusion Criteria	x																								
Subject Identification Card	x																								
Demographics and Medical History	x																								
Prior and Concomitant Medication	x	x		x		x		x		x		x		x		x		x		x	x	x			
Treatment allocation	x[f]																								
Pembrolizumab Administration		x		x		x		x		x		x		x		x		x							
Gemcitabine Administration[h]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x						
Post-study anticancer therapy status																					x	x	x	x	
Survival Status																					x	x	x	x	
Clinical Procedures/Assessments																									
Review Adverse Events[h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Full Physical Examination	x	x																		x	x	x			
Directed Physical Examination[h]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x						
Vital Signs[h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Height	x																								
Weight	x	x		x		x		x		x		x		x		x		x			x	x			
Urinalysis	x	x																							
ECOG Performance Status[h]	x	x[b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Laboratory																									
Pregnancy Test[e]	x	x		x		x		x		x		x		x		x		x		x					
PT/INR and aPTT	x	x																							
CBC with Differential[h]	x	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x	x	x			
Comprehensive Serum Chemistry Panel[h]	x	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x	x	x			
T3, FT4 and TSH	x	x				x[l]				x[l]				x[l]				x[l]		x	x	x			
Efficacy Measurements																									
Tumour Imaging	x						x[c]						x[c]					x[c]		x			x[g]		
Tumour Biopsies/Archival Tissue																									
Archival Tissue -request	x																								
Tumour biopsy	x						x[d]																		
Correlative Studies Blood Collection	x						x[d]													x					
OPTIONAL Tissue & blood samples																				x					x[m]

Visit Schedule Key:

a: Prior to any study specific assessments or procedures
b: Within 72 hours prior to study drug administration on D1 and D8
c: Imaging to be repeated at the end cycle 3 and cycle 6 and after every 3 additional cycles until discontinuation
d: During week 3 of cycle 3
e: Pregnancy test to be performed up to 72hrs prior to starting treatment and on a monthly basis during the trial period.
f: Within 7 days prior to starting treatment
g: Every 6-8 weeks for 1 year, and every 12 weeks thereafter
h: To be performed on D1 & D8 for as long as patient is receiving Gemcitabine on day 8
i: To be performed at cycle 3, 5 and 7 and every 3 cycles thereafter
j: These visits are only for patients who discontinue study treatment for a reason other than disease progression.
k: in the event of a pandemic, follow-up visits of patients who have discontinued GEMMK can be conducted through telephone consultations and blood tests should be arranged by local GP if deemed appropriate by the study team. This is a preventative measure for infections that pose serious risk to human health.
l: In the event of a pandemic state, telemedicine-based consultations may be used to assess patients after C3 in place of in-person visits if deemed safe and appropriate by the investigator or sub-investigator. Patients are required to attend in person to the Royal Marsden Hospital for observations, blood tests and treatment. This would be a preventative and patient protective measure for infections that pose a significant risk to human health.
m: Optional bloods for germline sequencing can be taken at any point in the trial. These bloods should only be collected once. Consent must be given for the bloods to be taken.

6.2 Administrative Procedures

The Visit Schedule summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

6.2.1. Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial. Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the HRA/REC approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to HRA/REC requirements, applicable laws and regulations.

6.2.2. Inclusion/exclusion criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

6.2.3. Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

6.2.4. Prior and concomitant medications review

Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in

sections 8.4 & 8.5

6.2.5. Disease details and treatment

Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

6.2.6. Assigning screening/treatment allocation numbers

During the screening phase, patients will be allocated a Trial ID number that will be used to identify the patient for all future assessments. Upon entering the study, patients will be enrolled with same trial ID which will become their Trial Enrolment ID. This will consist of the Investigator site number followed by the next sequential patient number. The order of entry into the study will determine a patient's cohort and corresponding dose level. The investigator for designated staff will be responsible for allocating and recording patient numbers.

6.2.7. Assigning a Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card after the subject provides written informed consent.

6.3. Clinical Procedures/Assessments

6.3.1. AE Monitoring and safety assessments

The primary endpoint for safety analysis is treatment emergent adverse events.

The following events will be recorded in the CRF as adverse events, from the time of administration of the first dose of study drug:

- CTCAEs all grades (including new events post dose and changes from baseline). All non-clinically significant out of range clinical chemistry, haematology and urinalysis results (in the opinion of the Investigator) will not be reported as adverse events.
- Abnormal findings during clinical assessments, including physical examination, BP and HR.
- Clinical chemistry, haematology, urinalysis results out of range and considered clinically significant in the opinion of the Investigator.
- Spontaneous patient reports.

The investigator or qualified designee will assess each subject to evaluate for potential new or

worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 14.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 8.3 for detailed information regarding the assessment and recording of AEs.

6.3.2. Full physical exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening.

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

6.3.3. Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Visit Schedule (Section 6.1). Vital signs should include temperature, pulse, respiratory rate, and blood pressure. Height will be measured at screening only.

6.3.4. ECOG Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix) at screening, prior to the administration of each dose of trial treatment (Day 1 of each cycle and at day 8 while patient is receiving Gemcitabine), discontinuation of trial treatment and at the safety follow-up visits as specified in the Trial Visit Schedule

6.3.5. Tumour Imaging and assessment of disease

Anti-tumour activity will be assessed according to RECIST v1.1 criteria – please refer to the Appendix for details. CT scans will be performed as appropriate for the RECIST evaluation.

RECIST evaluation will be performed at baseline and at the end of cycle 3 and cycle 6.

Thereafter RECIST evaluation will be performed at the end of every 3 additional cycles for the duration of the study, or more frequently if deemed necessary by the Investigator.

6.3.6. Tumour tissue collection (mandatory) and correlative studies Blood sample

Mandatory tumour biopsies will be collected before the start of therapy and following 3 cycles of therapy. Biopsies will be performed according to local procedures, usually under ultrasound guidance, and handled in accordance with the procedures described in theStudy Sample Manual for the Trial. Mandatory tumour biopsies will be examined by a pathologist to identify parts of the specimen needed for routine histopathological examination. Any remaining material will be used to generate FFPE tissue, fresh frozen samples (snap frozen); and cellular material will be transferred on ice or viably frozen for xenograft implantation into mice.

Bloods will be performed according to local procedures, and handled in accordance with the procedures described in the Study Sample Manual.

30-40ml blood will be collected for correlative research studies at the time-points specified in the Visit Schedule in Section 6.1. 18 mls of blood (2xEDTA tubes) will be collected at the time of pre-treatment biopsy and post-treatment biopsy following 3 cycles of treatment. In addition, 2.5ls of blood will be collected in PAXgene tubes to extract RNA.

6.3.7 Optional blood and tissue collection at significant toxicity

When a patient suffers a significant toxicity blood and tissue samples may be collected; if considered safe and the patient has consented to do so. Tissue will only be collected if it can be obtained as part of a clinically indicated investigation or a therapeutic procedure to treat the toxicity (i.e. colonoscopy for colitis).

6.3.8. Optional research blood collection

Optional research bloods for germline analysis can be taken at any point in the trial and should be taken at the most appropriate timepoint/visit to allow for the collection. Five tubes of bloods will be taken; EDTA 3ml, two EDTA 9ml vacutainer blood and two PAXgene® 2.5mL Blood RNA tubes. Optional research bloods will be collected once. Consent must be given prior to sample collection.

Sample collection will be performed according to local procedures and handled in accordance with the procedures described in the Study Sample Manual. The results of the germline analysis will not be distributed to trial participants.

6.4. Laboratory Procedures/Assessments

Laboratory tests for hematology, chemistry, urinalysis and others are specified in Table 2. Additional blood test results can be collected at the clinician's discretion. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Study Sample Manual.

Bloods for determination of clinical chemistry and haematology will be taken at the times given in the Study Visit Schedule but blood tests can be performed at additional time-points if deemed necessary by a clinician. The date and time of collection will be recorded on the appropriate CRF.

Laboratory tests for screening should be performed within 28 days prior to the first dose of treatment. During treatment, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing at each cycle. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

The clinical chemistry and haematology analysis will be performed at the local laboratory of the Department of Haematology and Clinical Biochemistry at the Royal Marsden Hospital.

Table 2 – Laboratory Tests

Haematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Amylase	Glucose	PT (INR)
Platelet count	Alkaline phosphatase	Protein	aPTT
WBC (total and differential)	Alanine aminotransferase (ALT)	Specific gravity	Total thriiodothyronine (T3)
Red Blood Cell Count	Aspartate aminotransferase (AST)	Microscopic exam *(If abnormal)*	Free tyroxine (T4)
Absolute Neutrophil Count	Lactate dehydrogenase (LDH)	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
Absolute Lymphocyte Count	Uric Acid		Blood for correlative studies
	Calcium		
	Chloride		
	Glucose		
	Phosphate		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Creatinine		
	Creatinine clearance		

	Urea		
	Bicarbonate		
	GGT (Gamma glutamyl transferase)		
† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. Additional blood test results can be collected at the clinician's discretion.			

6.5. Other Procedures

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section **Second Course Phase (Retreatment Period)**. After discontinuing treatment following assessment of CR, these subjects should return to the site for Safety Follow-up Visits and then proceed to the Follow-Up Period of the study (both described in Section 6.6).

6.6. Visit Requirements

Visit requirements are outlined in Section 6.1 – Visit schedule. Specific procedure-related details are provided above in Section 6 – Study Plan and Procedures.

6.6.1. Screening Visit

The screening visit will be conducted prior to the start of gemcitabine and pembrolizumab. (Please refer to Visit Schedule for specific timeframes for screening assessments).

The following procedures will be carried out at screening:

- Written informed consent obtained from patient.
- Demographic data, including date of birth, sex, height, and race.
- Medical and surgical history, including all previous, now resolved, significant medical conditions, date of diagnosis, extent of disease, disease staging, radiation and oncology surgical history.
- Prior and Concomitant medication review
- A Full Physical examination
- Vital signs including height and weight
- ECOG performance status
- Collection of blood sample for haematology and biochemistry profile as per Haematology and Chemistry laboratory tests in Table 2. Thyroid function tests (T3, FT4 & TSH) and PT/INR and aPTT will also be measured.
- A pregnancy test, where appropriate
- Urinalysis
- Confirmation patient meets the study selection criteria (Note: documented evidence of histological confirmation of disease and, if applicable, post-menopausal/sterile status is required for monitoring purposes).
- Tumour Biopsies & correlative studies blood collection
- Tumour Imaging with RECIST evaluation
- Request made for consent for archival tumour material to be requested for transfer to The Royal Marsden for future review.

If a procedure is performed as part of a patient's routine care prior to consent and screening, data from these procedures may be used as part of the screening data, provided they are performed within 72 hours of the screening assessments, thereby not subjecting the patients to repeat assessments.

6.6.2. Treatment Period

Treatment cycles can occur within a scheduling window of +/- 3 days, apart from cycle 1 day 1. Please refer to the Visit Schedule.

Cycle 1

- In addition to the assessments below, adverse events will be recorded on every day that the patient attends the clinic.

Pre-dose (Cycle Day 1)

- A Full Physical examination, including weight.
- Collection of blood sample for haematology and biochemistry profile (as listed in Table 2), thyroid function tests, PT/INR and aPTT and pregnancy test where indicated.

Please Note: Pre-dose bloods must demonstrate Adequate Organ Function Laboratory Values as per Table 1. in order to commence treatment.

If bloods are out of range, cycle 1 day 1 will be delayed until blood results are within ranges stipulated in Table 1.

If cycle 1 day 1 is delayed, please check screening assessment are all still valid on first day of treatment, i.e all assessment completed within 28 days of cycle 1 day 1.

- Vital signs
- Urinalysis
- ECOG performance
- RECIST evaluation when indicated (Note: in Cycle 1, the screening assessment will be used as the pre- dose disease status).
- Review of Adverse Events
- Concomitant medication review
- Recheck eligibility criteria

Administration of study medication (Cycle Day 1)

- Gemcitabine and pembrolizumab should be administered as an intravenous infusion via peripheral or central venous access. The appropriate doses and treatment regime is detailed in section 7.

• Vital signs on Cycle Day 1 are measured every 4 hours +/- 1 hour or as clinically indicated, if the patient is an in-patient during the infusion. (If the patient is an out-patient for the infusion, vital signs on Cycle Days 1 are measured as clinically indicated).

- Recording of concomitant medication

Pre-dose (Cycle Day 8)

- Physical examination
- Collection of blood sample for haematology and biochemistry profile as per Haematology and Chemistry laboratory tests in Table 2.
- ECOG Performance Status
- Vital signs
- Adverse Events review

Cycle 2

- Physical examination on D1 and D8 (D8 assessment needed if patient is receiving Gemcitabine on day 8), including weight on Day 1.
- ECOG performance on Day 1 and day 8 (D8 assessment needed if patient is receiving Gemcitabine on day 8).
- Recheck eligibility criteria.
- Vital signs on Day 1 and Day 8 (D8 assessment needed if patient is receiving Gemcitabine on day 8).
- Recording of concomitant medications on Day 1
- Collection of blood sample for haematology and biochemistry profile as per Haematology and Chemistry laboratory tests in Table 2 (within 72 hours of D1 and D8 while patient is receiving gemcitabine)
- Pregnancy test

Cycles 3, 4 and subsequent cycles

• In addition to the assessments below, adverse events will be recorded on every day that the patient attends the clinic.

- Physical examination, including weight on Day 1
- ECOG performance on Day 1 (and Day 8 while patient is receiving Gemcitabine).
- Vital signs on Day 1 (and day 8 while patient is receiving Gemcitabine).
- Recording of concomitant medications on Day 1

• Collection of blood sample for haematology and biochemistry profile as per Haematology and Chemistry laboratory tests in Table 2 (within 72 hours of D1 and D8 while patient is receiving gemcitabine) and pregnancy test.

• At the end of cycle 3, an additional tumour biopsy will be done. Blood samples for correlative studies will be collected at the same time (See GEMMK Trial Study Sample Manual).

• In the event of a pandemic state, telemedicine-based consultations may be used to assess patients after C3 in place of in-person visits if deemed safe and appropriate by the investigator or sub-investigator. Patients are required to attend in person to the Royal Marsden Hospital for observations, blood tests and treatment. This would be a preventative and patient protective measure for infections, such as covid-19, that pose a significant risk to human health.

RECIST evaluation for subsequent cycles

• RECIST evaluation will be performed at the end of cycle 3 and cycle 6.

• After cycle 6, RECIST evaluation will be performed at the end of every 3 additional cycles for the duration of the study, or more frequently if deemed necessary by the Investigator.

Final Assessment or study withdrawal

The following assessments will be carried out within 30 days of the start of the last dose of study medication or at study withdrawal:

- Collection of blood sample for haematology and biochemistry profile as per Haematology and Chemistry laboratory test in Table 2, including Thyroid function tests.

  • Recording of adverse events.

  • Pregnancy test (where applicable)

  • Concomitant medications.

  • A Full Physical examination.

  • Vital signs.

  • ECOG performance status.

  • Tumour Imaging & RECIST evaluation

  • Collection of blood samples for correlative studies

- In the case of grade 3 and 4 toxicity at discontinuation, blood and samples from affected tissue can be collected if the patient has given consent for this. Tissue should only be collected if it can be obtained as part of a clinically indicated investigation or therapeutic procedure to treat toxicity.

- In the event of a pandemic, follow-up visits of patients who have discontinued GEMMK may be conducted through telephone consultations and blood tests should be arranged by local GP if deemed appropriate by the study team. This is a preventative measure for infections that pose serious risk to human health.

6.6.3. Safety Follow up visits

The mandatory Safety Follow-Up Visits should be conducted approximately 30 and 135 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti- neoplastic therapy, whichever occurs first. SAEs that occur prior to the safety follow-up visit or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab (as described in Section 6.6.6) may have up to three safety follow-up visits, two after the Treatment Period and one after the Second Course Phase. In the event of a pandemic, follow-up visits may be conducted through telephone consultations.

6.6.4. Follow up visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 6-8 weeks by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 12 weeks (± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section 6.6.6. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated. In the event of a pandemic, follow-up visits may be conducted through telephone consultations

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 6.6.6 will move from the follow-up phase to the Second Course Phase when they experience disease progression.

6.6.5. Survival Follow up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.6.6. Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab with SD or better may be eligible for up to one year of additional pembrolizumab therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

Either

- Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1, and

- Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy
- Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

OR

- Had SD, PR or CR and stopped pembrolizumab treatment after 24 months of study therapy for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in **Table – 1**
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 6 months after the last dose of study medication (Reference Section 7.7.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male subject should agree to use an adequate method of contraception starting with the first dose of study therapy through 6 months after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab. Treatment will be administered for up to one additional year.

7. TRIAL TREATMENTS

The treatment to be used in this trial is outlined below in **Table 3 – Trial Treatment**

Drug	Dose/Potency	Dose frequency	Route of Administration	Regimen/Treatment Period	Use
pembrolizumab	200 mg	Day 1 Every 3 weeks	IV infusion over 30 min.	Until disease progression or withdrawal criteria are met; for up to 24 months of uninterrupted treatment or 35 administrations whichever is later.	Experimental

The pembrolizumab dosing interval may be increased due to toxicity as described in Section 7. Pembrolizumab may be continued alone if gemcitabine was stopped because of cumulative toxicity and the patient continues to demonstrate SD or ongoing response

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment period	Use
Gemcitabine	Fixed dose rate Incremental doses of 800mg/m^2 1000mg/m^2 1200mg/m^2	Day 1, day 8 every 3 weeks	IV infusion over 120 min.	For 6-8 cycles depending on tolerability and response. Further cycles of Gemcitabine (up to 35 in total) can be administered if clinically indicated. or withdrawal criteria are met	Experimental

Gemcitabine can be dose band as per standard of care (in line with NHS England guideline)

Trial treatment should begin on the day of registration or as close as possible to the date on which treatment is allocated/assigned.

7.1. Dose Selection/Modification

7.1.1. Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

Pembrolizumab

The dose amount required to prepare the pembrolizumab infusion solution will be a fixed 200 mg IV dose. Details on preparation and administration are provided in the Pharmacy Manual. The pembrolizumab infusion will be administered on day 1 and repeated every 21 days until disease progression or withdrawal criteria are met; for up to 24 months of uninterrupted treatment or 35 administrations whichever is later.

Gemcitabine

A starting dose of 800 mg/m^2 of single agent gemcitabine administered as a fixed dose rate (FDR) of 10 mg/m^2/min during a 120-minute intravenous infusion, on days 1 and 8, every 21 days was selected with subsequent incremental doses to 1000 mg/m^2 and 1200 mg/m^2 depending on dose limiting toxicity (see rationale of dose selection in section 4.0). Cycles will be repeated every 21 days for 6-8 cycles depending on tolerability and response. Further cycles of Gemcitabine can be administered if clinically indicated for up to 24 months of uninterrupted treatment or 35 cycles whichever is later.

Single agent gemcitabine is considered a low risk agent for emesis. Steroids should be avoided for premedication prior to gemcitabine infusion. Premedication will consist of metoclopramide 10 mg IV infusion 30 min prior to gemcitabine infusion. Acute and delayed emesis can be managed with dopamine receptor antagonists (metoclopramide and domperidone), 5-HT3 antagonists (ondansetron), and neurokinin-1 receptor antagonists (aprepitant) in refractory cases. Steroids should be avoided.

7.1.2. Dose Modification (escalation/titration/other)

The investigator will assess the causality of reported SAEs to either single agent gemcitabine or pembrolizumab.

Interventions administered in combination can be difficult to attribute of an adverse event to a single component. The investigator may attribute a toxicity event to the combination, to gemcitabine alone or to pembrolizumab alone, for adverse events listed in [Table 4]. Both interventions must be held according to the criteria in Table 6 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Pembrolizumab. If the AE is considered immune-related, both interventions should be held according to recommended dose modifications.

If an SAE is thought to be related to pembrolizumab (see the investigator's brochure for more details), pembrolizumab will be withheld for drug-related Grade 4 hematologic toxicities, non-haematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per Table 4 below. Adverse events (both non-serious and serious) associated with pembrolizumab exposure, including coadministration with additional compounds may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. See Section 7.6.1 for supportive care guidelines, including use of corticosteroids.

Participants may not have any dose modifications (no change in dose or schedule, as described in Table 4) of pembrolizumab in this study. If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions. If the toxicities do resolve and conditions are aligned with what is

defined in Table 4, the combination of gemcitabine and pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to gemcitabine alone, re-initiation of pembrolizumab as a monotherapy may be considered at the investigator's discretion.

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab monotherapy and IO CombinationsGeneral instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last study intervention treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If study intervention has been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v4.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v4.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
				• 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
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone 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 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue		

irAEs	Toxicity Grade (CTCAE v4.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	Grade 3 or 4	Withhold or permanently discontinue [d]	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v4.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

Dose modification for Gemcitabine

A dose-limiting toxicity is defined as:

- Neutropenia <0.5 x 109/L for >5 days. This must be confirmed with repeat blood tests at the Royal Marsden Hospital within 6 days of the diagnosis of neutropenia.
- Febrile neutropenia as per definition by ESMO (>38.3°C or two consecutive readings of >38.0°C for 2 hours and an absolute neutrophil count (ANC) of <0.5 x 109/L or expected to fall below <0.5 x 109/L)
- Thrombocytopenia <25 x 109/L.
- Any non-haematological CTCAE Grade 3 or 4 toxicity that is, in the opinion of the investigator, clinically significant.

The toxicities listed above must be, in the investigator's opinion, likely to be causally linked with the administration of Gemcitabine

If a patient experiences dose-limiting toxicity, treatment will be stopped (including pembrolizumab infusions) and supportive therapy administered as required. A delay of up to 14 days is permitted to allow for resolution of toxicity.

If the toxicity resolves or reverts to CTCAE Grade 0 or 1 or the Baseline (pre-study) level within 14 days of onset of the DLT and the patient is showing clinical benefit, treatment with gemcitabine and pembrolizumab may be restarted at the preceding dose level (at the investigators discretion)

If after a 14-day delay the toxicity has not resolved to CTCAE Grade 0 or 1 or baseline, the patient must be withdrawn from the study or continue with pembrolizumab alone if considered safe.

If unacceptable toxicity occurs after 14 days of therapy, doses may be reduced after consultation with the responsible project physician. Patients requiring dose reductions during the first cycle of treatment will be considered non-evaluable. The dose can be de-escalated by 1 dose level in an individual patient. Thereafter if a patient experiences drug-related CTCAE Grade 3 or greater then no further gemcitabine therapy may be administered and the patient must be withdrawn from the study or continue with pembrolizumab alone if considered safe.

Toxicities which are, in the Investigator's opinion, a consequence of treatment with Gemcitabine will be managed according to the Royal Marsden Sarcoma Unit's standard procedures for managing Gemcitabine-related toxicity. Patients will be clinically assessed prior to the administration of every dose of Gemcitabine.

Following 6 cycles of chemotherapy, if the patient has ongoing response to therapy (stable disease or tumour regression) and gemcitabine had to be stopped because of cumulative toxicity or patient choice, pembrolizumab infusions can be continued every 3 weeks until discontinuation criteria are met.

Re-treatment with Gemcitabine

Before a patient can start a second or subsequent cycle of treatment, the following blood count parameter criteria must be met:

- Absolute neutrophil count ≥1.5 x 10^9/L.
- Platelet count ≥100 x 10^9/L.
- No non-haematological, drug-related toxicity > CTCAE grade 1 or greater than pre-existing baseline level.

If the patient does not meet the criteria, then a subsequent cycle of treatment may be delayed for a maximum period of 14 days. If after 14 days the criteria remain unmet the patient must be withdrawn from the study and the toxicity or haematological finding must be captured on the CRF as an adverse event.

The re-treatment criteria apply to the start of a second or subsequent cycle only and are not applicable to the entire cycle, i.e. it is acceptable to have grade 2 or above toxicity following treatment however, this must have recovered or improved prior to re-treatment.

7.2. Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the visit schedule (Section 6.1). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis, other than the first patient in the study, who will be monitored as an in-patient for 72 hours.

Gemcitabine

Gemcitabine will be administered first (before pembrolizumab) at a fixed dose rate (FDR) of 10 mg/m^2/min during a 120-minute intravenous infusion, on day 1. It will be subsequently re-administered on day 8 and the cycle repeated every 3 weeks.

Pembrolizumab

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. The site should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

7.3. Trial Blinding/Masking

This is an open-label trial; therefore the investigator and subject will know the treatment administered.

7.4. Treatment Allocation

The first 12 recruited patients fulfilling the inclusion criteria will be allocated to the dose

escalation cohort. Once the maximum tolerated dose is determined, a further 12 patients will be allocated to the maximum tolerated dose cohort.

7.5. Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the MSD Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

7.5.1. Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over- the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in sections 8.2 & 8.5.

7.5.2. Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab and Gemcitabine
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the investigator.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial. There are no prohibited therapies during the Post-Treatment Follow-up Phase

7.6. Rescue Medications & Supportive Care

7.6.1. Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). For events which are considered to be related to Gemcitabine, the Royal Marsden Sarcoma Unit's standard procedures for Gemcitabine-related toxicity management will be followed. Refer to Section 7.1.2 for dose modification guidance.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

- **Pneumonitis**

In clinical trials, dyspnea, unrelated to underlying disease, has been reported in association with gemcitabine therapy. Dyspnea was occasionally accompanied by bronchospasm. Pulmonary toxicity and pneumonitis has been reported with the use of gemcitabine. The etiology of these effects is unknown. If such effects develop, gemcitabine should be discontinued. Early use of supportive care measures may help ameliorate these conditions. Pneumonitis induced by gemcitabine or pembrolizumab cannot be distinguished on clinical grounds. Any suspicion of therapy-related pneumonitis should be treated as follow:

- For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhoea/Colitis**

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- All subjects who experience 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. For Grade 2 or higher diarrhoea, consider GI consultation and endoscopy to confirm or rule out colitis.

- For **Grade 2 diarrhoea/colitis,** administer oral corticosteroids.
- For **Grade 3 or 4 diarrhoea/colitis,** treat with intravenous steroids followed by high dose oral steroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)
    - For **T1DM** or **Grade 3-4** Hyperglycemia
        - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
        - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- **Hypophysitis:**
    - For Grade 2 events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
    - For Grade 3-4 events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism:**
    - Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

        - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
            - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
            - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
        - **Grade 3-4** hyperthyroidism
            - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hepatic:**
        - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
            - Treat with IV or oral corticosteroids
        - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
        - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal Failure or Nephritis:**
    - For **Grade 2** events, treat with corticosteroids.
    - For **Grade 3-4** events, treat with systemic corticosteroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 5 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500- 1000 mg po (or equivalent dose of antipyretic).

<u>Grades 3 or 4</u> Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

7.7. Diet/Activity/Other Considerations

7.7.1. Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhoea, nausea or vomiting.

7.7.2. Contraception

Pembrolizumab may have adverse effects on a foetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast- feeding women may be enrolled if they are willing to use 2 methods of birth control (1 effective form of contraception from the list provided below and a condom) or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as one of those:

1. Surgically sterilized
2. Postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal)
3. Not heterosexually active for the duration of the study

Patients should start using birth control from study Visit 1 throughout the study period up to 6 months after the last dose of study therapy. The following are considered as effective birth control methods:

1. Combined oral/intravaginal/transdermal contraceptive agent associated with inhibition of ovulation (which contains estrogen and progestogen both)
2. Progestogen-only oral/injectable/implantable hormonal contraception associated with inhibition of ovulation
3. Copper intrauterine device (IUD)
4. Intrauterine hormone-releasing system (IUS)
5. Bilateral tubal occlusion
6. Vasectomised partner
7. Sexual abstinence

Patients should be informed that taking the study medication may involve unknown risks to the foetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the safety follow-up period. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

7.7.3. Use in Pregnancy

If a patient inadvertently becomes pregnant while on treatment with pembrolizumab, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to MSD without delay and within 24 hours if the outcome is a serious adverse event (e.g., death, abortion, congenital anomaly, or other disabling or life- threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the foetus or newborn to the RM-CTU.

7.7.4. Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

7.8. Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 6.5 – Other Procedures.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent
- Confirmed radiographic disease progression
  Note: For unconfirmed radiographic disease progression please see Section 6.3.5.
  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved.
- Unacceptable adverse experiences as described in Sections 7 & 8.
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later

  Note: *24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 6.6.6.*

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6.1 (Visit schedule) and Section 6.6 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 8.4). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non- study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.8.1. Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 6.6.6.

7.9. Subject Replacement Strategy

If a patient is withdrawn from the study for reasons other than DLT before the end of the first treatment cycle, the patient must be replaced. This will be done for both parts A and B.

If a patient withdraws from the study prior to completion of their current cycle of treatment, and for reasons other than progression or non-tolerability, the reason for withdrawal should be sought and recorded on the case report form. AEs should be followed up until resolution.

When patients are withdrawn from the study, they can ask for their sample to be destroyed. In the event that testing has already been performed, requests to destroy test results will not be possible as the associated data may be required for audit purposes by a regulatory authority.

Patients that withdraw from the study or discontinue treatment after completion of the first treatment cycle will not be replaced.

7.10. Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete.

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

4. Plans to modify or discontinue the development of the study drug

In the event of MSD decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

8. PHARMACOVIGILANCE

8.1. Adverse events

8.1.1. Adverse Event Definition

An AE is defined as any untoward, undesired or unplanned occurrence (including deterioration of a pre-existing medical condition) in a patient administered a pharmaceutical product or undertaking a protocol-specified procedure.

An AE can be an unfavourable and unintended sign, symptom, disease, and/or laboratory or physiological observation associated with the use of a medicinal product of protocol-specified procedure but does not necessarily have to have a causal relationship to this treatment or procedure.

Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre- existing condition (present at baseline) that is temporally associated with the use of the pembrolizumab or Gemcitabine, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited

to, onset of menses or menopause occurring at a physiologically appropriate time.

Adverse events may also occur in screened patients during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, or a procedure.

8.1.2. Adverse Reaction Definition

An AE assessed by the Principal Investigator and / or Chief Investigator as reasonably likely to be related to the administration of a medicinal product or protocol-specified procedure.

8.1.3. Disease Progression

Disease progression of the cancer under study is not considered an adverse event unless it results in hospitalisation.

8.1.4. New Cancers

The development of a new cancer should be regarded as an SAE and reported accordingly.

8.1.5. Abnormal Laboratory Test Results

All clinically important abnormal laboratory test results occurring during the study will be recorded as AEs. The clinically important abnormal laboratory tests will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator, or until a diagnosis that explains them is made.

8.1.6. Pregnancy and Lactation

Pregnancy and lactation are not considered adverse events, however these events should be reported to the RM-CTU following guidance in section 8.7.

8.2. Assessing and Recording Adverse Events

All adverse events will be recorded from the time of consent until 135 days after the date of the administration of the last dose of Pembrolizumab. They will be followed up according to local practice until the event has stabilised or resolved, or the follow-up visit has taken place, whichever is the sooner. Serious Adverse Events (SAEs) will also be recorded throughout the study. The reporting timeframe for adverse events meeting any serious criteria is described in section 8.4.

Follow-up of AEs with a causality of possible, probable or highly probable will continue until the events resolve, stabilise or the patient completes the trial. Any unresolved AEs at the patient's last visit should be followed up for as long as medically indicated, but without further recording in the eCRF.

If an Investigator learns of any AE that he/she consider serious, including death, at any time after a patient has completed the study and he/she considers there is a reasonable possibility that the event is related to pembrolizumab or Gemcitabine, the Investigator should notify the RM-CTU.

The following details will be collected in the eCRF for each AE:

- AE description / diagnosis
- Date of onset and date of resolution
- NCI-CTCAE grade maximum intensity
- Seriousness
- Investigator causality rating against the study medication (yes/no)
- Action taken with regard to study medication
- Outcome

For the pre-registration period adverse events will not be collected in patients that have not undergone any

protocol-specified procedure or intervention. If the patient requires a blood draw, fresh tumour biopsy etc. for the study then the patient will be required to consent to the main study and AEs will be captured as described above. In the case of grade 3 and 4 toxicity, blood and samples from the affected tissue can be used for immune analysis, genomic and proteomic studies. Tissue will only be collected if it can be obtained as part of a clinically indicated investigation or therapeutic procedure to treat toxicity. This is not mandatory.

8.3. Evaluating Adverse Events

AEs will be evaluated by an investigator who is a qualified physician.

Determining AE Severity and Grade

AE severity and grade will be evaluated according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grades which change indicating an improvement in toxicity are not reported as AEs.

Grade 1	Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation or hospitalisation indicated; disabling; limiting self-care ADL.
Grade 4	Life threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE

Determining AE Causality

The Principal Investigator must endeavor to obtain sufficient information to assess the causality of the AE and must provide his/her opinion whether the event has any relationship to the administered study treatment / procedure. This may require instituting supplementary investigations of significant AEs based on their clinical judgment of the likely causative factors and/or include seeking a further opinion from a specialist in the field of the AE.

Causality is the relationship of an AE to the IMP and it will be determined by criteria that are given in **Table 6 Determining AE Causality.**

Definite:	• There is clear evidence to suggest a causal relationship. • Starts within a time related to the IMP administration and • No obvious alternative medical explanation.
Probable:	• There is evidence to suggest a causal relationship • Starts within a time related to the IMP administration and • Cannot be reasonably explained by known characteristics of the patient's clinical state.
Possible:	• A causal relationship between the IMP and the AE is at least a reasonable possibility. • Starts within a time related to the IMP administration • However, the influence of other factors may have contributed to the event (e.g.the patient's clinical condition, other concomitant treatments).
Unlikely:	• There is little evidence to suggest there is a causal relationship. • There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment). • The time association is such that the trial drug is not likely to have had an association with the observed effect.
Not related:	• The AE is definitely not associated with the IMP administered.

8.4. Serious Adverse Events (SAEs)

A 'serious adverse event' is defined as follows:

Any untoward medical occurrence or effect that at any dose that:

- results in death;
- is life-threatening or places the patient, in the view of the investigator, at immediate risk of death from the event as it occurred[1];
- requires in-patient hospitalisation or prolongs existing in-patient hospitalisation[2]
- results in persistent or significant incapacity or disability;

- is a congenital anomaly or birth defect;
- is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event.
- is any other medically important event.[3]

[1]This does not include an AE which hypothetically might have caused death if had it occurred in a more severe form.

[2]Hospitalisation is defined as an unexpected inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).

[3] A medically important event may not result in death, not be life threatening, or not require hospitalisation but may be considered a serious adverse event when, based upon appropriate medical judgment, the event that may jeopardise the patient and require medical or surgical intervention to prevent one of the outcomes listed above.

8.4.1. Reporting SAEs

All SAEs regardless of causality, pregnancy or overdose that occur from the time of the first dose of pembrolizumab until the safety follow-up or the initiation of a new anticancer therapy, whichever is earlier, must be reported on the SAE report form within 24 hours of the investigator / designee becoming aware of the event. The SAE form should be sent to the RM-CTU by Fax 02089156762 who will in turn notify the sponsor and MSD of the event.

Assessment of causality for all SAEs will be made by the PI/designee or delegate. Assessment of expectedness will be made by the Chief Investigator (CI). The Investigator Brochure for Pembrolizumab and Summary of Product Characteristics for Gemcitabine as last amended and approved by the national competent authority serve as the reference safety information for the assessment of the expectedness of any adverse reaction that might occur during the clinical trial. The report will then be reviewed by the Chief Investigator (or a nominated representative) to confirm relatedness and expectedness. The NCI CTCAE Version 4 must be used to grade each SAE, and the worst grade recorded. If new or amended information on a previously reported SAE becomes available, the Investigator should report this to the RM-CTU on a new SAE report form. If the SAE has not been reported within the specified timeframes, a reason for lateness must be included when sending the SAE report form. The RM-CTU will in turn submit the updated report to the sponsor and MSD. Please refer to the SAE completion guidelines for further information.

Additionally, any SAE, considered by an investigator who is a qualified physician to be related to the IMP or protocol-specified procedure that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the RM-CTU who will inform the Sponsor and MSD.

8.4.2. Events exempt from being reported as SAEs.

Events specified in this section do not require reporting as SAEs in this trial, unless hospitalisation is prolonged for any reason and then an SAE form must be completed. The events must still be recorded in the appropriate section of the eCRF.

1. Elective admissions to hospital for procedures which were planned and documented in the medical records at the time of consent are not SAEs, and do not require SAE reporting.

2. Hospitalisation for administration of the IMP, or to facilitate study procedures such as pharmacokinetic sampling according to the trial protocol, is also exempt from being reported as an SAE.

3. Progressive disease and death due to disease are not considered SAE's but should be reported in the eCRFs

8.5. Events of Clinical Interest (ECI)

8.5.1. Definition of ECIs

Selected non-serious and serious adverse events can also be classified as Events of Clinical Interest (ECI) and must be reported as described below.

Events of clinical interest for this trial include:

1. an overdose of MSD product, as defined in Section 8.6 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*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.

3. Any AEs identified in the below table 7 can be classified as immune-related events of clinical interest. All irECIs should be reported as described in section 8.5.2:

Table 7-Immune related AEs considering ECIs

Pneumonitis - ***(classified as ECI if ≥ Grade 2)***		
Acute interstitial Pneumonitis	Interstitial Lung Disease	Pneumonitis
Colitis - ***(classified as ECI 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
Necrotising colitis	Diarrhoea	
Endocrine - ***(classified as ECI 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 *(classified as ECI)*		
Type 1 diabetes mellitus (if new onset)		
Hematologic - ***(classified as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)***		
Autoimmune haemolytic anaemia	Aplastic anaemia	Thrombotic thrombocytopenic purpura
Idiopathic thrombocytopenia purpura	Disseminated intravascular coagulation	Haemolytic uraemic syndrome
Hepatic - ***(classified as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)***		
Hepatitis	Autoimmune hepatitis	Transaminase elevations (ALTand/or AST)
Infusion reactions - ***(classified as ECI for any grade)***		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic - ***(classified as ECI for any grade)***		

Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular - ***(classified as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)***		
Uveitis	Iritis	
Renal - ***(classified as ECI for ≥ Grade 2)***		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations - (classify as ECI if ***≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)***	
Skin - ***(classified as ECI for any grade)***		
Dermatitis exfoliate	Erythema multiforme	Stevens-Johnson Syndrome
Toxic epidermal necrolysis		
Skin - ***(classified as ECI for ≥ Grade 3)***		
Pruritus	Rash	Rash generalised
Rash maculo-papular	Any rash clinical significant in the physicians judgement.	
Other - ***(classified as ECI for any grade)***		
Myocarditis	Pancreatitis	Percarditis
Any other grade 3 event which is considered immune-related by the physician.		

Patients should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and patients should be asked for signs and symptoms suggestive of an immune-related event. Patients who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

8.5.2. Reporting of ECIs

For the time period beginning at treatment allocation through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to MSD product, must be reported using the SAE/ECI report form within 24 hours of the PI/designee becoming aware of the event to the RM-CTU by fax 02089156762 who will in turn notify who will inform the Sponsor and MSD.

8.6. Definition of an Overdose for this Protocol and Reporting of an Overdose

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab.

Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a MSD product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of MSD's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose either SAE or ECI must be reported within 24 hours of the PI or designee becoming aware of the event to the RM-CTU by Fax 0208 915 6762 who will inform MSD.

8.7. Reporting of Pregnancy and Lactation

It is the responsibility of investigators or their designees to report any pregnancy or lactation in a patient (spontaneously reported to them), that occurs during the trial or within 120 days of completing the trial, or 12 weeks following cessation of treatment if the patient initiates new anticancer therapy, whichever is earlier. All patients who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious adverse events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported with the parents' consent. Such events must be reported within 24 hours to RM-CTU by Fax 0208 915 6762 who will inform MSD.

8.8. Definition of Serious Adverse Reaction (SAR)

A SAR is defined as an SAE that is judged to be related to any dose of study drug administered to the patient.

8.9. Definition of Suspected Unexpected Serious Adverse Reaction (SUSARS)

A SUSAR is a serious adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product).

8.10. Reporting of SUSARs

All SUSARs must be reported using the SAE report form within 24 hours of the PI/designee becoming aware of the event to the RM-CTU by fax 02089156762. The RM-CTU will in turn notify the Sponsor, MSD, relevant Independent Ethics Committee (IEC) / Institutional review, appropriate regulatory authorities and the participating Principal Investigators in accordance with regulatory requirements and within the timelines as defined below:

- For fatal and life-threatening SUSARs the sponsor should report at least the minimum information as soon as possible and in any case no later than seven days after being made aware of the case. In addition, follow-up reports for fatal and life-threatening SUSARs will be provided within 8 days of the date of the initial report.
- SUSARs which are not fatal and not life-threatening are to be reported within 15 days

Follow up of patients who have experienced a SUSAR should continue until recovery is complete or the condition has stabilised.

8.11. Annual Reporting of Serious Adverse Events

The Development Safety Update Report (DSUR) will be submitted annually on the anniversary of regulatory approval for the trial. This report will be submitted to regulatory authorities and Independent Ethics Committees (IEC) in accordance with all applicable global laws and regulations. Copies will be forwarded to the Sponsor and Investigators.

8.12. Urgent Safety Measures

The Sponsor or Investigator may take appropriate urgent safety measures (USMs) in order to protect the patient of a clinical trial against any immediate hazard to their health or safety. This includes procedures taken to protect patients from pandemics or infections that pose serious risk to human health.

USMs may be taken without prior notification from the competent authority. However the CI/DI must notify the Medicines and Healthcare Products Regulations (MHRA) the Research Ethics Committee (REC) and the Sponsor of the new events and the measures taken and the plan for further action immediately via telephone, and in writing within 3 days of the measure being implemented. Should the site initiate a USM, the Investigator must inform the RM-CTU immediately by:

- Email: GEMMK.Trial@rmh.nhs.uk
- Telephone: 020 88642 6011 Ext: 6766
- Fax: 020 8915 6762

The notification must include:

- The date of the USM
- Who took the decision; and
- Why the action was taken

RM-CTU will then inform the Sponsor, the MHRA and the REC immediately via telephone, and in writing within three days of USM initiation. RM-CTU will distribute the response and any subsequent amendments to the trial site.

9. STATISTICAL AND DATA ANALYSIS PLAN

9.1. Sample Size

There will be a maximum of 18 patients in part A. The trial will continue to recruit a further 12 patients in part B at the MTD determined in part A. We expect to recruit all patients in part A (3+3 design) within the first 12 months of the study recruitment period. Since the part B (expansion phase) will be descriptive 12 patients will be sufficient as it is expected to recruit a further 12 patients in the last 12 months of the study recruitment period.

9.2. Statistical Analysis

9.2.1. Primary Endpoint

Toxicities will be tabulated as frequencies and proportions.

9.2.2. Secondary Endpoints

All patients in part A and part B will be included in the secondary endpoint analysis regardless of which dose level they are treated.

Overall best response rate will be presented as a proportion of patients with a response of CR or PR at 9 weeks of starting treatment according to the RECIST criteria. This will be presented with the appropriate 95% CI.

Best reduction in tumour size will be presented as waterfall plots.

Progression free survival will be calculated using Kaplan Meier methods. This will be defined from starting treatment to date of progression or death where any progression free surviving patients will be censored at last follow up. The median and 9 week PFS will be presented with the 95% CI.

9.2.3. Exploratory Endpoints

All patients in part A and part B will be included in the exploratory endpoint analysis.

Immunophenotype of pre and post treatment (9 weeks), location of tumour infiltrating lymphocytes and response stratification according to tumour PD-L1 expression will be presented as descriptive statistics where any qualitative data will be presented as frequencies, proportions and 95% CIs and any quantitative data will be presented with mean, SD, median, IQR and ranges.

To identify predictive biomarkers of immune response to PD-L1, univariate binary logistic regression analyses will be conducted. Any biomarkers with a p value<0.1 will be entered into a forward stepwise multivariate model with known prognostic factors.
To identify predictive biomarkers of immune response to PD-L1, univariate binary logistic regression analyses will be conducted. Any biomarkers with a p value<0.1 will be entered into a forward stepwise multivariate model with known prognostic factors.

10. LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

10.1. Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies for Pembrolizumab will be provided by MSD as summarized in Table 8. Clinical supplies for Gemcitabine as summarised in table 8 below will be obtained from hospital stock.

Table 8 – Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/ 4mL	Solution for Infusion

Product Name & Potency	Dosage Form
Gemcitabine 38mg/ml	Concentrate for solution for Infusion

10.2. Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

10.3. Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the investigator are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

10.4. Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

10.5. Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from MSD or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

11. REGULATORY, ETHICAL AND LEGAL ISSUES

11.1. Good Clinical Practice

The study will be conducted in accordance with the conditions and principles of GCP as defined in the clinical trials regulations.

11.2. Research Ethics Committee-REC/ Regulatory Authority – RA

11.2.1. Initial Approval

Before starting the trial, the protocol, patient information sheet, consent form, any other written information that will be provided to the patients and any advertisements that will be used and details of any patient

compensation must be approved by the Royal Marsden/Institute of Cancer Research joint Committee for Clinical Research. Once approved, the study will then be submitted to the relevant Ethics Committee for their review and approval.

Prior to the shipment of IMP and the enrolling any patients the Investigator at each site is responsible for any site specific assessments and obtaining local R&D approval for the study. The participating site will be required to sign an agreement with RM-CTU which includes requirement to sign and adhere to the trial protocol.

11.2.2. Approval of Amendments

Any protocol amendment should be agreed with the trial management group (TMG) and be approved by the sponsor prior to submission and review by the relevant Ethics Committee. Once favourable opinion from IEC has been obtained the amendment can be distributed to site and implemented. It is the responsibility of the Principal Investigator to submit amendment to their R&D department for R&D approval Amendments requiring REC approval may be implemented only after a copy of the REC/RA's approval letter has been obtained. Amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented prior to receiving Sponsor or REC/RA approval. However, in this case, approval must be obtained as soon as possible after implementation.

11.2.3. Annual Safety Reports and End of Trial Notification

It is the responsibility of the sponsor to submit the Development Safety Update Report annually to the MHRA/ REC on the anniversary of the studies MHRA/REC approval. This will facilitate the authorities continuing review of the study. These authorities will also be informed of the end of the study by the sponsor within 90 days of the trial completion. Copies of these reports will also be held within the main trial master file.

11.3. Regulatory Authority Approval

The study will be performed in compliance with UK regulatory requirements. Clinical Trial Authorisation (CTA) from the Medicines and Healthcare products Regulatory Authority (MHRA) will be obtained prior to the start of the study. In addition, the MHRA must approve amendments (as instructed by the Sponsor), receive SUSAR reports and annual safety updates, and be notified of the end of the trial.

11.4. Notifications of Serious Breaches to GCP and / or the Protocol

The Sponsor will notify the MHRA and REC in writing of any serious breaches of:

a. The condition and principles of GCP in connection with the trial
b. The protocol

This will be done within 7 days if becoming aware of that breach, in accordance with the applicable UK regulations as amended from time to time.

For the Purpose of the regulations a "serious breach" is a breach which is likely to effect to a significant degree

a. The safety or physical integrity of the subjects of the trial; or
b. The scientific integrity of the trial.

Systematic or persistent non-compliance by the site with GCP and/or the study protocol, including failure to report SAEs occurring on trial within the specified timeframes, may be deemed a serious breach.

11.5. Insurance and Liability

The Sponsors have secured indemnity from the manufacturer of pembrolizumab for patients in relation to adverse side effects for medicine-induced injury. Indemnity for participating hospitals is provided by the usual NHS indemnity arrangements for clinical negligence. A copy of the relevant insurance policy/indemnity scheme or summary shall be provided on request.

11.6. Contacts with General Practitioner (GP)

It is the Investigator's responsibility to inform the patient's GP by letter that the patient is taking part in the study provided the patient agrees to this, and information to this effect is included in the PIS and ICF. A copy of the letter should be filed in the Site File. A template letter approved by the REC/RA will be provided by the Sponsor to the participating site.

11.7. Patient Confidentiality

11.7.1. Patient Confidentiality and Data Sharing

The Principal investigator must ensure that the patient's confidentiality is maintained in compliance with the UK Data Protection Acts of 1998 & 2018. In all study correspondence submitted to the RM-CTU all participants will be identified by their initials and unique Trial Reference study number only which will be used in all e-CRFs or other documents submitted to the RM-CTU. In compliance with GCP guidelines, it is required that the investigator and institution permit authorised representatives of the sponsor and of the regulatory agency(s) direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analysing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

11.7.2. Pharmacogenetic Confidentiality

All pharmacogenetic samples and the information associated with the samples will be coded and stored appropriately to ensure confidentiality of the patient's information and to enable destruction of the samples if requested. Since the evaluations are not expected to benefit the patient directly or to alter the treatment course, the results will not be placed in the patient's medical record and will not be made available to members of the family, the personal physician, or other third parties, except as specified in the informed consent.

11.8. Data Collection and Documentation

It is the Investigator's responsibility to ensure that all relevant data is clearly recorded in the medical records. The Investigator must allow the Trial Monitors direct access to relevant source documentation for verification of data entered into the e-CRF, taking into account data protection regulations. The clinical data should be recorded in the e-CRF and the must be verifiable by the source data.

The patients' medical records, and other relevant data, may also be reviewed by appropriate qualified personnel independent from the sponsor appointed to audit the trial, or by REC. Details will remain confidential and patients' names will not be recorded outside the hospital.

The Principal Investigators at each centre are confirming agreement with his/her local NHS Trust to ensure that:

- sufficient data is recorded for all participating patients to enable accurate linkage between hospital records and e-CRFs
- source data and all trial related documentation are accurate, complete, maintained and accessible for monitoring and audit visits
- original consent forms are dated and signed by both patient and investigator and are kept together in a central log together with a copy of the specific patient information sheet(s) given at the time of consent

- all essential documents must be retained after the trial ends to comply with current legislation
- No study document will be destroyed without prior written agreement between the Sponsor and the PI. Should the PI wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

11.9. End of Trial

The end of the trial is defined as the last patient's last visit.

12. DATA AND STUDY MANAGEMENT

12.1. Source Data

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial are classified as source data. Source data are contained in source documents; these are defined as original documents, data, and records e.g., hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial.

12.2. Language

All e-CRFs will be in English. Generic names for concomitant medications should be recorded in the CRF wherever possible. All written material to be used by patients must use vocabulary that is clearly understood, and be in the language appropriate for the study site.

12.3. Data Collection

The medical records/medical notes should be clearly marked and to allow for easy identification of a patient's participation in the clinical trial. The Investigator (or delegated member of the site study team) must record all data relating to protocol procedures, IMP administration, laboratory data, safety data and efficacy data into the e-CRF.

12.4. Electronic Recording of Data

Patients' data will be documented on a trial specific e-CRF designed by RM-CTU. Should the eCRF not be available before the study is ready to begin paper CRFs will be used until the switch can be made.

The Investigator is responsible for ensuring the accuracy, completeness, clarity and timeliness of the data reported in the e-CRFs. Only the Investigator, and those personnel who have completed the Study Team Responsibilities Signature Log/Delegation Log as authorised by the PI, should enter or change data in the e-CRFs. All protocol required investigations must be reported in the e-CRF. The Investigators must retain all original reports, traces and images from these investigations for future reference. The data will be entered in a clinical trials database (Macro). If a patient withdraws from the study, the reason must be noted on the e-CRF.

Authorised site personnel must not enter study-specific data directly into e-CRFs and ensure all results are appropriately documented in the patients' medical records. The e-CRF will be signed electronically by the Investigator or by an authorised staff member. Study specific information will be entered into an e-CRF visit by

visit. Data that are derived should be consistent with the source documents or the discrepancies should be explained. All e-CRF data should be anonymous, *i.e.* identified by study patient trial enrolment ID number only.

12.5. Data Management

Data management will be carried out by RM-CTU using an electronic database and in accordance with the data management plan agreed by the RM-CTU and RDSU. Data entry will be carried out by appropriately trained personnel at participating centres. Queries will be raised centrally by the trial manager / trial monitor and sent to the participating centre for resolution.

12.6. Study Management Structure

12.6.1. Delegation of Responsibilities

This trial is sponsored by the Royal Marsden. This trial will be conducted in accordance with the professional regulatory standards required for non-commercial research in the NHS under the research governance framework for health and social care and good clinical practice. The following responsibilities have been delegated to:

12.6.1.1. RM-CTU

RM-CTU has overall responsibility for facilitating and coordinating the conduct of the trial and is also responsible for collating data obtained, and undertaking and reporting all analyses. The responsibilities of RM-CTU for the day-to-day management of the trial will include the following;

- ensuring an appropriate ethics opinion has been sought, and any amendments have been approved
- giving notice of amendments to protocol, make representations about amendments to the Main REC, HRA and MHRA as applicable
- notifying site and Sponsor that the trial has ended
- registering patients
- raising and resolving queries with local investigators
- keeping records of all serious adverse events (SAEs), overdose incidents, pregnancies and ECI's reported by investigators (as outlined in section 8 above)
- notifying the Main REC, MHRA and Investigators of related Serious Adverse Events

12.6.1.2. Merck Sharp & Dohme (MSD) Corp.

MSD will be providing study funding and an investigational medicinal drug - pembrolizumab.

12.6.1.3. Sarcoma Research Fund

A grant from the Sarcoma Research Fund will fund the translational research.

12.7. Protocol Compliance and amendments

The participating site will be required to sign an agreement with RM-CTU which includes requirement to sign and adhere to the trial protocol.

Any protocol amendment should be agreed with the trial management group (TMG) and be approved by the sponsor prior to submission and review by the relevant Ethics Committee and the MHRA where required. Once favourable Opinion from REC and if applicable the MHRA has been obtained the amendment may be disseminated to site and implemented. It is the responsibility of the Principal Investigator to submit amendment to their R&D department for R&D approval.

12.8. Trial Management

The RM-CTU will be responsible for the day-to-day coordination and management of the trial. This includes all duties relating to safety reporting. A trial agreement will be signed between the site and RM-CTU. Once all relevant trial approvals are in place an initiation (visit or teleconference) will be conducted. In addition, training and ongoing advice will be provided by trial training workshop(s), site initiation and ongoing site support to each participating site by Trial Management Group (TMG).

12.8.1. Trial Management Group

A Trial Management Group (TMG) will be set up and membership will include Chief Investigator, Chief Co Investigator, Trial Statistician and Trial Manager. Principal Investigators and other key study personnel will be invited to join the TMG as appropriate. The TMG have operational responsibility for the conduct of the trial.

At the beginning of the study the TMG will meet every 2 weeks until the first 6 patients registered to receive gemcitabine and pembrolizumab have completed 12 weeks of treatment.

Once all 6 patients have completed 12 weeks of treatment a safety assessment will be conducted reviewing all AE's, SAE's and radiation toxicities occurring in this population.

12.8.2. Safety Review Committee (SRC)

The SRC will include the Chief investigator for the trial (Dr Robin Jones), a Representative from RM-Clinical Trials Unit, a Statistician and be chaired by a clinician, independent of study investigators. The SRC will meet at every dose escalation point. The role of the SRC is to:

- Review relevant safety data and make dose escalation decisions for all studies
- Reviews all SAEs and emerging safety data both from RM Sponsored studies and external SUSARS received from MSD
- Monitor progress of the trials and ensure emerging safety information is evaluated and protocol and GCP principles are adhered to.

The SRC terms of reference, roles and responsibilities will be defined in a charter. Further internal or external experts may be consulted as necessary.

12.9. Monitoring

During the trial the Royal Marsden Monitoring Team is responsible for monitoring data quality in accordance with relevant standard operating procedures (SOPs). Incoming data will be monitored for protocol compliance and if any inconsistent or missing data is identified queries will be sent to the site for resolution. Any systematic inconsistencies may trigger an onsite monitoring visit.

The trial statistician will periodically examine the data for anomalies and outliers, such as too few or too many events. Queries will be raised by the trial coordinators in such situations and communication with the clinical teams will take place. In addition, statistical monitoring of unusual dates and inconsistent data will take place. Again, these will raise queries via the trial coordinators.

If an on-site monitoring visit is required, RM-CTU will contact the site to agree convenient date. The site must ensure that relevant site file and patient notes are available for review. Royal Marsden Monitoring Team staff conducting onsite monitoring will review the investigator site file and carry out source data verification to confirm compliance with the protocol, trial agreement.

12.10. Quality Control and Quality Assurance

Quality Control (QC) will be performed according to RM-CTU internal procedures. The study may be audited by a Quality Assurance (QA) representative of the Sponsor. All necessary data and documents will be made available for inspection.

12.11. Clinical Study report

Clinical data will be presented at the end of the trial based on final data listings. The CI/designee together with the trial statistician will prepare a brief clinical study report / publication based on the final data listings. A summary of the report must be provided to the Research Ethics Committee and the MHRA within 1 year from the submission of the end of trial notification.

12.12. Record Retention

Essential documents are documents that individually and collectively permit evaluation of the conduct of the trial and substantiate the quality of the data collected. During the clinical trial and after trial closure the Investigator must maintain adequate and accurate records to enable both the conduct of a clinical trial and the quality of the data produced to be evaluated and verified in accordance with current legislation.

RM-CTU will maintain essential documents to facilitate the management of the trial, audit and inspection in accordance with RM G-SOPs and in compliance with the clinical trial regulatory requirements. The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice. All medical records and TMF documentation will be retained for a minimum of 5 years after the study has concluded.

12.13. Reporting and Publication

The trial results will be submitted for publication in a relevant medical journal with authorship according to the criteria defined by the ICMJE (http://www.icmje.org). These state that: Authorship credit should be based 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Draft publications (manuscripts, abstracts, slides and posters) should be submitted to the RM-CTU for circulation to the relevant parties to allow sufficient time for review prior to submission. There will be a 15 day period to review abstracts, posters or slides and a 40 day period to review manuscripts and respond to the author with any revisions.

12.14. Ethical considerations

Before starting the trial, the protocol, patient information sheet and consent form must be approved by the RM/ICR joint Committee for Clinical Research. Once approved, the study may then be submitted to the relevant regulatory authorities.

It is the Chief and Principal Investigator's responsibility to update patients (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the patient's willingness to continue in the trial. The Chief and Principal Investigator must ensure this is documented in the patient's medical records and the patient is re-consented, where appropriate.

The Sponsor and Chief and Principal Investigator must ensure that the trial is carried out in accordance with the GCP principles and requirements of the UK Clinical Trials regulations (SI 2004/1031 and SI 2006/1928 as amended) and The Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/).

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14. APPENDICES

14.1. Appendix 1 – ECOG Performance Status

Grade	Description
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.

* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis,T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern

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Oncology Group, Robert Comis M.D., Group Chair.

14.2. Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

14.3. Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumours

RECIST version 1.1* will be used in this study for assessment of tumour response. While

either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer:
E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

In addition, volumetric analysis will be explored by central review for response assessment.