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Sponsor Reference:	CFTSp148

The CAPER study: A Phase Ib clinical trial of **C**yclophosphamide **A**nd **PE**mbrolizumab in metastatic **R**enal cell carcinoma (CAPER Trial)

Sponsor:
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Study Protocol Approval

I, the undersigned, hereby approve this clinical study protocol:

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Signature:	Date: 12/12/19
Dr Tom Waddell **Chief Investigator** Consultant Medical Oncologist The Christie NHS Foundation Trust	

Sponsor Representative	
Signature: pp Sian Harrison	Date: 12/12/19
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pp Richard Sechson Signature:	Date: 12.12.19
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General Information

This document describes the CAPER clinical trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the coordinating centre (Liverpool Clinical Trials Centre (LCTC)) to confirm they have the current version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator (CI) /Co-Investigator via the LCTC.

This protocol defines the patient characteristics required for study entry and the schedule of treatment and follow-up. Patient recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements and waivers to authorise non-compliance are not permitted.

Incidence of protocol non-compliance, whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

The template content structure is consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority (HRA) guidance.

Relationship Statements

The Christie NHS Foundation Trust is the Sponsoring organisation and will formally delegate specific sponsoring roles to the CI, Research Sites and the Clinical Trials Unit (CTU), but remains legally responsible for the trial.

The LCTC of the University of Liverpool in collaboration with the CI, Dr Tom Waddell, will have overall management responsibility for the trial from a CTU perspective and will be responsible for the co-ordination of centres.

The LCTC is built upon the experience of the Liverpool Clinical Trials Collaborative, which has full registration with the UK Clinical Research Collaboration (www.ukcrc.org) as their standards and systems were assessed by an international review panel as reaching the highest quality.

Statement of Compliance

This study is designed to comply with the guideline developed by the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and will be conducted in compliance with the protocol, LCTC Standard Operating Procedures and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004.

UK Registration

This study will undergo HRA review and Approval before opening to recruitment. The HRA approval will bring together the assessment of governance and legal compliance in addition to an independent Research Ethics Committee (REC) review provided the through the UK research ethics service. Each centre will confirm they have the capability and capacity to deliver the study locally prior to being open to recruitment.

Furthermore, the study will hold a Clinical Trials Authorisation issued by the Medicines and Healthcare products Regulatory Agency (MHRA).

Liverpool Clinical Trials Centre Merger

During the management of the CAPER Trial the Liverpool Cancer Trials Unit (LCTU) and the Clinical Trial Research Centre (CTRC) have merged to become the Liverpool Clinical Trials Centre (LCTC). The LCTC will continue to use the LCTU PORTAL as a legacy system for the duration of this trial, for the purposes of this protocol it will be referred to as the PORTAL only. For clarity, where SOPs or LCTC SOPs are referred to within this protocol a list of specific unit SOPs used for this trial has been compiled in document SSCAP_D016 CAPER SOP Record.

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Contact/Group	Document Title
Trial Management Group (TMG)	See TMG Term of Reference and Membership Document: TOR009
Trial Steering Committee (TSC)	See TSC Charter CAPER Trial Steering Committee Charter (SSCAP_D011)

Contact Details: Research Site and Principal Investigators

Principal Investigators	Details of the Principal Investigators and research sites are stored in the individual research site files held in the LCTC and on the PORTAL. Please contact the Trial Co-ordinator for further details

Contact Details: Individuals

Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:	**Chief Investigator (CI):**	**Medical Expert who will Evaluate SAE Reports (If CI unavailable):**
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1.0 TRIAL SUMMARY

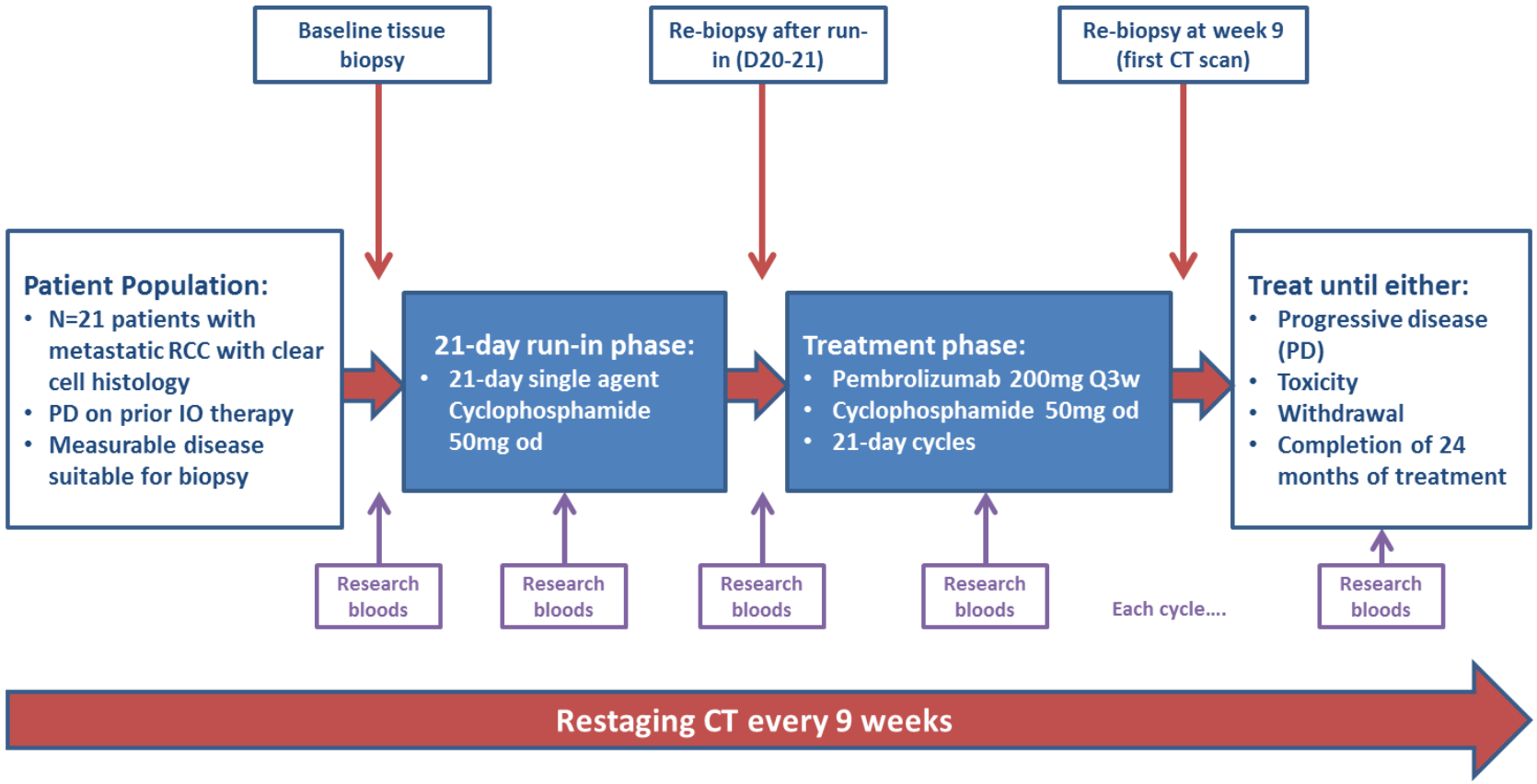
Study Full Title	A phase Ib clinical trial of cyclophosphamide and pembrolizumab in metastatic renal cell carcinoma (RCC) (CAPER Trial)
Abbreviated Title	CAPER Trial
Target Condition	Metastatic Renal Cell Carcinoma
Trial Phase	Ib
Clinical Indication See sections 6.3/6.4 for details list of inclusion/exclusion criteria	**Key Inclusion / Exclusion:** Metastatic RCC with clear cell component Following failure of previous immuno-oncology (IO) therapy: • First-line Ipilimumab / Nivolumab combination • Second- line Nivolumab • Other PD-1 / PD-L1 / anti-CTLA-4 within clinical trials Measurable disease by Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1 criteria Site(s) of disease which are suitable for biopsy Performance status 0-1 Satisfactory organ function; standard FBC / urea and electrolytes / liver function test criteria No evidence of brain metastases No prior treatment with pembrolizumab or cyclophosphamide No prior intolerance to IO therapy No history of autoimmune conditions (apart from standard exclusions) No need for systemic corticosteroids above 10mg/day of prednisolone or equivalent No other malignancy within the last 3 years

	No medically significant co-morbidity in opinion of investigator (e.g. significant cardiac history within last 12 months, stroke within last 12 months, known HIV / Hep B / Hep C)
Trial Type	**Single arm, non–randomised, open label, multi-centre study**
Trial drugs and route of administration	**Cyclophosphamide** • Oral tablet • 50mg once daily (OD) dosing (metronomic schedule) • 21-day run-in period prior to commencing pembrolizumab • Continuous dosing in 21-day cycles throughout (Q3W) **Pembrolizumab** • IV infusion • 200mg flat dosing Q3W • Commenced at C2D1 (following cyclophosphamide run-in) • Continuous dosing Q3W throughout
Endpoints	**Primary:** Objective Response Rate (ORR) per RECIST 1.1 **Secondary / Exploratory:** 1. Progression Free Survival (PFS) 2. Overall Survival (OS) 3. Safety profile of cyclophosphamide and pembrolizumab combination 4. Evaluate dynamic changes in tissue and blood that may correlate with treatment response / resistance
Number of trial participants	21
Number of sites	3-4
Estimated enrolment period	15 months

Estimated duration of trial	36 months
Duration of Participation	**Treatment will be continued until first occurrence of either:** • Disease Progression • Toxicity requiring treatment cessation • Withdrawal for any reason • Completion of 24 months of combination therapy (approximately 34 doses of pembrolizumab) • Complete response (CR) after at least 8 cycles of pembrolizumab and investigator decision to stop
Estimated average length of treatment per patient	**Median 18 weeks** Estimate based on average patient developing progressive disease (PD) according to RECIST 1.1 at time of 2nd CT scan

1.1 Trial Flow Diagram

Figure 1: CAPER study schema



1.2 Trial Schedule of Events

Table 1: CAPER per patient trial procedures

Trial Period:	**Screening Phase**	**Treatment Cycles**							**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Main Study Screening	1 (Cyclo run-in)	2 (Cyclo + Pembro)	3	4	To be repeated beyond 7 cycles			Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up
						5	6	7				
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	At time of discon ± 3	30 days post discon ± 3	Every 9 weeks post discon ± 3	Every 12 weeks ± 3
Administrative Procedures												
Informed Consent[a]	X											
Inclusion/Exclusion Criteria	X											
Demographics and Medical History[b]	X											
Prior and Concomitant Medication Review[c]	X	X	X	X	X	X	X	X	X	X	X	
Cyclophosphamide Compliance Check[d]			X	X	X	X	X	X	X			
Trial Treatment Administration		X	X	X	X	X	X	X				
Post-Study Anticancer Therapy Status									X	X	X	X
Survival Status	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Procedures/Assessments												
Review of Adverse Events[e]		X	X	X	X	X	X	X	X	X		
Physical Examination[f]	X	X	X	X	X	X	X	X	X	X		
Vital Signs and Weight[g]	X	X	X	X	X	X	X	X	X	X		
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X		
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory												
Pregnancy Test – Urine or Serum β-HCG	X[s]	X	X	X	X	X	X	X	X	X	X[u]	X[u]
FBC with Differential[h]	X[t]	X	X	X	X	X	X	X	X	X		
Biochemistry Panel[j]	X[t]	X	X	X	X	X	X	X	X	X		
Urinalysis[k]	X[t]	X	X	X	X	X	X	X	X	X		

Trial Period:	**Screening Phase**	**Treatment Cycles**							**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Main Study Screening	1 (Cyclo run-in)	2 (Cyclo + Pembro)	3	4	To be repeated beyond 7 cycles			Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up
						5	6	7				
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon ± 3	30 days post discon ± 3	Every 9 weeks post discon ± 3	Every 12 weeks ± 3
Thyroid Function[m]	X	X	X	X	X	X	X	X	X			
Efficacy Measurements												
Tumour Imaging[n]	X				X			X	X		X	
Tumour Tissue Collection and Research Blood Sampling												
Archival Tissue Collection[p]	X											
Newly Obtained Tissue Biopsy[q]	X		X		X							
Research Blood Sampling[r]	X	X	X	X	X	X	X	X	X			

a Informed consent must be provided prior to performing any other trial-specific procedures. During the informed consent process, male patients should be advised of the risk of infertility due to use of cyclophosphamide; where this is of potential relevance or concern to the participant, they should be provided with information regarding sperm cryopreservation. Reference to infertility and sperm cryopreservation is included within the Patient Information Sheet.

b Medical history will include any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator

c Prior medication should include all medications taken within 28 days before starting trial medication. All prior cancer treatments will also be recorded. Concomitant medications will be recorded at the beginning of each treatment cycle, and at each safety follow-up visit.

d No medication diaries will be completed for cyclophosphamide. However, site clinical team should record number of missed cyclophosphamide doses in previous cycle alongside reasons for missed doses. Returned medication will also be recorded on the Patient Accountability Log by pharmacy.

e Throughout the study and follow-up period, Adverse Events (AEs) will be graded and recorded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (see Appendix 2).

f As a minimum, this should include evaluation of skin, extremities, cardiovascular, respiratory and abdominal systems at each timepoint. Other targeted examinations (e.g. neurological) should be performed if indicated by patient symptoms.

g Vital signs should include temperature, pulse, oxygen saturations, weight and blood pressure. Height will be measured at screening only.

h Must include haemoglobin, white cell count (total and differential), platelet count, red cell count, haematocrit, absolute neutrophil count, and absolute lymphocyte count.

j Must include sodium, potassium, urea, creatinine, calcium, chloride, magnesium, phosphate, bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), protein, albumin, and glucose

k Must include assessment of urinary blood, glucose, protein, nitrites and specific gravity. Sample should be sent for microscopy if abnormal results are noted.

m Must include free T4 and TSH.

n Tumour imaging will be performed every 9 weeks during study and should not be adjusted for delays in treatment. Imaging should include all assessment of all known sites of disease at each timepoint and should use the same imaging modalities as were performed at baseline during screening. Imaging should be obtained at the timepoint of treatment discontinuation, unless already performed within the preceding 4 weeks. Patients who discontinue treatment without documented disease progression should continue to have imaging performed every 9 weeks.

p All patients will consent to provision of available archival tumour tissue at trial entry

q Fresh tissue biopsies will be obtained from a non-target lesion at 3 timepoints: during screening; at completion of the cyclophosphamide run-in (day 20-21); and at the time of the first imaging assessment (week 9).

r Research blood samples will be taken during screening, on day 1 of each treatment cycle (prior to administration of pembrolizumab) and at treatment discontinuation.

s A negative pregnancy test must be obtained within 72 hours of starting study treatment. If there is any uncertainty on urine pregnancy testing then a serum sample should be obtained.

t Full blood count (FBC), biochemistry and urinalysis results must be within 14 days of starting study treatment.

u Pregnancy testing should continue while the patient is on follow-up until 180 days after the last dose of treatment or until commencement of next systemic therapy, whichever occurs first.

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PROTOCOL ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
CI	Chief Investigator
CNS	Central Nervous System
CR	Complete Response
CrCl	Creatinine Clearance
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTLA-4	Cytotoxic T-Lymphocyte-Associated protein 4
CTU	Clinical Trials Unit
CV	Curriculum Vitae
DSUR	Development Safety Update Report
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme-Linked Immunosorbent Assay
FACS	Fluorescence Activated Cell Sorting
FBC	Full Blood Count
FFPE	Formalin Fixed Paraffin Embedded
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCSF	Granulocyte Colony Stimulating Factor
GDPR	General Data Protection Regulation
GFR	Glomerular Filtration Rate
GMP	Good Manufacturing Practice
HCG	Human Chorionic Gonadotropin

HRA	Health Research Authority
HRT	Hormone Replacement Therapy
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IFN-γ	Interferon-γ
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
IO	Immuno-oncology
ISRCTN	International Standard Randomised Controlled Trials Network
IUD	Intrauterine Device
IUS	Intrauterine hormone-releasing System
IV	Intravenous
LCTC	Liverpool Clinical Trials Centre
LDH	Lactate Dehydrogenase
mAb	Monoclonal antibody
MDT	Multidisciplinary Team
MHRA	Medicines and Healthcare products Regulatory Agency
MSD	Merck, Sharpe and Dohme
NCI	National Cancer Institute
NIHR	National Institute for Health Research
NK	Natural Killer
OD	Once Daily
ORR	Objective Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PBPK	Physiologically Based Pharmacokinetics
PD	Progressive Disease
PD-1	Programmed cell death protein-1

PD-L1	Programmed cell death ligand-1
PD-L2	Programmed cell death ligand-2
PFS	Progression Free Survival
PI	Principal Investigator
PIS	Patient Information Sheet
PK	Pharmacokinetic
PR	Partial Response
PT	Pro-thrombin Time
RCC	Renal cell carcinoma
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria In Solid Tumours
RNA	Ribonucleic Acid
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Stable Disease
SOP	Standard Operating Procedure
SPIRIT	Standard Protocol Item: Recommendations for Interventional Trials 2013
SUSAR	Suspected Unexpected Serious Adverse Reaction
Th-1	Type 1 T-helper cell
Th-2	Type 1 T-helper cell
TIIML	Tumour Immunology and Inflammation Monitoring Laboratory
TKI	Tyrosine Kinase Inhibitor
TMG	Trial Management Group
T-reg	Regulatory T cell
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
ULN	Upper limit of normal
WOCBP	Women of child-bearing potential

2.0 BACKGROUND & RATIONALE

2.1 Background to Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin (Ig) G4 monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator's Brochure.

2.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, 2010]. Accumulating evidence shows a correlation between tumour-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and RCC. Tumour-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumour responses in cancers such as melanoma [Dudley et al, 2005; Hunder et al, 2008].

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 cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald et al, 2005; Okazaki et al, 2001].

The structure of murine PD-1 has been resolved [Zhang et al, 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signalling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signalling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of

effector molecules such as CD3 zeta, protein kinase C-theta, and zeta-chain-associated protein kinase, which are involved in the CD3 T-cell signalling cascade [Okazaki et al, 2001; Chemnitz et al, 2004; Sheppard et al, 2004; and Riley, 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signalling proteins [Parry et al, 2005; Francisco, 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in RCC.

2.1.2 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for Preclinical and Clinical data in relation to pembrolizumab.

2.2 Background to Cyclophosphamide

Cyclophosphamide is an oxazaphosphorine nitrogen mustard alkylating agent which has been in use as a cytotoxic chemotherapy agent since 1958. Over the years, cyclophosphamide combination regimens have been used for the treatment of autoimmune disorders, lymphoproliferative disorders and solid organ tumours, and the drug is directly cytotoxic to lymphoid cells at high doses.

However, there is currently a renewed interest in cyclophosphamide use due to the discovery that low doses of cyclophosphamide can significantly alter the immune composition of the tumour microenvironment. Specifically cyclophosphamide promotes upregulation and expansion of Type 1 T-helper (Th1) cells, leading to increased production of interleukin-2 (IL-2) and interferon γ (IFN-γ), and reduction of T-reg populations (Ahlmann, 2016). In preclinical studies, cyclophosphamide has been shown to enhance the anti-tumour activity of both tumour vaccines and adoptively-transferred T cells (North, 1982).

In humans, low-dose cyclophosphamide has been demonstrated to selective decrease T-regs whilst improving cytotoxic T cell and natural killer (NK) cell-mediated immunity in patients with a variety of different tumour types (Ghiringhelli et al, 2007). In a phase II study in patients with heavily pre-treated, IL-2 refractory metastatic melanoma, lympho-depleting chemotherapy with cyclophosphamide and fludarabine followed by adoptive T cell transfer resulted in significant tumour regression in 18 out of 35 patients (51%) (Dudley et al, 2005). Additionally, in patients with metastatic breast cancer, metronomic cyclophosphamide results in a transient but statistically significant decrease in T-reg numbers, accompanied by an increase in tumour-specific T cells (Ge et al, 2012).

Thus, cyclophosphamide in low doses appears to be selectively toxic to T-regs.

2.3 Rationale for the Trial and Selected Population

There have been several recent successes in using immuno-oncologic approaches for treating patients with clear cell renal carcinoma. The Checkmate-025 trial established single-agent Nivolumab therapy as a standard of care second/third line therapeutic option with an ORR of

25%, median PFS of 4.6 months and median OS of 25 months (Motzer et al, 2015). More recently, the Checkmate-214 trial reported practice-changing results in the first-line setting with the combination of Ipilimumab and Nivolumab (Motzer et al, 2018). The results presented by Escudier et al at European Society for Medical Oncology 2017 (subsequently published in New England Journal of Medicine) confirmed an ORR of 42% in intermediate / poor risk patients (9% CRs), with median PFS of 11.6 months in the same group and median OS not reached (data immature for OS).

A number of ongoing studies are evaluating the combination of IO drugs with anti-VEGF tyrosine kinase inhibitors (TKIs) in the first-line setting (see https://clinicaltrials.gov/). However, despite the efficacy of IO agents in patients with metastatic clear cell carcinoma, the data above highlights that 75% of patients will not demonstrate an objective response to single agent Nivolumab in the second/third line setting. Furthermore, even with combination IO therapy in previously untreated patients the response rates remain less than 50%. This has resulted in considerable ongoing research to identify drug combinations that may overcome resistance to IO therapy and improve therapeutic outcomes.

One of the key reasons for IO failure is known to be the presence of an 'immuno-suppressive' tumour micro-environment. Typically this is represented by increased numbers of T-regs and myeloid-derived suppressor cells (MDSCs) and decreased numbers of cytotoxic CD8+ T cells. This leads to increased production of immunosuppressive cytokines such as IL-6 and IL-10 and transforming growth factor-β (helper T cell type 2 response (Th-2)) which inhibit several macrophage functions including phagocytosis. There is also a corresponding decrease in production of IL-2, tumour necrosis factor-α and IFN-γ which are normally associated with the Th-1 response and macrophage activation.

Cytotoxic chemotherapies have historically been ineffective in treating patients with clear cell RCC, and there are therefore no cytotoxic chemotherapies in current use as standard of care treatments. However, the immunomodulatory effects of low-dose cyclophosphamide make it an attractive choice for combination with an immune checkpoint inhibitor in this disease. Several studies have demonstrated that chronic administration of low doses cytotoxic agents in more frequent schedules (metronomic delivery) is as effective as maximum tolerated dose regimens, but with reduced toxicity. Oral metronomic cyclophosphamide allows participants to take the tablet on a daily basis at home; it also has a favourable toxicity profile for combination. Oral cyclophosphamide has already been combined with pembrolizumab in an ongoing phase II trial in sarcoma, where the side effect profile appears favourable with the most frequently reported AEs being grade 1 or 2 fatigue, diarrhoea, and anaemia (Toulmonde et al, 2018).

In light of all of the above background and evidence, the current phase Ib trial will evaluate the combination of oral metronomic cyclophosphamide and pembrolizumab in patients with metastatic clear cell renal carcinoma who have previously progressed on IO therapy. The trial

aims to determine whether cyclophosphamide can alter the immune micro-environment and increase the likelihood of response to IO therapy.

2.3.1 Justification for Pembrolizumab Dose

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

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

Among the 8 randomised dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumour types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumour type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

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

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

2.3.2 Justification for Cyclophosphamide Dose

As outlined above, the dose of cyclophosphamide used in this study will be 50mg daily taken as an oral tablet. This schedule is defined as 'low-dose, metronomic' cyclophosphamide use.

This schedule is expected to be selectively toxic to T-regs and MDSCs whilst promoting recruitment of increased cytotoxic T cells. It is also associated with a low level of toxicity and successful combination with other therapies. Furthermore, the oral administration route is more convenient for participants and healthcare professionals.

2.4 Primary Endpoint and Rationale

The primary endpoint of the trial is ORR according to RECIST version 1.1.

This endpoint results from a direct anti-tumour effect of therapy, with associated tumour shrinkage. Given that the trial population will have already failed IO therapy, any tumour shrinkage seen with the combination of cyclophosphamide and pembrolizumab would support the immunomodulatory hypothesis, and provide an encouraging readout warranting further evaluation of this combination.

2.5 Secondary Endpoints and Rationale

The secondary endpoints of the trial will also include other important readouts in this patient population including:

- PFS
- OS
- Safety and tolerability of the combination of cyclophosphamide and pembrolizumab

PFS is an important endpoint as the combination therapy may potentially provide prolonged disease stabilization without necessarily inducing a RECIST response. OS is a key endpoint as IO therapy has frequently been found to be associated with marked improvements in OS, even in the absence of an identifiable effect on PFS.

2.6 Biomarker Research and Rationale

The exploratory biomarker endpoints of the trial will be crucial in understanding the specific immunomodulatory effects of the treatments administered, and how these changes may lead to treatment response / resistance.

The baseline biopsy and research blood samples will allow evaluation of the tumour immune microenvironment as well as circulating cytokines and immune cells at the point of trial entry (time of resistance to prior IO therapy). Subsequent evaluation of the dynamic changes between this baseline time-point and the repeat biopsy and research blood sample at Day 20-21 will determine the direct immunomodulatory effects of the single agent oral cyclophosphamide run-in. These changes may identify potential predictive biomarkers for response to the cyclophosphamide plus pembrolizumab combination.

Subsequent serial blood tests and the repeat biopsy at week 9 will allow evaluation of the ongoing dynamic changes in relation to combination therapy. By timing this third biopsy at the time-point of the first assessment CT scan it will be possible to correlate dynamic changes with either treatment response or resistance.

Biomarker analyses are expected to include but will not be limited to the following:

1. Immunohistochemistry (IHC) analysis of biopsy samples to determine immune cell composition
2. Multiplex enzyme-linked immunosorbent assay (ELISA) of circulating serum cytokines
3. Fluorescence activated cell sorting (FACS) of peripheral blood mononuclear cells (PBMCs) from blood samples
4. Nanostring analysis of ribonucleic acid (RNA) from formalin-fixed, paraffin embedded (FFPE) blocks using a pan-cancer immune-profiling panel

2.7 Overall Risk/Benefit

The side-effect profiles of both oral cyclophosphamide and IV pembrolizumab are both very well studied. In addition, as described in Section 2.3 above, they have previously been combined without any apparent increase in unexpected side effects. The risks associated with evaluation of this treatment combination are therefore felt to be low and not expected to be greater than the risks associated with either treatment alone.

However, despite the sound scientific rationale outlined previously, there is currently no clinical evidence to confirm that the use of this combination can overcome resistance to immunotherapy. For this reason, the study is aiming to recruit a small number (n=21) of carefully selected patients to evaluate the clinical efficacy of this combination. Participant safety is of key importance and an interim futility analysis is planned to ensure that recruitment does not

continue if there is no clinical efficacy seen in the first 12 recruited patients. Oversight will be maintained by the TMG and TSC to further protect participant safety.

We therefore believe the overall risk / benefit assessment of the study to be acceptable.

2.7.1 Risk Category

The study has been classified as:

Type B = somewhat higher than the risk of standard medical care.

Both drugs are licensed within the EU but are being used in combination outside of their current marketing authorisation

2.8 Lay Summary of Study

The CAPER Trial will investigate if adding an additional drug (cyclophosphamide) to an immunotherapy drug (pembrolizumab) increases the response of cancer to the immunotherapy. We will be looking at patients with metastatic clear cell renal cell carcinoma (a type of kidney cancer that has spread to other parts of the body) for which there are no standard existing chemotherapies available and who have had previous treatment with immunotherapy which has not been effective.

Immunotherapy is a type of cancer treatment that boosts the body's natural defences to fight cancer. Every cancer has a slightly different environment in which the tumour exists this includes the surrounding blood vessels, immune cells and signalling molecules. This environment affects the way our body responds to cancer treatment and how well it works at reducing the cancer growth and spread. The trials aims to see if adding cyclophosphamide can alter the tumour environment and lead to better response to the pembrolizumab.

Patients who join the study will take cyclophosphamide 50mg tablets once a day for 21 days before adding intravenous (given directly into your blood through a drip) pembrolizumab treatment one day every three weeks. Patients will be on both treatments until there are signs that cancer is growing and treatment is no longer working. Treatment will also be stopped if patients have too many side effects; a maximum 24 months of treatment; or the tumour has shown a good response.

Patients will be scanned every 9 weeks and will also have additional blood and biopsies taken to assess response.

3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objective & Hypothesis

Objective: To evaluate whether the combination of oral metronomic cyclophosphamide and pembrolizumab will lead to objective tumour responses in metastatic clear cell renal carcinoma patients who have previously progressed on IO therapy.

Hypothesis: The combination of oral metronomic cyclophosphamide and pembrolizumab will result in a target ORR of $\geq$ 20%, making it worthy of further evaluation in a phase II trial.

3.2 Secondary Objectives & Hypotheses

Objectives:

1. To evaluate the median PFS and OS in patients receiving cyclophosphamide and pembrolizumab in combination
2. To evaluate the safety profile of the combination of oral cyclophosphamide and pembrolizumab

Hypothesis:

1. The combination of cyclophosphamide and pembrolizumab will result in delayed disease progression and prolongation of OS in some patients.
2. Cyclophosphamide and pembrolizumab in combination will have an acceptable toxicity profile.

3.3 Exploratory Objective

Objective: To perform serial biopsies and collect research blood samples which will allow evaluation of the dynamic changes in the immune-cell composition of the tumour microenvironment and cytokine profile of the blood throughout treatment. These changes may correlate with response / resistance to therapy.

4.0 METHODOLOGY

4.1 Overview

This is a prospective biomarker study of immunological signatures in metastatic RCC. This study will be performed according to the Research Governance Framework for Health and Community Care (second edition 2006) and the Human Tissue Act Code of Practice (2014). All investigators and key trial personnel will be appropriately trained in GCP.

4.2 Study Population

Potential study participants will be identified and assessed through outpatient Renal Oncology Clinics in participating centres. All potential study participants will be provided with a Patient Information Sheet (PIS) and invited to voluntarily consent to participate in the CAPER study. It should be made clear to the potential trial participant that consent is voluntary and can be withdrawn at any time without any impact on ongoing medical care. Potential study participants should be given an appropriate amount of time (a minimum of 24 hours is ideal) to consider participation in this study before consent is elicited. No screening activities for the study can be undertaken before consent has been obtained.

After consent has been obtained, the patient will be formally assessed for eligibility for the study at the screening visit against inclusion and exclusion criteria of the study protocol.

4.3 End of Trial Definition

Unless early termination is required, the end of trial is defined as once all patients have died / come off study for other reasons or reached 24 months treatment/follow-up whichever is sooner together with sufficient time to collect outstanding data and resolve queries. The final statistical analysis will not be triggered until the end of study is reached (whether this is planned or early termination).

The TSC may recommend that the trial be stopped prematurely for safety. Such premature termination or suspension of the trial will be notified to the MHRA and EC as required. Ongoing patients must be contacted to notify them of the end of the study.

Merck, Sharpe and Dohme (MSD) will be informed of any decision relating to termination or suspension

5.0 SELECTION OF CENTRES/CLINICIANS

5.1 UK Centres

Each participating centre (and Principal Investigator) has been identified and selected for their expertise in the treatment of RCC and expertise and track record in carrying out Renal cancer clinical trials. Each of the centres must have the required Clinical Research Network research nurses, pharmacy support, and radiology and laboratory equipment to undertake their delegated roles in the study. Each centre will complete a CAPER feasibility questionnaire which will ensure that the centre has the appropriate facilities, qualified personnel and capacity to set up and run the study to the current approved protocol and GCP standards. This feasibility questionnaire will also ensure that there are no operational concerns that were not previously considered.

The study will be adopted on to the National Institute for Health Research (NIHR) Portfolio. All staff working on the study must be qualified by education, training and experience to perform their respective tasks and have the applicable employment contact and status within the research site.

Local study delivery in a geographical region may be required to take place across multiple centres to facilitate the treatment and surgical requirements of the trial.

5.2 Centre/Clinician Inclusion criteria - Surgical Centre and/or Treatment Centre

a. Completed site feasibility questionnaire returned to the LCTC for review and approval.

b. Confirmation of local capacity and capability to conduct the study via the HRA

c. Be listed on the application given approval by MHRA

d. Be listed on the application given approval by the REC

e. Completed/executed Research Site Agreement including material transfer clauses

f. Completion and return of Signature and Delegation Log to LCTC

g. Suitable Multidisciplinary Team (MDT) meeting structure to identify potential patients

h. Curriculum Vitae (CV) and a certificate of ICH-GCP training for the Principal Investigator

i. CV and ICH-GCP training certificate for all other personnel on the delegation log

j. Clinical Study Protocol receipt form

k. Investigator's Brochure document receipt forms

l. Site Initiation visit conducted and attended by PI, research nurse(s) and pharmacist, with the Initiation Report signed off

m. PIS, consent form and GP letter on trust headed paper

n. Emergency contact details inserted into PIS

o. Local laboratory accreditation/quality check provided

p. Local laboratory reference ranges provided

q. Pharmacy local practice form completed

r. Ability to recruit required number of patients

s. Ability to perform RECIST measurements on patients

t. A centrifuge capable of generating 1000g RCF

u. A freezer able to store samples at -80°C

v. Ability to process blood samples and provide FFPE tissue samples

5.3 Centre/Clinical Exclusion criteria

Those centres who do not fulfil the above inclusion criteria will not be permitted to participate in the trial.

6.0 STUDY POPULATION

6.1 Target Population

The target population for the trial is metastatic RCC with clear cell histology.

6.2 Patient Selection Criteria

All patients must meet all of the inclusion criteria and none of the exclusion criteria for this study at the time of allocation. Under no circumstances can there be exceptions to this rule.

6.3 Participant Inclusion Criteria

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

1. Histological confirmation of RCC of predominantly (>50%) clear cell type.
2. Presence of metastatic / locally advanced inoperable disease.
3. Current evidence of disease progression on IO therapy as determined by CT / MRI imaging performed within 28 days prior to the first dose of study drug. Last dose of IO therapy must have been administered within 42 days prior to the first dose of study drug. IO therapy may consist of either:
    a. First-line Ipilimumab / Nivolumab combination OR
    b. Second / Third-line single agent Nivolumab OR
    c. Other PD-1 / PD-L1 / anti-CTLA-4 therapy within a clinical trial
4. Measurable disease according to RECIST version 1.1 criteria.
5. Site(s) of disease which are easily accessible and suitable for repeated biopsies (bone metastases are not suitable as a biopsy site).
6. Provision of archival tumour tissue sample FFPE tissue blocks) and a newly obtained core or excisional biopsy of a tumour lesion not previously irradiated.
7. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Evaluation of ECOG is to be performed within 7 days prior to the first dose of study drug.
8. Age > 18 years.
9. Have adequate organ function as defined in the following table (Table 2). Specimens must be collected within 14 days prior to the start of study treatment.

Table 2 - Adequate Organ Function Laboratory Values:

System	Laboratory Value
Haematological	
Absolute neutrophil count (ANC)	≥1.5 x10^9/L
Platelets	≥100 x10^9/L
Haemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (CrCl) (Glomerular Filtration Rate (GFR) can also be used in place of creatinine or CrCl	≤1.5 × ULN[c] OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST and ALT	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalised ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell transfusion within last 2 weeks.

[b] CrCl should be calculated per institutional standard.

[c] Upper limit of normal (ULN)

10. Able to take oral medications.
11. Life expectancy of ≥ 6 months in the opinion of the investigator.
12. Male participants must agree to use a form of contraception as detailed in Appendix 3 of this protocol during the treatment period and for at least 180 days after the last dose of study treatment and refrain from donating sperm during this period.
13. Female participants are eligible to participate if they are not pregnant (see Appendix 3), not breastfeeding, and at least one of the following conditions applies:
    a. Not a woman of childbearing potential (WOCBP) as defined in Appendix 3 OR
    b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 180 days after the last dose of study treatment.
14. The participant provides written informed consent for the trial including consent to all samples.

6.4 Participant Exclusion Criteria

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

1. Treatment with more than one prior line of IO therapy (including previous standard of care and trial treatments).
2. High burden / symptomatic disease which in the opinion of the treating investigator requires TKI / alternative therapeutic approach.
3. Prior treatment with either pembrolizumab or cyclophosphamide.
4. Known severe hypersensitivity (≥Grade 3) to pembrolizumab, cyclophosphamide and/or any of their excipients.
5. Prior intolerance to IO therapy (any ≥ Grade 2 toxicity which required permanent IO treatment discontinuation).
6. Ongoing AEs due to previous therapies or surgery which have not resolved to ≤ Grade 1 or baseline. Participants with ≤ Grade 2 neuropathy may be eligible.
7. 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 (e.g. levothyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

8. Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisolone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.
9. Known additional malignancy that is progressing or has required active treatment within the past 3 years. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, superficial transitional cell carcinoma of the bladder / urothelial tract, or carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
10. Prior radiotherapy within 2 weeks of start of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS (Central Nervous System) disease.
11. Live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. FluMist®) are live attenuated vaccines and are not allowed.
12. Currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment. Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.
13. Known previous or current CNS metastases and/or carcinomatous meningitis. Note: no testing is required.
14. History of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
15. Active infection requiring systemic therapy or has had requirement for antibiotics within 14 days prior to first dose of study treatment.
16. Known history of Human Immunodeficiency Virus (HIV). Note: no testing for HIV is required.
17. Known history of Hepatitis B (defined as Hepatitis B surface antigen (HBsAg) reactive) or known active Hepatitis C virus (defined as HCV RNA positive) infection. Note: no testing for Hepatitis B and Hepatitis C is required.

18. Known history of active tuberculosis (Bacillus Tuberculosis). Note: no testing for TB is required.
19. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
20. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
21. Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 180 days after the last dose of trial treatment. Note: WOCBP must have a negative urine pregnancy test within 72 hours prior to trial entry (see Appendix 3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. In the event that 72 hours have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for subject to start receiving study medication.

6.5 Additional Restrictions

6.5.1 Lifestyle Restrictions

6.5.1.1 Meals and Dietary Restrictions

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

6.5.1.2 Contraception

Pembrolizumab and cyclophosphamide may have adverse effects on a foetus in utero. Refer to Appendix 3 for approved methods of contraception.

For this study, male participants will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Both male and female patients should wait at least 180 days (6 months) up to 365 days (1 year) after stopping treatment before attempting to conceive or father a child.

6.5.2 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab or cyclophosphamide, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported

to MSD within 2 working days if the outcome is a serious adverse experience (e.g. death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the foetus or new-born to MSD. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to MSD and followed as described in Section 11.5.

6.5.3 Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Cyclophosphamide is known to be excreted in human milk and may be harmful to breastfeeding infants. Since many drugs are excreted in human milk, and because of the potential for Serious Adverse Reactions (SARs) in the nursing infant, participants who are breast-feeding are not eligible for enrolment.

7.0 SCREENING AND REGISTRATION

7.1 Screening

Start of screening is defined as when a patient has been provided with the PIS and ICF and has had a discussion with their clinical care team regarding their treatment and the possibility of entry into a trial requiring additional tests.

A screening-log of patients who are assessed for eligibility but registered or not on to the study will be maintained as this will provide important information for monitoring purposes. At the start of screening as defined above the patient details must be documented on the PORTAL ***"Screening and Enrolment log".*** Screening details should be entered into the portal and this will automatically generate a screening number and a confirmation email with these details will be sent to site staff. The screening log can be printed at any time from the Portal to allow for storage in the Investigator Site File. The screening-log **WILL NOT** collect any patient identifiable information e.g. date of birth.

A step-by-step guide to using the log will be issued to research site staff prior to green light and the process will also be demonstrated during site initiations.

The potential eligibility of patients will be assessed at the earliest opportunity following referral of patients with suspected RCC to MDT/trial clinicians.

Depending on other eligibility criteria being met, the patient will then give FULL informed consent and will be registered for the study.

Patient hospital notes should be screened by the research team prior to the patient being approached to ensure no obvious ineligibility criterion is apparent. Screening assessments must have been completed within **28 days** of patient registration. The patient`s written informed consent must be obtained before any trial related procedures are undertaken.

7.2 Study Registration

Patients who have given Informed Consent and have been found to comply with the trial inclusion and exclusion criteria will be enrolled and registered onto the study by trained staff at the LCTC.

To ensure the essential criteria are fulfilled, registration can only occur following the completion and forwarding of the study registration document by the Investigator/research site team.

The following documents are required:

- Completed Registration Case Report Forms (CRFs) Form signed by an Investigator
- A copy of the Signed Consent Form signed by both the patient and the investigator
- **Anonymised** copy of the pathology report (biopsy)

- **Anonymised** copy of screening haematology/serum chemistry

For sites using remote data entry the pages up to registration on MACRO can be completed and the paper CRFs only completed as worksheets to be kept at site.

The registration documents should be faxed/uploaded to the PORTAL/emailed to the LCTC on Monday - Friday from 09:00 to 17:00 GMT, fax number: 0151 794 8930, email: caper@liverpool.ac.uk or the MACRO pages up to registration completed (and ICF sent separately). Prior to sending documents, site staff should telephone 0151 795 5289 to inform the LCTC staff of the incoming registration.

Registration documents sent by email should be sent with identifiable data (ICF) encrypted with the password in a separate email. Clinical data and identifiable data should not be sent in the same email unless sending from an nhs.net account to an nhs.net account. Documents faxed or uploaded via the PORTAL may be sent together.

Trial Registration– Tel: **0151 795 5289**

Fax: 0151 794 8930

Email: caper@liverpool.ac.uk

(Note that the LCTC is open from 09:00 – 17:00, Monday – Friday, excluding public holidays)

Personnel from the LCTC will review the documents; confirm eligibility and record essential demographic data. The LCTC will query any issues with the documents listed above prior to registration. Once the documentation is complete, the LCTC trial team will register the patient using the CAPER MACRO system.

The patient will be given a unique study number by the system, which will also automatically generate a confirmation email which will be communicated to the LCTC trial team and all relevant members of the site staff and pharmacy, notifying them of the patient trial number.

This study number should then be filled in on each subsequent page of the patients CRF.

8.0 INVESTIGATIONAL MEDICINAL PRODUCTS (IMP)

The Investigational Medicinal Products (IMPs) to be used in this trial are outlined below in Table 3.

Table 3 - Investigational Medicinal Products

Drug	Dose / Potency	Dose Frequency	Route of Administration	Regimen / Treatment Period	Status	Supply Route
Cyclophosphamide	50 mg	OD	Oral	Days 1-21 of each 3 week cycle from C1D1	IMP	Hospital stock[1]
Pembrolizumab (Keytruda, MK-3475)	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle from C2D1 onwards	IMP	Supplied by MSD

1 Cyclophosphamide is to be sourced locally by investigator sites using commercially available licensed stock and must be labelled locally in accordance with Annex 13 and local hospital policy. Descriptive information can be found in the package insert and drug should be stored as detailed on the product label, according to manufacturer's instructions and SmPC.

As this is a single-arm non-randomised phase Ib trial, all patients will commence a single agent cyclophosphamide run-in for 21 days followed by combination therapy with cyclophosphamide and pembrolizumab (Keytruda, MK-3475).

Trial treatment should begin within 5 working days of receiving confirmation of registration from the LCTC.

8.1 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 trial procedures table (Section 9.2). 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.

Cyclophosphamide will be administered from Cycle 1. Cyclophosphamide 50mg tablets should be swallowed with sufficient fluid without chewing. The tablets are coated and should not be divided before use.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks, starting from Cycle 2. Sites 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.

8.1.1 Missed Dose and Vomiting

It is not expected that patients will miss doses of pembrolizumab except as part of dose modification, interruption or discontinuation.

Patients will report any missed doses of cyclophosphamide to the clinical team at each clinic visit, along with the reasons why the dose(s) were missed.

In the case of missed or vomited doses of cyclophosphamide, patients should continue to take the treatment as usual the following day. If vomiting recurs then the clinical team should be contacted for advice.

8.2 Dose Modifications for Cyclophosphamide

As cyclophosphamide tablets are manufactured as 50mg tablets which cannot be divided, no dose reductions will be possible for cyclophosphamide therapy.

All cyclophosphamide-related AEs should be managed according to standard of care practice with reference to the Summary of Product Characteristics.

For Grade 1 and tolerable Grade 2 AEs related to cyclophosphamide therapy, treatment should be continued with initiation of supportive medications where appropriate. Secondary prophylaxis with GCSF may be used for neutropenia related to cyclophosphamide at the discretion of the treating investigator.

8.3 Cyclophosphamide Interruption / Discontinuation

For Grade 3 or intolerable Grade 2 AEs deemed related to cyclophosphamide therapy, treatment should be temporarily withheld until resolution to $\leq$ Grade 1. Cyclophosphamide should then be restarted at the same dose of 50mg daily with use of supportive medications where appropriate. Patients should be reviewed weekly whilst treatment is being withheld to determine the appropriate timing of cyclophosphamide reintroduction. Secondary prophylaxis with GCSF may be used for neutropenia related to cyclophosphamide at the discretion of the treating investigator.

If there is recurrent Grade 3 or recurrent intolerable Grade 2 AEs deemed related to cyclophosphamide therapy then treatment should be permanently discontinued.

If cyclophosphamide treatment is interrupted for any reason then the doses will be missed (not delayed) and pembrolizumab therapy should continue as per the protocol-defined schedule. If cyclophosphamide treatment is permanently discontinued then pembrolizumab therapy should continue as single agent.

8.4 Dose Modifications for Pembrolizumab

The following sections outline the management algorithms for use in patients who develop any immune-related AEs (irAEs) or infusion reactions with pembrolizumab therapy. If pembrolizumab therapy is unable to proceed on day 1 of any treatment cycle then both treatments should be deferred.

If any criteria for permanent pembrolizumab discontinuation are met then both treatments should be permanently discontinued (as cyclophosphamide is not expected to have any single agent toxicity).

8.4.1 Dose Modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic aetiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm aetiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 4.

8.4.2 Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 5.

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants 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 clearly documented in the patient's study record.

8.5 Dose modification and toxicity management tables for pembrolizumab

Table 4 - Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisolone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv5.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisolone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections as per local guidelines
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhoea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisolone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (i.e. diarrhoea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. peritoneal signs and ileus).

	Grade 4	Permanently discontinue		• Participants with ≥ Grade 2 diarrhoea suspecting colitis should consider gastrointestinal consultation and performing endoscopy to rule out colitis. • Participants with diarrhoea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisolone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisolone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycaemia	Newly onset T1DM or Grade 3 or 4 hyperglycaemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycaemic in participants with hyperglycaemia	• Monitor participants for hyperglycaemia 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[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g. levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.

Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisolone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm aetiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm aetiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Decision to withhold or permanently discontinue pembrolizumab is at the discretion of the CI or principal investigator.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withholding of pembrolizumab is required, pembrolizumab may be resumed when the AE resolves to ≤ Grade 2 and is controlled with HRT or achieved metabolic control (in case of T1DM).

Table 5 - Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy and infusion interruption but responds promptly to symptomatic treatment (e.g. IV antihistamines, IV hydrocortisone, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids IV antihistamines IV hydrocortisone Paracetamol Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be pre-medicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate pre-medication should be permanently discontinued from further study drug treatment**	Participant may be pre-medicated 30 minutes prior to infusion of pembrolizumab with: Chlorphenamine 10 mg IV bolus Ranitidine 50 mg IV bolus
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; vasopressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Adrenaline** IV fluids IV antihistamines IV hydrocortisone Paracetamol Oxygen Vasopressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, adrenaline should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and an investigator readily available during the period of drug administration. For further information, please refer to the CTCAE v5.0 (CTCAE) at http://ctep.cancer.gov		

8.6 Participant Withdrawal/Discontinuation Criteria

Participants should be reminded that trial participation is voluntary and that they may discontinue study treatment at any time for any reason. The investigator may also advise that they discontinue study treatment should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 10.6 – Other Procedures.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- Confirmed radiographic disease progression according to RECIST 1.1 outlined in Section 10.4.1.
- Unacceptable AEs requiring discontinuation of pembrolizumab as described in Sections 8.4 – 8.5.
- The participant or participant's legally acceptable representative requests to discontinue study treatment (patient choice).
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, places the participant at unnecessary risk from continued administration of study treatment (physician choice).
- Discontinuation of treatment may be considered for participants who have attained a confirmed CR and have been treated for at least 8 cycles (at least 24 weeks), receiving at least 2 further cycles of cyclophosphamide and pembrolizumab beyond the date when the initial CR was declared. These participants may be eligible for second course treatment described in Section 8.8
- Completion of 34 treatments (approximately 2 years) with pembrolizumab. Note: The number of treatments is calculated starting with the first dose. Participants who stop the combination or pembrolizumab after receiving 34 doses may be eligible for retreatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 8.8. Participants may be retreated in the Second Course Phase (Retreatment) for up to an additional 17 cycles (approximately 1 year).
- Recurrence of any prior malignancy, or occurrence of another malignancy that requires active treatment
- The participant has a confirmed positive serum pregnancy test
- Noncompliance with study treatment or procedure requirements

- The participant is lost to follow-up

8.7 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 may be required. The final decision on any supportive therapy or vaccination rests with the CI and/or the principal investigator.

8.7.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with standard medical care. All concomitant medication will be recorded on the CRF including all prescription, over-the-counter, 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 Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs) as necessary (defined in Section 11.6).

8.7.2 Prohibited Concomitant Medications

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

- Any other non-trial anti-cancer therapy, including:
    - Chemotherapy
    - Biological therapy
    - Immunotherapy
    - Other investigational agents
    - Radiation therapy (Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the Chief Investigator's discretion).
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and

typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. FluMist®) are live attenuated vaccines and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AESI of suspected immunologic aetiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the CI and/or the principal investigator. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

8.7.3 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic aetiology are outlined along with the dose modification guidelines in Section 8.5 (Table 4). Where appropriate, these guidelines include the use of oral or IV 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 of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to Table 5 in Section 8.5 for guidelines regarding dose modification and supportive care.

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

8.8 Second Course

All participants who stop study treatment with stable disease (SD) or better may be eligible for up to an additional 17 cycles (approximately 1 year) of cyclophosphamide plus pembrolizumab treatment if they progress after stopping study treatment from the initial treatment phase. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the participant meets the following conditions:

Either

- Stopped initial treatment with study treatment after attaining an investigator-determined confirmed CR based on RECIST 1.1, and
    - Was treated with at least 8 cycles of study treatment before discontinuing treatment, and
    - Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared

OR

- Had SD, partial response (PR), or CR and stopped study treatment after completion of 34 administrations (approximately 2 years) of study treatment for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined radiographic disease progression by RECIST 1.1 after stopping initial treatment, and
    - No new anticancer treatment was administered after the last dose of study treatment, and
    - The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
    - The study is ongoing

Written confirmation from the CAPER Trial Team is required before commencing retreatment for any patient.

An objective response or disease progression that occurs during the Second Course Phase for a participant will not be counted as an event for the primary analysis of either endpoint in this study.

8.9 Participant Replacement Strategy

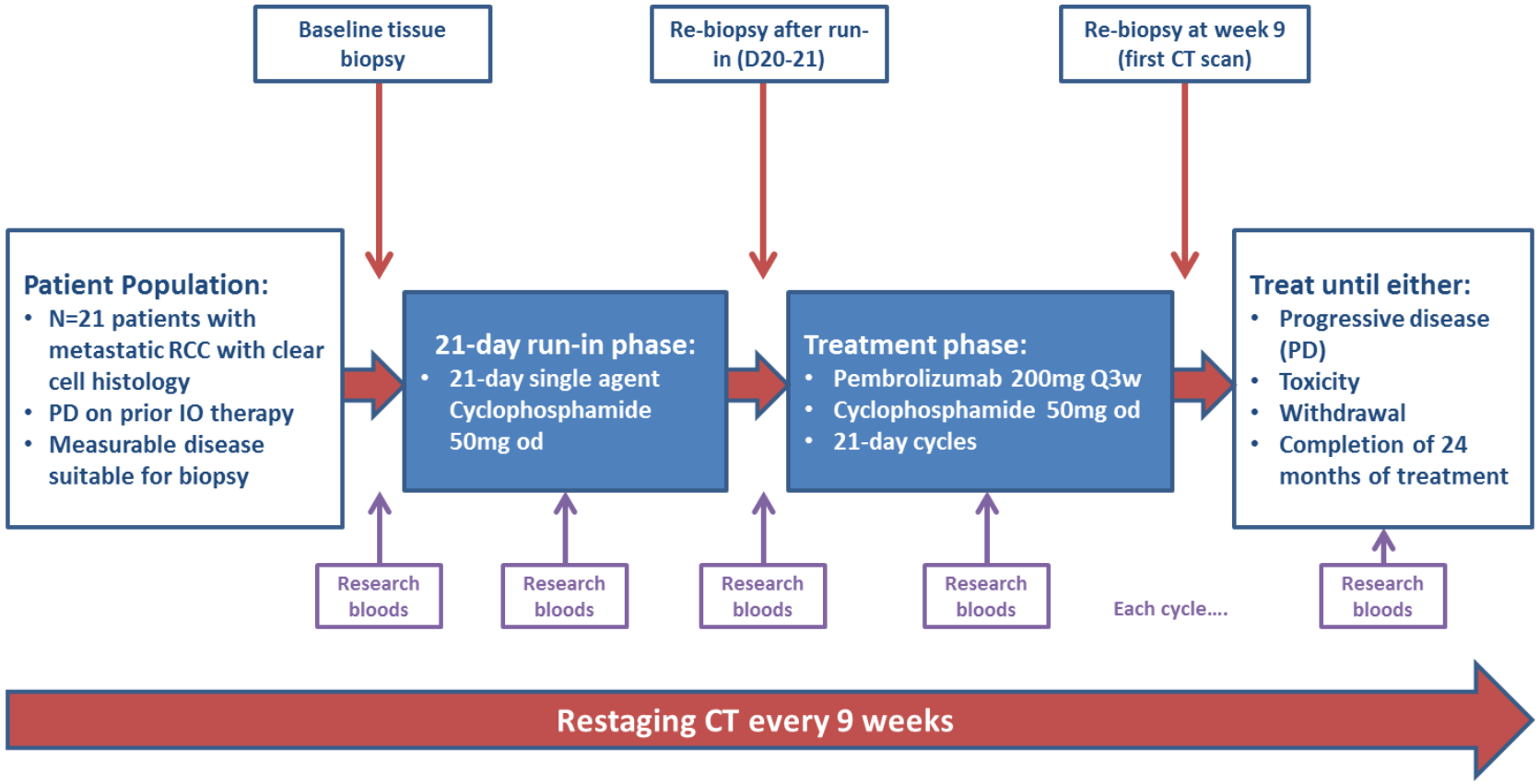
Patients that do not successfully undergo **both** the first research biopsy (in screening) **and** the second research biopsy (C1D20-21) will be withdrawn and replaced.

Any patients who are subsequently confirmed to be ineligible following trial entry will also be withdrawn and replaced.

All other recruited patients will count towards the overall trial recruitment target of 20 participants.

9.0 TRIAL SCHEDULES

9.1 Study Flow Chart



9.2 Trial Schedule of Events

Trial Period:	**Screening Phase**	**Treatment Cycles**							**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Main Study Screening	1 (Cyclo run-in)	2 (Cyclo + Pembro)	3	4	To be repeated beyond 7 cycles			Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up
						5	6	7				
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	At time of discon ± 3	30 days post discon ± 3	Every 9 weeks post discon ± 3	Every 12 weeks ± 3
Administrative Procedures												
Informed Consent[a]	X											
Inclusion/Exclusion Criteria	X											
Demographics and Medical History[b]	X											
Prior and Concomitant Medication Review[c]	X	X	X	X	X	X	X	X	X	X	X	
Cyclophosphamide Compliance Check[d]			X	X	X	X	X	X	X			
Trial Treatment Administration		X	X	X	X	X	X	X				
Post-Study Anticancer Therapy Status									X	X	X	X
Survival Status	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Procedures/Assessments												
Review of Adverse Events[e]		X	X	X	X	X	X	X	X	X		
Physical Examination[f]	X	X	X	X	X	X	X	X	X	X		
Vital Signs and Weight[g]	X	X	X	X	X	X	X	X	X	X		
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X		
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory												
Pregnancy Test – Urine or Serum β-HCG	X[s]	X	X	X	X	X	X	X	X	X[u]	X[u]	X[u]
FBC with Differential[h]	X[t]	X	X	X	X	X	X	X	X	X		
Biochemistry Panel[j]	X[t]	X	X	X	X	X	X	X	X	X		
Urinalysis[k]	X[t]	X	X	X	X	X	X	X	X	X		

Trial Period:	**Screening Phase**	**Treatment Cycles**							**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Main Study Screening	1 (Cyclo run-in)	2 (Cyclo + Pembro)	3	4	To be repeated beyond 7 cycles			Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up
						5	6	7				
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon ± 3	30 days post discon ± 3	Every 9 weeks post discon ± 3	Every 12 weeks ± 3
Thyroid Function[m]	X	X	X	X	X	X	X	X	X			
Efficacy Measurements												
Tumour Imaging[n]	X				X			X	X		X	
Tumour Tissue Collection and Research Blood Sampling												
Archival Tissue Collection[p]	X											
Newly Obtained Tissue Biopsy[q]	X		X		X							
Research Blood Sampling[r]	X	X	X	X	X	X	X	X	X			

a Informed consent must be provided prior to performing any other trial-specific procedures. During the informed consent process, male patients should be advised of the risk of infertility due to use of cyclophosphamide; where this is of potential relevance or concern to the participant, they should be provided with information regarding sperm cryopreservation. Reference to infertility and sperm cryopreservation is included within the Patient Information Sheet.

b Medical history will include any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator

c Prior medication should include all medications taken within 28 days before starting trial medication. All prior cancer treatments will also be recorded. Concomitant medications will be recorded at the beginning of each treatment cycle, and at each safety follow-up visit.

d No medication diaries will be completed for cyclophosphamide. However, site staff should record number of missed cyclophosphamide doses in previous cycle alongside reasons for missed doses.

e Throughout the study and follow-up period, AEs will be graded and recorded according to NCI CTCAE Version 5.0 (see Appendix 2).

f As a minimum, this should include evaluation of skin, extremities, cardiovascular, respiratory and abdominal systems at each timepoint. Other targeted examinations (e.g. neurological) should be performed if indicated by patient symptoms.

g Vital signs should include temperature, pulse, oxygen saturations, weight and blood pressure. Height will be measured at screening only.

h Must include haemoglobin, white cell count (total and differential), platelet count, red cell count, haematocrit, absolute neutrophil count, and absolute lymphocyte count.

j Must include sodium, potassium, urea, creatinine, calcium, chloride, magnesium, phosphate, bilirubin, ALP, ALT, AST, LDH, protein, albumin, and glucose

k Must include assessment of urinary blood, glucose, protein, nitrites and specific gravity. Sample should be sent for microscopy if abnormal results are noted.

m Must include free T4 and TSH.

n Tumour imaging will be performed every 9 weeks during study and should not be adjusted for delays in treatment. Imaging should include all assessment of all known sites of disease at each timepoint and should use the same imaging modalities as were performed at baseline during screening. Imaging should be obtained at the timepoint of treatment discontinuation, unless already performed within the preceding 4 weeks. Patients who discontinue treatment without documented disease progression should continue to have imaging performed every 9 weeks.

p All patients will consent to provision of available archival tumour tissue at trial entry

q Fresh tissue biopsies will be obtained from a non-target lesion at 3 timepoints: during screening; at completion of the cyclophosphamide run-in (day 20-21); and at the time of the first imaging assessment (week 9).

r Research blood samples will be taken during screening, on day 1 of each treatment cycle (prior to administration of pembrolizumab) and at treatment discontinuation.

s A negative pregnancy test must be obtained with 72 hours of starting study treatment. If there is any uncertainty on urine pregnancy testing then a serum sample should be obtained.

t FBC, biochemistry and urinalysis results must be within 14 days of starting study treatment.

u Pregnancy testing should continue while the patient is on follow-up until 180 days after the last dose of treatment or until commencement of next systemic therapy, whichever occurs first.

10.0 TRIAL PROCEDURES

The Trial Flow Chart and per patient schedule - Section 9 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.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or MSD for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

10.1 Administrative Procedures

10.1.1 Informed Consent

The Investigator must obtain documented consent from each potential participant prior to participating in a clinical trial. Consent to enter the study must be sought from each participant only after full explanation has been given, a PIS offered and time allowed for consideration.

Consent must be documented by the participant's dated signature on a consent form along with the dated signature of the person conducting the consent discussion. The site PI is responsible for ensuring that the person conducting the consent discussion is suitably qualified by training or experience to take informed consent.

A copy of the signed and dated consent form should be given to the participant before participation in the trial. The original completed consent form must be retained at each site in the appropriate section of the Investigator Site File, and a photocopy placed in the patient's medical records. A copy will also be forwarded to the LCTC for verification purposes.

Verification of appropriate informed consent will be enabled by the provision of copies of patients' signed informed consent/assent forms being supplied to the LCTC by recruiting centres. This requires the transfer of name data to the LCTC, which is explained in the PIS. The LCTC will preserve the confidentiality of patients taking part in the study and the University of Liverpool is a Data Controller registered with the Information Commissioners Office.

The initial Informed Consent Form (ICF), any subsequent revised written ICF and any written information provided to the participant must receive the REC's approval / favourable opinion in advance of use. The participant should be informed in a timely manner if new information becomes available that may be relevant to the participant'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 participant'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 REC requirements, applicable laws and regulations and Sponsor requirements.

During the informed consent process, male patients should be advised of the risk of infertility due to use of cyclophosphamide; where this is of potential relevance or concern to the participant, they should be given information regarding sperm cryopreservation. Reference to infertility and sperm cryopreservation is included within the Patient Information Sheet.

10.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the trial (Section 6.3 and 6.4).

10.1.3 Demographics and 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.

In addition, the investigator is qualified designee will record the details regarding the disease for which the participant has enrolled in this study. They will also record all prior cancer treatments including systemic treatments, radiation and surgeries.

10.1.4 Prior and Concomitant Medication Review

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

At each subsequent attendance during treatment and follow-up, the investigator or qualified designee will record any changes to concomitant medications. All medications related to reportable SAEs and AESIs should be recorded as defined in Section 11.

10.1.5 Cyclophosphamide Compliance Check

At the start of each treatment cycle from cycle 2 onwards, the investigator or qualified designee will record the number of days where treatment was missed or omitted during the previous cycle along with the explanations for any missed doses. Any remaining

cyclophosphamide from the previous cycle should be returned to pharmacy for accountability. Medication diaries will not be provided for this study.

10.1.6 Trial Treatment Administration

At the start of each treatment cycle, the investigator or qualified designee will confirm whether or not they are happy for the participant to continue on the planned trial treatment. If a participant is proceeding as planned then they will be dispensed a further 21-day supply of cyclophosphamide and will receive pembrolizumab as planned.

For guidance regarding dose delays / omissions due to AEs see sections 8.2 - 8.5. If patients permanently discontinue treatment then please refer to section 8.6.

10.1.7 End of Treatment

Patients who are ending treatment for reasons other than disease progression should have tumour imaging performed as soon after discontinuation as possible unless a scan was performed within 4 weeks prior to discontinuation. CT scans should continue to be performed every 9 weeks as part of follow-up until documented disease progression.

All patients should continue to be followed up for AEs and SAEs, and any existing or emerging AEs/SAEs should be followed up until resolution. The End of Treatment Form should be completed and the LCTC informed that the patient has come off treatment along with the reason why. Research blood samples should be collected during the visit.

10.1.8 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 participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up assessments should be performed prior to the first dose of the new therapy. Once new anti-cancer therapy has been initiated the participant will move into survival follow-up.

10.1.9 Survival Status

Confirmation of survival status will be completed at the time of every patient review.

Following completion of treatment and evidence of documented disease progression, patients will continue to be followed for survival status every 12 weeks. This can be conducted via review of case records or by telephone contact where necessary.

10.2 Clinical Procedures/Assessments

10.2.1 Review of Adverse Events (AEs)

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the Trial procedures and more frequently if clinically

indicated. Throughout the study and follow-up period, AEs will be graded and recorded according to NCI CTCAE Version 5.0 (see Appendix 2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to Section 11 for detailed information regarding the assessment and recording of AEs.

10.2.2 Physical Examination

The investigator or qualified designee will perform a physical examination during the screening period, on day 1 of each treatment cycle and during follow-up. As a minimum, this should include evaluation of skin, extremities, cardiovascular, respiratory and abdominal systems at each timepoint. Other targeted examinations (e.g. neurological) should be performed if indicated by patient symptoms. Clinically significant abnormal findings at screening should be recorded as medical history. Clinically significant abnormal findings which develop during treatment should be recorded as AEs.

10.2.3 Vital Signs and Weight

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 Flow Chart (Section 9.1). Vital signs should include temperature, pulse, oxygen saturations, weight and blood pressure. Height will be measured at screening only.

10.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator or qualified designee will assess ECOG Performance Status (see Appendix 1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Schedule of Events (Section 9.2).

10.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Analysis of laboratory assessments will be performed by local laboratories at the participants host institution.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 14 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

10.3.1 Pregnancy Test – Urine or Serum β-hCG

WOCBP must have a negative urine pregnancy test within 72 hours prior to the first dose of study treatment (see Appendix 3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. In the event that 72 hours have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for subject to start receiving study medication.

Pregnancy testing must be repeated at each visit prior to the next dose of IMP being administered and for visits up to 180 days since the last dose of treatment or until commencement of next systemic therapy, whichever occurs first. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. If a pregnancy test is confirmed to have a positive result, IMP must not be administered and the patient must be withdrawn from the trial, this pregnancy must be reported in line with Section 11.5.

10.3.2 Other Laboratory Tests

Details of the laboratory tests for haematology, chemistry, urinalysis, and thyroid function testing are specified in Table 6.

Table 6 - Laboratory Tests

Haematology	**Chemistry**	**Urinalysis**	**Other**
Haemoglobin	Sodium	Blood	Serum β-human chorionic gonadotropin†
White Blood Cell (total and differential)	Potassium	Glucose	(β-hCG)†
Platelet count	Urea	Protein	Free thyroxine (T4)
Red Blood Cell Count	Creatinine	Nitrites	Thyroid stimulating hormone (TSH)
Haematocrit	Calcium	Specific gravity	
Absolute Neutrophil Count	Chloride	Microscopic exam *(If abnormal*	Research blood samples
Absolute Lymphocyte Count	Magnesium	*results are noted)*	
	Phosphate	Urine pregnancy test †	
	Total Bilirubin		
	Alkaline phosphatase (ALP)		
	Alanine aminotransferase (ALT)		
	Aspartate aminotransferase (AST)		
	Lactate dehydrogenase (LDH)		
	Total protein		
	Albumin		
	Glucose		
† Perform on WOCBP during screening only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.			

10.4 Efficacy Measurements

10.4.1 Tumour Imaging

Tumour imaging is strongly preferred to be acquired by computed tomography (CT) of chest, abdomen and pelvis. If iodinated contrast is contraindicated, then non-contrast CT chest with magnetic resonance imaging (MRI) of the abdomen and pelvis may be used. MRI is the strongly preferred modality for imaging the brain. The same imaging modality, use of contrast, and ideally the same scanner should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumour burden and improve the accuracy of the assessment of response or progression.

RECIST 1.1 will be used as the primary measure for assessment of tumour response, date of disease progression, and as a basis for all protocol guidelines related to disease status (e.g. discontinuation of study treatment).

Confirmation scans for PR / PD will not be required in this trial as the purpose of the research is only to identify any signal which would warrant further evaluation.

10.4.2 Initial Tumour Imaging

Initial tumour imaging at screening must be performed within 28 days prior to the date of commencing trial treatment. The site study team must review screening images to confirm the participant has at least one non-irradiated site of measurable disease as per RECIST 1.1 which must not be the planned site for trial biopsies.

10.4.3 Tumour Imaging During the Study

The first on-study imaging assessment should be performed at 9 weeks (63 days ±7 days) from the date of commencing trial treatment. Subsequent tumour imaging should be performed every 9 weeks (63 days ±7 days) or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in treatment. Imaging should continue to be performed until disease progression is identified by the Investigator.

10.4.4 End of Treatment and Follow-up Tumour Imaging

In participants who discontinue study treatment, tumour imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For participants who discontinue study treatment due to documented disease progression, this is the final required tumour imaging.

For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumour imaging using the same imaging schedule used while on treatment (every 9 weeks) to monitor disease

status until either the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

10.4.5 Second Course (Retreatment) Tumour Imaging

Tumour imaging must be performed within 28 days prior to restarting treatment with cyclophosphamide and pembrolizumab. Local radiology reporting and investigator assessment will be used to determine eligibility.

The first on-study imaging assessment should be performed at 12 weeks (84 days ±7 days) after the restart of treatment. Subsequent tumour imaging should be performed every 12 weeks (84 days ±7 days) or more frequently, if clinically indicated.

Imaging should continue to be performed until disease progression, the start of a new anticancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first.

In participants who discontinue study treatment, tumour imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. In participants who discontinue study treatment due to documented disease progression, this is the final required tumour imaging.

In participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 12 weeks (84 days ±7 days) until either the start of a new anticancer treatment, disease progression, pregnancy, death, or the end of the study, whichever occurs first.

10.5 Tumour Tissue Collection and Research Blood Sampling

Full details of the tumour tissue collection / processing and research blood sampling / processing are contained within the CAPER trial laboratory manual.

10.5.1 Archival Tissue Collection

All trial participants will be asked to provide consent for retrieval of any available archival RCC tissue. This may represent diagnostic tissue from either primary tumour or metastatic sites, or may be tissue from prior surgical interventions (e.g. nephrectomy of metastatectomy).

Archival tissue will usually have been stored as FFPE blocks / slides.

10.5.2 Newly Obtained Tissue Biopsy

As per the Trial Schedule of Events, there are 3 timepoints for mandatory research biopsy collection in all trial participants:

1. **Baseline:** during 28-day screening period

2. **At day 20-21:** towards end of cyclophosphamide run-in period and MUST be prior to initiation of pembrolizumab

3. **At week 8-9:** immediately prior to first CT scan timepoint

These 3 biopsies should be scheduled at the time of initial trial consent to try and maximize the number of patients successfully undergoing all 3 biopsies. The biopsy site should be the same for all 3 biopsies where possible, and the biopsied lesion should not be included as a marker lesion for RECIST 1.1 assessments.

All research biopsy procedures will be carried out by medically qualified personnel, a member of the surgical team or a qualified radiologist with experience in biopsy/interventional radiology. All patients are required to sign a consent form prior to undergoing a research biopsy. Each patient will have a consultation with an investigator/ healthcare professional to discuss the procedure prior to signing the consent form. Procedure related information such as technique used to guide the biopsy, location of the biopsy, number of samples obtained and biopsy needle size (length and gauche), etc. will be collected and recorded in patient's clinical record. Tumour tissue will be collected from patients through the least invasive and safest approach. Patients will receive informed consent detailing risks and benefits of the specific procedure. Procedures will not involve general anaesthesia but patients can receive local anaesthesia.

Details of the sample collection / processing requirements are contained within the CAPER Laboratory Manual.

10.5.3 Research Blood Sampling

Research blood samples will be collected during screening, on day 1 of each treatment cycle (prior to administration of pembrolizumab), and at the time of treatment discontinuation. Where possible, research samples should be collected at the time of the patient having their other blood samples taken to avoid additional unnecessary venepuncture.

Details of the sample collection / processing requirements are contained within the CAPER Laboratory Manual.

10.6 Other Procedures

10.6.1 Treatment Withdrawal/Discontinuation

When a participant discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any AEs which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 11 - Assessing and Recording Adverse Events.

Participants 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 8.8. After discontinuing treatment following assessment of CR, these participants should return to the site for a Safety Follow-up Visit (described in Section 10.6.2) and then proceed to the Follow-Up Period of the study (described in Section 10.6.3).

After withdrawal from trial treatment an end of treatment CRF and withdrawal CRF should be completed. In the event of a patient's decision to withdraw from the trial, centres should explain the importance of remaining on trial follow-up, or failing this, of allowing routine follow-up data to be used for trial purposes. At the point of withdrawal the investigator should ascertain from which aspects of the trial the patient wishes to withdraw and record this on the withdrawal CRF.

SAEs will be collected until the patient ceases to undergo evaluations. After discontinuation of the study drugs, patients will be treated according to standard practice in the region. All information and blood/tissue samples collected up until point of retraction will be retained and analysed.

10.6.2 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study 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. Participants 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-cancer therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Participants who are eligible for retreatment/crossover with pembrolizumab (as described in Section 8.8) may have up to two safety follow-up visits, one after the Initial Treatment Period and one after the Second Course Treatment.

10.6.3 Follow-up Visits

Participants who discontinue study treatment for a reason other than disease progression will move into the Follow-Up Phase and should continue to undergo radiological assessments every 9 weeks (63 ± 7 days) to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of the study or if the participant begins retreatment with pembrolizumab as detailed in Section 8.8. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 8.8 will move from the follow-up phase to the Second Course Phase when they experience disease progression.

10.6.4 Survival Follow-up

Participants who experience confirmed disease progression or start a new anticancer therapy, will move 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 trial, whichever occurs first.

10.6.5 Withdrawal of Consent

If at any time a patient expresses a wish to withdraw their consent for ongoing study participation, then there should be a discussion with the patient to explain that they can withdraw from study treatments whilst still consenting to ongoing collection of clinical data. If they still decide to withdraw their consent for any further study participation then the following procedures will be observed:

1. Withdrawal of consent will be clearly documented in the study documentation and the study participant's medical record.

2. No further clinical data will be collected for the study participant. However existing clinical data held will be retained unless the trial participant specifically requests for removal from trial database.

3. No further biospecimens will be collected. However, the study participants existing biospecimens will be preserved unless the trial participant specifically requests their destruction.

4. The study participant's privacy will be respected and preserved.

10.6.6 Patient Transfers

For patients moving from the area or transferring to the care of another clinician, every effort should be made for the patient to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the patient or for follow-up via GP.

A copy of the patient CRFs should be provided to the new site. The patient will have to sign a new consent form at the new site, and until this occurs, the patient remains the responsibility of the original centre. The LCTC should be notified in writing of patient transfers and the planned arrangements

11.0 ASSESSING AND RECORDING ADVERSE EVENTS

11.1 Terms and Definitions

The following definitions have been adapted from European Directive 2001/20/EC and ICH-GCP E6

Adverse Event (AE)

Any untoward medical occurrence (i.e. any unfavourable or unintended sign including abnormal laboratory results, symptom or disease) in a research participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e. any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of study medication(s) is also an AE.

Adverse Reaction (AR)

Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR)

An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:

a) In the case of a product with a marketing authorization, in the summary of product characteristics for that product

b) In the case of any other investigational medicinal product, in the Investigator's Brochure relating to the trial in question.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

Any untoward medical occurrence that at any dose:

a) results in death

b) is life-threatening[1] (subject at immediate risk of death)

c) requires in-patient hospitalisation or prolongation of existing hospitalisation[2]

d) results in persistent or significant disability or incapacity

e) is a congenital anomaly or birth defect

f) is an important medical event that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

g) results in suspected transmission of an infectious agent (e.g. pathogenic or non-pathogenic) via the study drug.

h) is a new cancer that is not the condition under study (ECI)

i) is an overdose of study medication (ECI)

11.2 Timeframes

All new AEs (both serious and non-serious) other reportable safety events **MUST** be recorded and reported in accordance with Section 11.11 from the point of written informed consent to participate in the study until 30 days after the discontinuation of dosing of pembrolizumab and/or cyclophosphamide

All AEs, SAEs and that occur after the consent form is signed but before commencement of study treatment must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

All AEs from the time of commencement of study treatment through 30 days following cessation of study treatment must be reported by the investigator.

[1] 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe

[2] Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

All AEs meeting serious criteria, from the time of commencement of study treatment through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.

All pregnancies and exposure during breastfeeding, from the time of commencement of study treatment through 180 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately by the investigator if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study medication(s) or study participation, the investigator must promptly notify the Sponsor

11.3 Notes on Adverse Event Inclusions and Exclusions

Include

- New cancer diagnosis (ECI)
- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event/condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the study/trial treatment
- Laboratory anomalies that require clinical intervention or further investigation (unless they are associated with an already reported clinical event)
- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention
- Injury or accidents
- Any component of the study endpoint (OS) that is within the reporting window or is considered to be related to study therapy

- Overdose of medication with or without out signs or symptoms – see Section 11.4 and Section 11.6.2
- Elevated AST or ALT ≥ 3x the ULN **and** elevated total bilirubin ≥ 2x the ULN **and**, at the same time, an ALP lab value that is less than 2x the ULN during protocol-specified laboratory testing or unscheduled laboratory testing. (ECI).

Do Not Include:

- Medical or surgical procedures used to treat a condition, the condition which leads to the procedure is the AE
- Pre-existing disease or conditions present before treatment that do not worsen
- Situations of elective surgery
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition
- The following hospitalisations are not considered SAEs :
    - a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
    - elective surgery, planned prior to signing consent
    - routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
    - Medical/surgical admission other than to remedy ill health and planned prior to entry into the study.
    - Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
    - Admission for administration of anticancer therapy in the absence of any other SAEs
- Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered AEs. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

11.4 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

For purposes of this study, 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. In the event of overdose, the participant should

be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an AE is associated with ("results from") the overdose of either study medication (cyclophosphamide or pembrolizumab), the AE is reported as an SAE, even if no other seriousness criteria are met.

If a dose of study medication(s) 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 AESI, using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an AE must be reported within 24 hours to the CTU (details below).

The following information should be included as a minimum:

- Patient Study Number
- Dose administered
- Patient follow-up/monitoring plan.

Trial Office– Tel: **0151 795 5289**

Email: caper@liverpool.ac.uk

(Note that the LCTC is open from 09:00 – 17:00, Monday – Friday, excluding public holidays)

In case of system failure fax a copy of the form to 0151 794 8930 or as a last resort leave a message on the Trial Office answering machine.

11.5 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and infant exposure during breast feeding are not considered AEs, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a participant (spontaneously reported to them) that occurs during the study.

Pregnancies and infant exposures during breastfeeding that occur after the consent form is signed but before commencement of study treatment must be reported by the investigator if they cause the participant to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and infant exposures during breastfeeding that occur from the time of commencing study treatment through 180 days following cessation of the product, or 30

days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, foetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the CTU.

The final Pregnancy Report Form is used to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy follow-up information on this form also includes an assessment of the possible relationship to the trial medication of any pregnancy outcome. Pregnancy outcomes should also be collected for the female partners of male patient participating in the trial. Consent to report information regarding these pregnancy outcomes should be obtained from the mother prior to completion and faxing of the final Pregnancy Report Form. Any SAE experienced during pregnancy must be reported on the SAE form.

11.6 Immediate Reporting of Adverse Events to the Sponsor

11.6.1 Serious Adverse Events

A serious adverse event definition is given in Section 11.1.

Refer to Table 7 for additional details regarding each of the serious criteria.

For the time period beginning when the consent form is signed until commencement of study treatment, any SAE, or follow up to an SAE, including death due to any cause that occurs to any participant must be reported within 24 hours to the CTU in accordance with Section 11.11.

For the time period beginning at commencement of study treatment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any SAE, or follow up to an SAE, including death due to any cause whether or not related to study medication(s), must be reported within 24 hours to the CTU.

Additionally, any SAE, considered by an investigator who is a qualified clinician to be related to study medication(s) that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All participants with SAEs must be followed up for outcome.

A copy of all SUSAR Reports and Development Safety Update Reports (DSURs) are submitted as required by the MHRA and other local regulators.

11.6.2 Adverse Events of Special Interest (AESI)

In addition to the above SAE criteria, selected non-serious and SAEs are also known as AESIs and must be reported to the CTU in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the CTU for collection purposes.

ECIs for this trial include:

- Development of a new cancer (that is not the condition under study);
- Any overdose of study medication(s), regardless of whether this is associated with clinical symptoms or abnormal laboratory results;
- Elevated AST or ALT $\geq$ 3x the ULN **and** elevated total bilirubin $\geq$ 2x the ULN **and**, at the same time, an ALP lab value that is less than 2x the ULN during protocol-specified laboratory testing or unscheduled laboratory testing. (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 aetiology).

For the time period beginning when the consent form is signed until commencement of study treatment, any AESI, or follow up to an AESI, that occurs to any participant must be reported within 24 hours to the CTU.

For the time period beginning at commencement of study treatment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any AESI, or follow up to an AESI, whether or not related to study medication(s), must be reported within 24 hours to the CTU.

11.7 Evaluating Adverse Events

An investigator who is a qualified clinician will evaluate all AEs according to the NCI CTCAE version 5.0. Any AE which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

All AEs regardless of CTCAE grade must also be evaluated for seriousness.

11.8 Sponsor Responsibility for Reporting Adverse Events

All AEs will be reported to regulatory authorities, REC and investigators in accordance with all applicable global laws and regulations.

The LCTC will take on all responsibilities for Safety reporting on behalf of the sponsor.

Table 7 - Evaluating Adverse Events

An investigator who is a qualified clinician will evaluate all AEs with regards to:

V5.0 CTCAE Grading	**Grade 1**	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
	Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
	Grade 3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activities of daily living.
	Grade 4	Life threatening consequences; urgent intervention indicated.
	Grade 5	Death related to AE
Seriousness	An SAE is any AE occurring at any dose or during any use of study medication(s) that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the participant, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an AE that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of study medication(s) and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of participant taking the product regardless of time to diagnosis);or	
	Is a new cancer (not the condition under study) (although not serious per ICH definition, is reportable to the Sponsor within 24 hours)	
	Is an overdose (whether accidental or intentional). Any AE associated with an overdose is considered an SAE for collection purposes. An overdose that is not associated with an AE is considered a non-serious adverse event of special interest and must be reported within 24 hours to the Sponsor	
	Is liver derangement meeting the following criteria: Elevated AST or ALT > 3x the ULN **and** elevated total bilirubin > 2x the ULN **and,** at the same time, an ALP lab value that is less than 2x the ULN during protocol-specified laboratory testing or unscheduled laboratory testing; or	

	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the AE. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the AE cause study medication(s) to be discontinued?	
Relationship	The determination of the likelihood that the study medication(s) caused the AE will be provided by an investigator who is a qualified clinician. The investigator's signed/dated initials on the source document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the study medication(s) and the AE based upon the available information. Relationship should be assessed separately for each of cyclophosphamide and pembrolizumab. **The following components are to be used to assess the relationship between study drugs and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study drugs caused the AE:	
	None	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
	Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
	Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
	Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
	Highly Probable	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Relationship (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	De-challenge	Was the study medication(s) discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive de-challenge. If no, this is a negative de-challenge.
	Re-challenge	Was the participant re-exposed to the study medication(s) in this study? If yes, did the AE recur or worsen? If yes, this is a positive re-challenge. If no, this is a negative re-challenge.
	Consistency	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding study medication(s) or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the CRFs /worksheets by an investigator who is a qualified clinician according to his/her best clinical judgment, including consideration of the above elements.		

Record one of the following in relation to each of cyclophosphamide and pembrolizumab	**Use the following scale of criteria as guidance**
Yes, there is a reasonable possibility of study medication relationship. **(Possibly / Probably /Highly Probable))**	There is evidence of exposure to study medication. The temporal sequence of the AE onset relative to the administration of study medication is reasonable. The AE is more likely explained by study medication than by another cause.
No, there is not a reasonable possibility of study medication relationship **(Unlikely /None)**	Participant did not receive the study medication OR temporal sequence of the AE onset relative to administration of study medication is not reasonable OR the AE is more likely explained by another cause than the study medication.

11.9 Expectedness

All events judged by the investigator or the sponsor clinical team to be reactions and fulfilling the definition of serious will be assessed for expectedness against the current approved reference safety information (RSI) (see section 11.10).

Events documented in the RSI are considered to be expected and those not included are considered unexpected. This review will be conducted to the sponsor delegated clinical team within the LCTC.

All events judged by the investigator to be possibly, probably, or highly probably related to the IMP, defined as serious and **unexpected** should be reported as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

11.10 Reference Safety Information (RSI)

The RSI to be used for this trial is as follows:

Pembrolizumab (Keytruda) – Investigator's Brochure – Section 7.2
Cyclophosphamide Tablets 50mg – Summary of Product Characteristics – Section 4.8

This will be updated as required and implemented only after approval from the appropriate regulatory authorities.

11.11 Reporting SAEs

Site can either complete paper forms or transmit SAEs via PHAROS (pharmacovigilance system). Sites will discuss their preferred method during site feasibility and initiation.

Blank SAE forms for paper reporting can be obtained by logging onto the PORTAL (www.lctu.org.uk) or contacting the trial team. The CAPER team will acknowledge receipt of the SAE on the same day if sent on a working day between 9am – 5pm or the next working day. If an acknowledgment is not received by site, they should contact the LCTC.

SAEs must be reported within 24 hours of sites becoming aware of them by emailing a completed SAE FORM to the LCTC or by logging on to PHAROS and imputing the data.

If all computer systems have failed and an SAE needs to urgently be reported a fax copy can be sent to 0151 794 8930, and as a last resort an answer phone message can be left on 0151 795 5289 detailing the SAE.

Steps for reporting:

i. The SAE form should be completed by the responsible investigator i.e. the consultant named on the 'signature list and delegation of responsibilities log' who is responsible for the patient's care. The investigator should assess the SAE for the likelihood that it is a response to an investigational medicine. In the absence of the responsible investigator the form should be completed and signed by a designated member of the site trial team. The responsible investigator should check the SAE form, make changes as appropriate and sign as soon as possible. The initial report shall be followed by detailed, written reports.

ii. The SAE form should be submitted to the LCTC.

iii. The responsible investigator must notify their R&D department of the event (as per standard local procedure).

iv. In the case of an SAE the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary.

v. Follow-up information is noted on the same SAE form. The SAE type check-box at the top of the form should be changed to 'follow-up'. Extra, annotated information and/or copies of test results may be provided separately.

vi. The patient must be identified by trial number, month and year of birth and initials only. The patient's name should not be used on any correspondence.

The minimum dataset required for a preliminary report should include the following.

- Research subject trial number and initials.
- Date of onset of event.
- Brief description of event and CTCAE (v5) grade.
- Causality relationship.
- Dated signature of investigator/co-investigator and clearly printed name.
- Date of last administration of study drug.

PLEASE ENSURE THAT MULITPLE SAEs ARE REPORTED SEPARATELY TO THE LCTC.

ONE SAE REPORT SHOULD ONLY RELATE TO ONE OVERALL DIAGNOSIS.

11.12 Suspected Unexpected Serious Adverse Reaction (SUSAR)

The CI and the LCTC will ensure that all SUSARs are reported to the Sponsor, Competent Authorities (MHRA Clinical Trials Unit) and Ethical Committees within the following timelines.

- Fatal or life threatening SUSARs within 7 days after receiving the initial information.

- All other SUSARs with 15 days after receiving the information.

The CI and the LCTC will inform all investigators of SUSARs as they occur.

All SUSARs are managed in accordance with TM031 Pharmacovigilance and Safety Reporting Standard Operating Procedure (SOP), along with associated documents, and the CAPER Pharmacovigilance plan.

11.13 Annual Reporting to MHRA and REC

The CTU will submit a DSUR. This will be done in accordance with the SOP TM026 and the current DSUR report plan.

The DSUR will present a comprehensive annual review and evaluation of pertinent safety information collected during the reporting period relating to the IMP it will cover the following 4 areas:

(1) Examine whether the information obtained by the sponsor during the reporting period is in accordance with previous knowledge of the investigational drug's safety.

(2) Describe new safety issues that could have an impact on the protection of clinical trial subjects.

(3) Summarise the current understanding and management of identified and potential risks.

(4) Provide an update on the status of the clinical investigation/development programme and study results.

11.14 Responsibilities

Investigator

The Investigator (PI or co-investigator) is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study product.

All SAEs must be reported immediately by the investigator to the LCTC on an SAE form unless the SAE is specified in the protocol as not requiring immediate reporting. All other AEs should be reported on the regular progress/follow-up reports.

LCTC

The LCTC is undertaking duties delegated by the trial sponsor, The Christie NHS Foundation Trust and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA, competent authorities of other European member states in which the trial is taking place and, if required, the RECs) as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the LCTC is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the LCTC first becoming aware of the reaction.
- A list of all SARs (expected and unexpected) must be reported annually.
- It is recommended that the following safety issues should also be reported in an expedited fashion:
    - An increase in the rate of occurrence or a qualitative change of an expected SAR, which is judged to be clinically important;
    - Post-study SUSARs that occur after the patient has completed a clinical trial and are notified by the investigator to the sponsor;
    - New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the subjects, such as:
        a. An SAE which could be associated with the trial procedures and which could modify the conduct of the trial;
        b. A significant hazard to the subject population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;
        c. A major safety finding from a newly completed animal study (such as carcinogenicity).
        d. Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same sponsor;
    - Recommendations of the Trial Steering Committee, if any, where relevant for the safety of the subjects.

Staff at the LCTC will liaise with the designated Clinical Co-ordinators who will evaluate all SAEs received for seriousness, expectedness and causality. Investigator reports of suspected SARs will be reviewed immediately and those that are SUSARs identified and reported to regulatory authorities and REC. The causality assessment given by the Local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report.

The LCTC will also send an annual safety report containing a list of all SARs to regulatory authorities and

Patient safety incidents that take place in the course of research should be reported to the National Patient Safety Agency by each participating NHS Trust in accordance with local reporting procedures.

11.15 Informing MSD

The CTU will ensure that all events listed below are forwarded within 2 working days to MSD Global Safety. Details of how to report to MSD Global Safety are recorded in the CAPER Pharmacovigilance Plan (SSCAP_D010).

- ECIs
- SAEs
- Pregnancy outcomes
- Overdose

The CTU will then ensure that the report is forwarded within 2 working days to MSD Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

12.0 STATISTICAL ANALYSIS PLAN

This phase Ib study is aimed at detecting an efficacy signal for the combination of cyclophosphamide and pembrolizumab that may warrant further evaluation in a larger patient cohort (phase II).

12.1 Primary Endpoint

The primary endpoint of the trial is ORR according to RECIST version 1.1 from baseline until end of study or death, and will be calculated using the best response achieved during study treatment for each participant.

12.2 Secondary Endpoints

Secondary endpoints include:

- PFS, measured from the time of first treatment to the time of first documented progression or the censor date in months
- OS, defined as the time from first treatment to death by any cause in months
- Safety and tolerability of the combination of cyclophosphamide and pembrolizumab, reported following the CTCAE version 5 guidelines.

12.3 Sample Size

Based on the primary ORR endpoint, it is planned to recruit a total of 21 eligible patients with the following statistical rationale:

- **Null hypothesis (H0):** 0-1 out of 21 patients will respond to cyclophosphamide and pembrolizumab (ORR $\leq$5%).
- **Alternative hypothesis (H1):** At least 3 out of 21 patients will respond to cyclophosphamide and pembrolizumab (ORR target 20%).

If the alternative hypothesis is met then this would confirm the combination as being worthy of further evaluation.

Using Simon's two-stage minimax design (Simon, 1989), the null hypothesis that the true response rate is 5% will be tested against a one-sided alternative. In the first stage, 12 patients will be accrued. If there are 0 responses in these 12 patients, the study will be stopped. Otherwise, 9 additional patients will be accrued for a total of 21. The null hypothesis will be rejected if 3 or more responses are observed in 21 patients. This design yields a type I error rate of 8% and power of 80% when the true response rate is 20%.

12.4 Interim Futility Analysis

If the combination of cyclophosphamide and pembrolizumab is not found to be demonstrating any clinical activity then it would be desirable to terminate the trial early and reduce the number of patients receiving an ineffective combination.

For this reason, it is planned to include an interim futility analysis after the 12th recruited patient has reached the first CT scan timepoint at 9 weeks. At this timepoint, the trial will be terminated if 0/12 have evidence of any anti-tumour activity as measured by RECIST objective response (PR or CR). If any patients have evidence of tumour shrinkage that does not yet meet criteria for PR then the TMG may be consulted to advise regarding early closure versus continuing treatment.

12.5 Analysis Plan

12.5.1 Primary Outcome

Objective response is defined as occurrence of CR or PR as defined by the RECIST version 1.1 at any point in follow-up until end of study or death. Deaths before assessment, non-assessable or missing values will be counted as non-response. Best Objective Response is the highest value achieved for each patient and will be used for the primary outcome analysis.

12.5.2 Secondary Outcomes

Progression-free survival

PFS events are defined as either disease progression or death from any cause. The event date used for analysis will be the first occurrence of either disease progression or death and the analysis will use the following formula:

Progression-free survival (months) = (exit date – date of first treatment)/30.4

Overall survival

OS events are defined as death from any cause. The event date used for analysis will be the confirmed date of death and the analysis will use the following formula:

Overall Survival (months) = (Exit date – date of first treatment)/30.4

Safety and tolerability

The number and percentage of patients reporting SAEs and Grade 3 or higher toxicity will be summarised overall and by preferred term (if severity is missing, the worst case will be assumed).

12.5.3 Presentation of results

Categorical variables, including details of baseline subject characteristics, will be summarised as N (%), continuous variables by mean (standard deviation) or median (Inter-quartile range (Q1-Q3)).

A separate analysis plan including the above details but with the addition of dummy figures and table shells will be approved before the final analysis.

Statistical analyses will be performed using Stata v15, R v3.3 or SAS v9.3.

12.6 Other Statistical Considerations

The statistical calculations above are based on an expected median duration on treatment of approximately 18 weeks (equivalent to 6 cycles of treatment with discontinuation at the time of the second CT assessment scan).

Patients that do not successfully undergo **both** the first research biopsy (in screening) **and** the second research biopsy (C1 D20-21) will be withdrawn and replaced.

Any patients who are subsequently confirmed to be ineligible following trial entry will also be withdrawn and replaced.

All other recruited patients will count towards the overall trial recruitment target of 21 participants.

12.7 Expected Timelines

Recruitment of 21 eligible patients who undergo planned biopsies in screening and C1 D20-21 is expected to take approximately 15 months (equating to approximately 1 recruited patient every 3 months at each of the 4 participating sites).

Given the relatively short follow-up period required to obtain response information, and expected median duration on treatment of approximately 18 weeks, the total trial duration is anticipated to be around 36 months.

12.8 Early Trial Termination

During the trial, it is possible that the trial may be terminated early for reasons other than futility. For the purposes of this trial, early trial termination may result from any 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 participants

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 participant treatment can be made.

13.0 LABELLING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

Detailed guidance on the preparation, dispensing and management of IMP will be provided to research sites in a Pharmacy Operating Manal

13.1 Investigational Medicinal 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. These responsibilities may be delegated using the trial delegation log to an appropriately qualified pharmacist once trial specific training has been undertaken.

Pembrolizumab will be provided by MSD as summarized in Table 8.

Funding will be provided to reimburse sites for the costs associated with use of oral cyclophosphamide.

Table 8 - Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/ 4mL	Solution for Injection
Cyclophosphamide 50mg	Tablet

13.2 Packaging and Labelling Information

Supplies will be labelled in accordance with regulatory requirements.

Drug labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

Label text MUST include:

a) name, address and telephone number of the sponsor (main contact for information on the product)
b) clinical trial number (EudraCT)
c) pharmaceutical dosage form, route of administration, quantity of dosage units, the name/identifier and strength/potency
d) the batch and/or code number to identify the contents and packaging operation
e) the trial subject identification number/treatment number and the visit number

f) the name of the investigator
g) directions for use (reference may be made to a leaflet or other explanatory document intended for the patient or person administering the product)
h) "For clinical trial use only"
i) the storage conditions
j) period of use (use-by date, expiry date), in month/year format and in a manner that avoids any ambiguity
k) "keep out of reach of children"

13.3 Clinical Supplies Disclosure

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

13.4 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.

13.5 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 participants and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used IMP will be destroyed at the site per institutional policy. It is the Principal 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.

14.0 TRIAL MONITORING

Central and site monitoring is conducted to ensure protection of patients participating in the trial, and that trial procedures, trial intervention administration, and laboratory and data collection processes are of high quality and meet sponsor and, when appropriate, regulatory requirements. A risk assessment will be carried out to determine the level of monitoring required, and a subsequent monitoring plan will be developed to document who will conduct the central (and potentially site) monitoring, at what frequency monitoring will be carried out and the level of detail at which monitoring will be conducted.

The monitoring activities for the CAPER trial are supporting by a project specific monitoring plan.

14.1 Risk Assessment

In accordance with the LCTC SOPs, a risk assessment has been completed in partnership with:

- Representatives of the Trial Sponsors
- CI
- Trial Co-ordinator
- Trial Statistician
- LCTC Director

In conducting this risk assessment, the contributors considered potential patient, organisational and study hazards, the likelihood of their occurrence and resulting impact should they occur.

The outcome of the risk assessment for a Clinical Trial of an Investigational Medicinal Product (CTIMP) is expressed as an overall risk level as set out below, assigned according to one of the following categories:

CTIMP Type A = Comparable to the risk of standard medical care

CTIMP Type B = somewhat higher than the risk of standard medical care

CTIMP Type C = markedly higher than the risk of standard medical care

Non-CTIMP

The risk assessment resulted in a CTIMP Type B = somewhat higher than the risk of standard medical care

14.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy and laboratory departments involved in the clinical trial.

14.3 Data Capture Methods

The study CRF is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained.

For sites using paper CRFs,if a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Completed paper CRFs should be completed and original copies sent to the LCTC within 1 month of the visit. Copies should be retained at the study centre in the patient files.

CRFs and completion guidelines will be made available for centres to access via the PORTAL.

For sites that wish to enter data directly onto the CAPER MACRO database, training will be provided or suitable evidence of previous training accepted, before access to the database is granted. Paper CRFs must be completed as worksheets and retained at site as an independent copy of data; these do not need to be sent to the LCTC.

All study data will be recorded on the CAPER MACRO database and PHAROS database by LCTC staff or appropriately trained site staff.

Further information is contained within the CAPER Data Management Plan.

14.4 Data queries

Data stored at LCTC will be checked for missing or unusual values (range checks) and checked for consistency within patients over time. If any such problems are identified, a PDF list of queries will be emailed to the local site for checking and confirmation or correction as

appropriate. Responses received from centres will then be used to amend data on MACRO. LCTC will send reminders for any overdue and missing data.

There are a number of monitoring features in place at the LCTC to ensure reliability and validity of the trial data.

14.5 Direct Access to data

In order to perform their role effectively, monitors and persons involved in Quality Assurance and Inspection will need direct access to primary subject data, e.g. patient records, laboratory reports, appointment books, etc. As this affects the patient's confidentiality, this fact is included on the PIS and ICF.

14.6 Quality Assurance and Quality Control of Data

Systems of quality assurance, including all elements described in this protocol have been/will be implemented within relevant institutions with responsibility for this trial. Quality control is applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

The CAPER trial centres, facilities, laboratories and all data (including sources) and documentation must be available for GCP audit and inspection by competent authorities or REC. Such audits/inspections may take place at any trial centre where the trial related activity is taking place (the Sponsor, study centres, LCTC, or at any investigator's centre including laboratories, pharmacies etc.).

The study centre staff should assist in all aspects of audit/inspection. This includes management systems such as the Green Light Process which conforms to the total Quality Management System currently operating within the LCTC.

15.0 ADMINISTRATIVE AND REGULATORY DETAILS

15.1 Trial Sponsor

The Christie NHS Foundation Trust, 550 Wilmslow Road, Manchester M20 4BX

15.2 Clinical Trials Unit

Liverpool Clinical Trials Centre, University of Liverpool, 1st floor Block C, Waterhouse Building, 3 Brownlow Street, Liverpool L69 3GL

15.3 Funding Body

Merck Sharp & Dohme (MSD) Limited

This study is an academic lead study that has been costed in accordance with Department of Health guidelines: Attributing the costs of health & social care Research & Development (AcoRD).

A contribution as detailed in the Research Site Agreement will be covered by the funder and payments will be managed by the LCTC.

The study has been submitted for adoption on the NIHR portfolio providing access to service support costs.

15.4 Ethics approval

As this study is within NHS England, assessment of governance and legal compliance will be undertaken by dedicated HRA staff, with the independent REC opinion provided through the UK Health Department. No patients will be entered onto the study before ethical approval has been confirmed.

The CI is responsible for updating the ethics committee of any new information related to the trial.

The trial protocol has received the favourable opinion of the HRA Ethics Committee <<insert REC>> Research Ethics Committee but all participating sites must undergo site specific assessment of capacity and capability via the HRA. Copies of site agreements to take part and copies of the PIS and ICF with local site headers and emergency contact details for patients must be forwarded to LCTC before patients are entered. The LCTC should receive a confirmation of capacity and capability for each new centre via the site's R&D department

The study will be conducted in accordance with, but not limited to, the Human Rights Act 1998, the Data Protection Act 2018, Freedom of Information Act 2000 subject to the provisions of sections 41 and 43 thereof, the EU Clinical Trials Directive, the Medicines for

Human Use (Clinical Trials) Regulations 2004, the Medicines Act 1968, the Human Tissue Act 2004, ICH-GCP, the Declaration of Helsinki 1996 and the UK Policy framework for Health and Social Care research as amended from time to time.

Where patients agree to take part in the study, they will be informed of how data are recorded, collected, stored and processed and may be transferred to other countries, in accordance with The General Data Protection Regulation (GDPR) (EU) 2016/679. As the sponsor of the CAPER clinical trial is a non-commercial organisation the legal basis for the handling and processing of data is 'task in the public interest.'

This study may be terminated at the request of the CI, REC or the MHRA if, during the course of the study, concerns about the safety of further dosing emerge.

The CI will update the ethics committee and/or the MHRA of any new information related to the study drug when appropriate and this will also be disseminated to the Principal Investigators at each trial centre.

15.5 Regulatory approval

This trial has been registered with the MHRA and has been granted a Clinical Trial Authorisation (CTA). The CTA reference is <<insert CTA number>>

15.6 Trial Registration

The CAPER study has been registered on the International Standard Randomised Control Trial Network (ISRCTN) database for clinical trial on <insert date> the study record number is <insert ISRCTN number>

15.7 Confidentiality

All information collected as part of this clinical study will remain confidential in accordance with GCP, GDPR and the 2018 Data Protection Act.

Key principles include:

- Obtaining consent from participants for access to their medical records by responsible individuals; research staff, regulatory authorities, the Christie NHS Foundation Trust, and MSD where it is relevant to study participation

- Appropriate storage, restricted access and disposal arrangements for patient's personal and clinical details.

- If a participant withdraws consent from participation in the study and / or further collection of data then existing data / research samples will remain on file. Existing

data / research samples will be included in the final trial analysis unless the participant specifically withdraws consent for this.

15.8 Study Oversight

The CAPER TMG will work to protect the confidentiality of the study data and ensure safety of study participants. This committee will consist of the CI, Principal Investigators, trial statistician, data manager and other members of the study team involved in the conduct of the study. The TMG will consider the study data in the context of ongoing scientific developments in the field and regularly review the safety and ethics of the study going forward.

Specifically, the TMG will be tasked to review the following important factors

- Study accrual
- Adherence to protocol (deviations / breaches)
- Safety of participants (SAE reporting)
- Success rates of mandatory research biopsies

The trial will also been overseen by a TSC consisting of an independent chairperson, 2-3 independent experts in the field of oncology, and an independent biostatistician. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC. Decisions regarding ongoing safety and data validity, that would normally fall into the remit of an independent safety and data monitoring committee, will also be made by the TSC as the trial is single arm, unblinded and non-randomised.

In addition to the above, the TSC will specifically be consulted following the interim futility analysis as outlined in the statistical section (Section 12.4). The results of this interim analysis will be made available to the TSC members and they will make a recommendation to the TMG as to whether the trial should continue accrual or be terminated early for futility.

15.9 Protocol Amendments

Any change to the trial protocol will require an amendment. Any proposed, non-administrative, protocol amendments will be initiated by the CI following discussion with the TMG. The CI and the TMG will liaise with sponsor to determine whether an amendment is non-substantial or substantial.

Amendment forms will be submitted to the regulatory authority, REC and sponsor as required. All amended versions of the protocol will be signed by the CI and sponsor representative. Before the amended protocol can be implemented favourable approvals

must be in place from relevant bodies including: original reviewing REC; HRA; trial sponsor; MHRA (if applicable); and participating site R&D offices.

An urgent safety measure may be put in place with immediate effect without gaining prior authorisation by the REC (and MHRA where applicable), in order to protect clinical trial participants from any immediate hazard to their health and safety. Sponsor, REC, HRA and MHRA must be notified by substantial amendment within 14 days of the measures being taken.

15.10 Liability and Indemnity

No special insurance is in place for patients in this study other than standard NHS liability insurance providing indemnity against clinical negligence. As this is a clinician-led trial, there are no arrangements for no-fault compensation; however, usual product liability will be covered by the manufacturer under the Consumer Protection Act 1987.

The Hospital Trust/Health Board at each participating site is responsible for the following:

- Ensuring the appropriate insurance administered by the National Health Service Litigation Authority is in place.

- Ensuring any non-NHS employees involved in the clinical trial have Honorary Contracts with the Trust/Board to cover access to patients and liability arrangements.

15.11 Participating Sites

The PI at each participating site is responsible for the management of the trial within their site. This includes ensuring that all relevant local approvals are in place, ensuring that the trial is conducted according to ICH-GCP requirements, and ensuring that the appropriate insurance or indemnity is in place.

15.12 End of Study Notification

The end of study notification will be submitted in writing to the REC within 90 days of the date of termination of the study as defined in section 4.3.

15.13 Study Summary Report

The CAPER TMG is responsible for compiling and submitting the final study report to the sponsor and REC within 1 year of study closure.

15.14 Archiving

The site files will be archived at each site under the custodianship of the site PI. Personal data will be stored for up to 25 years after the end of the study. Data will be stored and archived by the site in line with requirements of ICH-GCP and the Data Protection Act 2018.

The PI at each investigational site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial ICH E6, Guideline for Good Clinical Practice]) including the Investigator Site File, until the LCTC informs the PI that the documents are no longer to be retained. In addition, the PI is responsible for the archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities). The PI is required to ensure the continued storage of the documents, even if the PI, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The LCTC undertakes to store original documents completed for the trial research e.g. ICF for the same period, except for source documents pertaining to the individual investigational site, which are kept by the PI only.

At the point where it is decided that the trial documentation is no longer required; the PI will be responsible for the destruction of all site trial specific documentation and the Sponsor/LCTC will be responsible for the destruction of all trial related materials retained by the Sponsor/LCTC.

15.15 Publication Policy

The data arising from the CAPER study will belong to the trial sponsor, the Christie NHS Foundation Trust. The TMG shall act as custodian of this data. No site or individual will publish data without prior approval of the TMG, Sponsor and the funding body (MSD).

The TMG is responsible for approving the content and dissemination of all publications, abstracts and presentations arising from the CAPER study. MSD will also review content prior to dissemination. The International Committee of Medical Journal Editors (ICMJE) criteria will be used to ensure all those who have contributed to the study are appropriately acknowledged.

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17.0 APPENDICES

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 Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

Appendix 2: Common Terminology Criteria for Adverse Events V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI CTCAE version 5.0 will be utilized for AE reporting.

(https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

Appendix 3: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

Contraception Requirements

Male Participants:

Male participants with partners who are WOCBP are eligible to participate if they agree to one of the following during the protocol defined time frame outlined in Section 6.5.1.2:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 8 when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.
- Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile**-**vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 9 during the protocol-defined time frame outlined in Section 6.5.1.2.

Table 9 - Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*

• Combined (oestrogen- and progestogen- containing) hormonal contraception [b, c]
  ○ Oral
  ○ Intravaginal
  ○ Transdermal
  ○ Injectable

• Progestogen-only hormonal contraception [b, c]
  ○ Oral
  ○ Injectable

Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen- only contraceptive implant [b, c] • Intrauterine hormone-releasing system (IUS) [b] • Intrauterine device (IUD) • Bilateral tubal occlusion
• Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [a] Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly).

[b] If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 180 days, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment.
[c] If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test and in accordance with local requirements. When applicable this test should be repeated a maximum of 24-hours before the first dose.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.