PROMPT: Phase II trial of maintenance pembrolizumab following weekly paclitaxel for recurrent ovarian, fallopian tube or peritoneal cancer

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Please note: This trial protocol must not be applied to patients outside the PROMPT trial. Cancer Research UK & UCL Cancer Trials Centre (CR UK & UCL CTC) can only ensure that approved trial investigators are provided with amendments to the protocol.

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1. PROTOCOL SUMMARY

1.1. Summary of Trial Design

Title:	Phase II trial of maintenance pembrolizumab following weekly paclitaxel for recurrent ovarian, fallopian tube or peritoneal cancer
Short Title/acronym:	PROMPT
EUDRACT no:	2017-003792-63
Sponsor name & reference:	UCL
Funder name & reference:	Merck Sharpe & Dohme (UK) Limited MISP: 51911
Clinicaltrials.gov no:	NCT03430700
Design:	Multi centre, single-arm phase II trial
Overall aim:	To demonstrate a clinically meaningful extension of progression free survival using maintenance pembrolizumab. Translational research to study the immune microenvironment before and during pembrolizumab treatment.
Primary endpoint:	Progression-Free Survival (PFS) at 6 months from the start of maintenance pembrolizumab
Secondary endpoints:	• PFS at 6 months from the start of weekly dose-dense paclitaxel • Overall survival (from the start of maintenance pembrolizumab, and from the start of weekly dose-dense paclitaxel) • Disease response (according to RECIST v1.1) • Toxicity and compliance
Exploratory endpoints	• See section 10 for immunological analysis • Further treatment following disease progression.
Immunological samples:	• Tumour biopsy at start and before cycle 4 to determine the immune microenvironment (if feasible). • Collection of blood to measure circulating immune cells • Collection of archival tumour to compare with trial samples
Target accrual:	28 patients
Inclusion & exclusion criteria (please refer to section 6.2.1 for full criteria):	**Inclusion**:

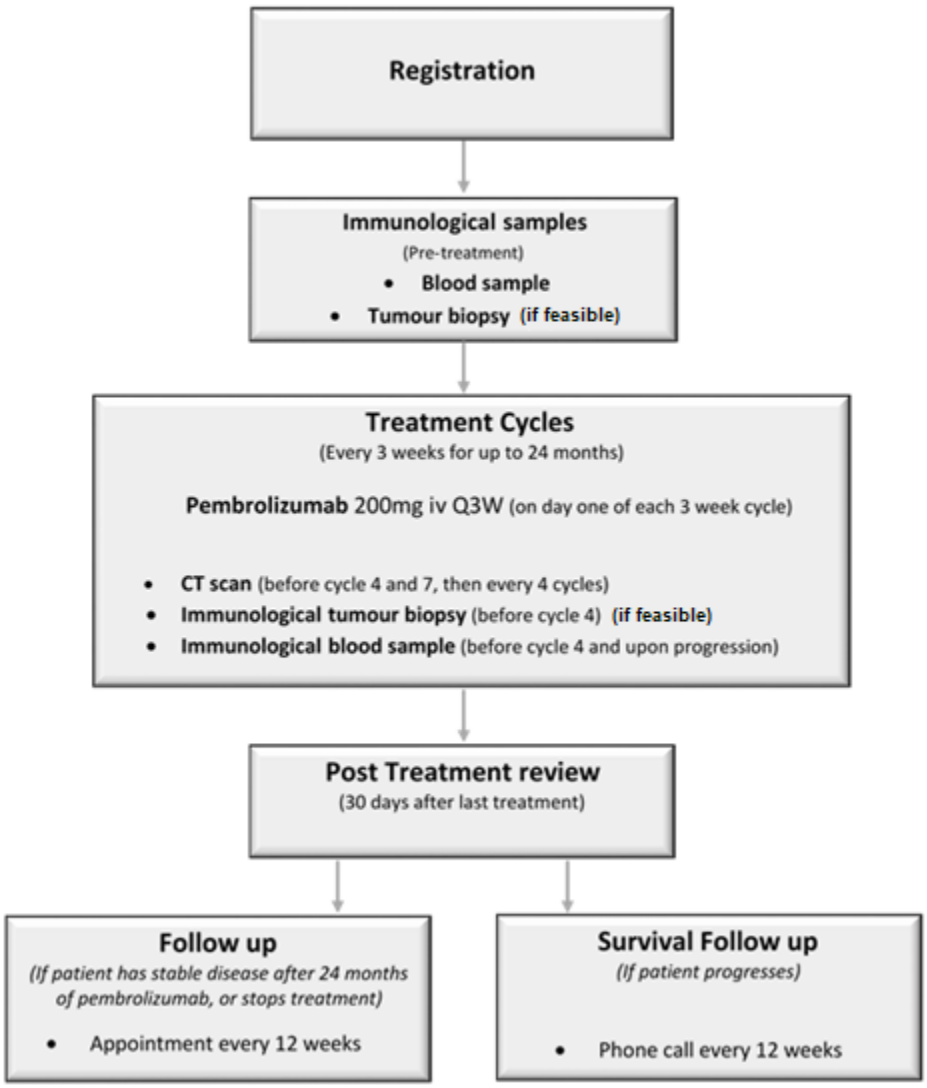
	1. Patients must have a diagnosis of high grade recurrent ovarian/fallopian tube or primary non-mucinous peritoneal cancer 2. Patients should be treated with a minimum of 4 cycles of weekly paclitaxel for recurrent disease [Non-platinum- based therapy given for CT/MR documented recurrence where further platinum therapy considered unsuitable]. Patients with a good interim response to paclitaxel could discontinue chemotherapy after 4 cycles and be considered for trial treatment 3. Patients can have had up to 3 lines of platinum-based chemotherapy for ovarian cancer before starting weekly paclitaxel 4. Patients must have achieved at least stable disease or response following a minimum of four cycles of weekly paclitaxel (measured by CT/MR) 5. Trial treatment with pembrolizumab must start within 8 weeks after last paclitaxel dose 6. Availability of archival tissue 7. Fresh tumour biopsy should be taken at baseline if this is judged by radiological assessment to be technically feasible. If a biopsy is taken at baseline, then a second biopsy should be taken, if feasible before the start of cycle 4. 8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 9. Willing and able to comply with the protocol for the duration of the study, including the treatment plan, investigations required and follow up visits 10. Demonstrate adequate organ function **Exclusion**: 1. Prior therapy with an anti-PD-1, anti-PD-L1 or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor 2. Low grade or mucinous ovarian cancer 3. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. (Use of inhaled steroids is permitted). 4. Known history of active TB (Bacillus Tuberculosis) 5. Known history of Hepatitis B or known Hepatitis C virus

	6. Has a known history of Human Immunodeficiency Virus (HIV) 7. Patients who have not recovered (i.e., ≤ Grade 1) from adverse events due to prior paclitaxel or previous lines of therapy 8. Has received prior radiotherapy within 2 weeks of start of study treatment. Patients must 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 disease 9. Patients with concurrent or previous malignancy within the last 5 years (except Stage I grade 1 endometrial cancer; in situ cervical cancer; DCIS of the breast) that could compromise assessment of the primary or secondary endpoints of the trial 10. Active central nervous system (CNS) metastases and/or carcinomatous meningitis; patients with previously treated brain metastases may participate provided they are: a) radiologically stable b) without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening) c) clinically stable d) without requirement of steroid treatment for at least 14 days prior to first dose of study treatment. 11. Has active autoimmune disease that required systemic treatment in past 2 years except vitiligo or resolved childhood asthma/atopy. Replacement hormone therapy is permitted 12. Has a corrected serum calcium of >1.5 x ULN despite maximal anti-hypercalcaemic therapy 13. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/ interstitial lung disease 14. Has a newly diagnosed venous thrombotic event (e.g. PE, DVT) untreated with anticoagulation. Patients are excluded if they have a history of arterial thrombosis 15. Has an active infection requiring systemic therapy

	16. Has symptoms of bowel obstruction in the past three months 17. Has received a live vaccine within 30 days of planned start of study treatment.
Number of sites:	4 sites UK
Treatment summary:	Pembrolizumab 200mg IV Q3W (on day one of each 3 week cycle) for a maximum of 24 months
Duration of recruitment:	30 months
Duration of follow up:	Patients will continue treatment to progression, toxicity or up to a maximum of 24 months. Following the end of treatment safety visit, data will be periodically collected on subsequent treatment and survival. All patients will be followed up until two years following registration of the last patient.
Definition of end of trial:	Two years following registration of the last patient and when laboratory sample analysis of human tissue collected for relevant protocol translational research is complete.

1.2. Trial Schema

Figure 1: Overview of PROMPT trial.



2. INTRODUCTION

2.1. Background

Ovarian cancer (OC) occurs in about 1 of 52 women in the UK. There are approximately 7,300 cases each year and it is the 5th most common cause of cancer death in women. Approximately 80% of women present with advanced stage disease, FIGO III or IV[1] and the 5 year survival rate is 19% for stage III and 3% for stage IV[1]. New treatments are needed to improve survival.

Fallopian tube and non-mucinous primary peritoneal cancer are treated in a similar way to ovarian cancer and this usually comprises surgery and chemotherapy. Most patients will respond to treatment but the median progression-free survival is approximately 18 months. For those women who have a recurrence after a chemotherapy interval of more than 6 months, second-line treatment usually involves platinum-based therapy. Platinum rechallenge for subsequent relapses usually occurs if the platinum-free intervals (PFI) remain > 6 months. These drugs may also be used in some cases for a recurrence occurring less than 6 months after platinum. Platinum resistance is now defined as progression on platinum-based therapy, or symptomatic progression within a few weeks of platinum treatment. Thus, platinum or non-platinum-based drugs may be used in women relapsing with a PFI < 6 months.

The outlook for women receiving non-platinum-based therapy is poor; responses to chemotherapy are less frequent and usually short-lived. The expected median progression-free survival (PFS) is 3-4 months[2] in women with platinum-resistant ovarian cancer, and a median overall survival is about one year. In the UK, single-agent chemotherapy with Pegylated Liposomal Doxorubicin (PLD) or weekly paclitaxel are commonly used in this group. The latter is gaining increasing favour as many patients have previously receive PLD with carboplatin. Data from the AURELIA trial showed the response rate to weekly paclitaxel was 30.2% and the median PFS was 3.9 months[3].

To date, improvements in this outcome have come principally from the addition of bevacizumab to paclitaxel. In the AURELIA trial, the median PFS of women receiving bevacizumab and weekly paclitaxel was 10.4 months. However, many patients are not able to access bevacizumab, either because they received it in the first-line setting, or because of clinical factors that preclude its use, such as bowel serosal involvement. Furthermore, bevacizumab in this setting is not funded by NHS England.

Alternative therapeutic strategies are needed, and immunotherapy, using immune checkpoint inhibitors represents an approach that has demonstrated significant beneficial effects in many types of solid tumours.

Pembrolizumab, a PD-1 inhibitor, has been shown to be active in recurrent ovarian cancer. In a phase 1b trial[4], 3/20 patients (15%) had a response lasting more than 24 weeks. Pembrolizumab is a potent and highly selective humanised monoclonal antibody of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This inhibitory signalling allows T cells to switch on their effector functions. Pembrolizumab has been shown to lead to durable remissions in patients with different solid tumours as melanoma, non-small-cell lung cancer, renal cancer, and in the patients with ovarian cancer, the median PFS was longer than six months.

Final results from the trial of pembrolizumab in platinum-resistant ovarian cancer (KEYNOTE-100; NCT02674061) showed modest anti-tumour activity, with a documented median OS of 18.7 months. Some durable (≥6 month) responses were seen, with higher

PDL-1 expression correlating with a better response rate and a trend toward a longer OS[5]. There are also emerging data that suggest T cells are activated by neoadjuvant chemotherapy, suggesting that chemotherapy might favour the use of immunotherapy[6]. It is not known whether chemotherapy for advanced disease may also potentiate checkpoint inhibitors, but there is an ongoing trial combining pembrolizumab with dose-dense paclitaxel in platinum-resistant ovarian cancer (NCT02440425), and a combination study of cisplatin-gemcitabine with pembrolizumab (NCT02608684).

The extensive experience of using pembrolizumab to-date has established a dose of 200mg intravenously every three weeks as the optimum schedule for treatment. Pembrolizumab is generally well-tolerated with the most common treatment-related adverse events being fatigue, pruritus, and decreased appetite. Adverse events of grade 3 or higher have been reported in about 9.5% of patients. Treatment-related adverse events of an inflammatory or immune-mediated nature that occurred in more than 2% of patients were infusion-related reactions in 3.0%, hypothyroidism in 6.9%, and pneumonitis in 3.6%. One infusion reaction led to treatment discontinuation. All the patients with hypothyroidism were successfully treated with medical therapy. Pneumonitis of grade 3 or greater was observed in 1.8%, including 1 patient (0.2%) who died. Autoimmune hepatitis, diarrhoea, hypophysitis, maculopapular rash, pancreatitis, pneumonitis, and rash are unusual occurrences and immune-mediated adverse events were generally manageable with treatment interruption and corticosteroid treatment. Only 2% of patients discontinued because of adverse events that were immune-related or of special interest[7].

In this study, we seek to investigate the effect of maintenance pembrolizumab in patients who have undergone treatment with weekly paclitaxel for recurrent ovarian cancer and have either responded or have not progressed after a minimum of 4 cycles of treatment. This approach has been selected for two main reasons: firstly maintenance pembrolizumab may build on the response to paclitaxel; secondly, chemotherapy prior to pembrolizumab may provide a better immune environment for pembrolizumab. In this study, patients will receive 3 weekly pembrolizumab until progression and, when possible, we will monitor the immune microenvironment by tumour biopsy and blood sampling before starting pembrolizumab and again before cycle 4 of treatment. The clinical endpoint will be to demonstrate a worthwhile improvement in the 6 month median PFS and to study possible predictive markers or response to pembrolizumab. This is a non-randomised phase II study, and the population may be different from those who received paclitaxel and bevacizumab. Nevertheless, we would anticipate a median PFS of 6 months, similar or better to that seen with the combination of paclitaxel and bevacizumab.

3. TRIAL DESIGN

- A phase II single arm maintenance treatment trial of pembrolizumab in patients who have received weekly paclitaxel for recurrent ovarian cancer
- Patients will receive pembrolizumab 200mg IV 3 weekly until disease progression or toxicity, for a maximum of 24 months
- If feasible, patients will have a biopsy before and after 3 cycles of pembrolizumab, i.e. at the time of the first CT assessment and before the 4th cycle of pembrolizumab.

3.1. Trial Objectives

- To demonstrate a clinically meaningful extension of progression free survival using maintenance pembrolizumab
- To evaluate immune response parameters in blood following pembrolizumab in patients with ovarian cancer in peripheral blood
- To study the immune microenvironment using fresh tumour biopsies collected at baseline and before the 4th cycle of pembrolizumab.
- To investigate the use of the immunological data in determining future selection of patients for maintenance treatment, and the effectiveness of pembrolizumab

3.2. Trial Endpoints

- Primary Endpoint
    - Progression Free Survival at 6 months, measured from the start of maintenance pembrolizumab
- Secondary Endpoint
    - Progression Free Survival at 6 months measured from the start of weekly paclitaxel
    - Overall survival
    - Disease response (RECIST v1.1)
    - Toxicity and compliance
- Exploratory Endpoint
    - Immunological analysis (See section 10)
    - Further treatment following disease progression

3.3. Trial Activation

UCL CTC will ensure that all trial documentation has been reviewed and approved by all relevant bodies and that the following have been obtained prior to activating the trial:

- Health Research Authority (HRA) approval, including Research Ethics Committee approval
- Clinical Trial Authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA)
- 'Adoption' into NIHR portfolio
- Adequate funding for central coordination
- Confirmation of sponsorship
- Adequate insurance provision

4. SELECTION OF SITES/SITE INVESTIGATORS

4.1. Site Selection

In this protocol trial 'site' refers to a hospital where trial-related activities are conducted.

Sites must be able to comply with:

- Trial treatment, imaging, clinical care, follow up schedules and all requirements of the trial protocol
- Requirements of the UK Policy Framework for Health and Social Care, issued by the Health Research Authority and the Medicines for Human Use Clinical Trials Regulation (SI 2004/1031) and all amendments
- Data collection requirements, including adherence to CRF submission timelines as per section 11.3 (Timelines for Data)
- Biological sample collection, processing and storage requirements
- Monitoring requirements, as outlined in protocol section 14 (Trial Monitoring and Oversight) and trial monitoring plan
- Obtaining relevant licenses in relation to medical radiation exposure in the study, and renewing as necessary

4.1.1. Selection of Principal Investigator and other investigators at sites

Sites must appoint an appropriate Principal Investigator (PI), i.e. a healthcare professional authorised by the site to lead and coordinate the work of the trial on behalf of the site. Co-investigators must be trained and approved by the PI. All investigators must be medical doctors and have experience of treating ovarian cancer. The PI is responsible for the conduct of the trial at their site and for ensuring that any amendments are implemented in a timely fashion. If a PI leaves/goes on a leave of absence, UCL CTC **must be informed promptly** and a new PI identified and appointed by the site.

4.1.2. Training requirements for site staff

All site staff must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log.

CVs for all staff must be kept up-to-date, signed and dated and copies held in the Investigator Site File (ISF). A current, signed copy of the CV with evidence of GCP training (or copy of GCP certificate) for the PI must be forwarded to UCL CTC upon request.

GCP training is required for all staff responsible for trial activities. The frequency of repeat training may be dictated by the requirements of their employing institution, or 2 yearly where the institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials.

4.2. Site initiation and Activation

4.2.1. Site initiation

Before a site is activated, the UCL CTC trial team will arrange a site initiation with the site which the PI, the pharmacy lead and site research team must attend. The site will be

trained in the day-to-day management of the trial and essential documentation required for the trial will be checked.

Site initiation will be performed for each site by site visit/teleconference/videoconference with site/investigator meeting. Re-initiating sites may be required where there has been a significant delay between initiation and enrolling the first patient, in accordance with the monitoring plan.

4.2.2. **Required documentation**

The following documentation must be submitted by the site to UCL CTC prior to a site being activated by the UCL CTC trial team:

- Trial specific UK Site Registration Form (identifying relevant local staff)
- Relevant institutional approvals
- A completed site delegation log that is initialled and dated by the PI (with all tasks and responsibilities delegated appropriately)
- Completed site contacts form (with contact information for all members of local staff)
- A signed and dated copy of the PI's current CV (with documented up-to-date GCP training, or copy of GCP training certificate)
- Trial specific prescription & labels

In addition, the following agreements must be in place:

- a signed site agreement between the Sponsor and the relevant institution (usually an NHS Trust/Health Board)

4.2.3. **Site activation letter**

Once the UCL CTC trial team has received all required documentation and the site has been initiated, a site activation letter will be issued to the PI, at which point the site may start to approach patients.

Following site activation, the PI is responsible for ensuring:

- adherence to the most recent version of the protocol
- all relevant site staff are trained in the protocol requirements
- appropriate recruitment and medical care of patients in the trial
- timely completion and return of CRFs (including assessment of all adverse events)
- prompt notification and assessment of all serious adverse events and adverse events of special interest
- that the site has facilities to provide **24 hour medical advice** for trial patients

5. INFORMED CONSENT

Sites are responsible for assessing a patient's capacity to give informed consent.

Sites must ensure that all patients have been given the current approved version of the patient information sheet, are fully informed about the trial and have confirmed their willingness to take part in the trial by signing the current approved consent form.

Sites must assess a patient's ability to understand verbal and written information in English and whether or not an interpreter would be required to ensure fully informed consent. If a patient requires an interpreter and none is available, the patient should not be considered for the trial.

The PI, or, where delegated by the PI, other appropriately trained site staff, are required to provide a full explanation of the trial and all relevant treatment options to each patient prior to trial entry. During these discussions, the current approved patient information sheet for the trial should be discussed with the patient.

A minimum of twenty four (24) hours should be allowed for the patient to consider and discuss participation in the trial. However, to prevent unnecessary return visits, patients may consent on same day as being given the information sheet, provided the member of staff taking consent is satisfied that the patient understands the trial and implications.

Written informed consent on the current approved version of the consent form for the trial must be obtained before any trial-specific procedures are conducted. The discussion and consent process must be documented in the patient notes.

Site staff are responsible for:

- checking that the current approved version of the patient information sheet and consent form are used
- checking that information on the consent form is complete and legible
- checking that the patient has initialled all relevant sections and signed and dated the form
- checking that an appropriate member of staff has countersigned and dated the consent form to confirm that they provided information to the patient
- checking that an appropriate member of staff has made dated entries in the patient's medical notes relating to the informed consent process (i.e. information given, consent signed etc.)
- following registration, adding the patients' trial number to all copies of the consent form, which should be filed in the patient's medical notes and investigator site file
- following registration, giving the patient a copy of their signed consent form, patient information sheet and patient contact card

The right of the patient to refuse to participate in the trial without giving reasons must be respected. All patients are free to withdraw at any time. Also refer to section 15 (Withdrawal of Patients).

Please note: the Informed Consent Form and Participant Information Sheet have been developed at UCL CTC, with significant input from clinicians and a patient representative.

6. SELECTION OF PATIENTS

6.1. Screening Log

A screening log must be maintained and appropriately filed at site. Sites should record all patients with high grade, non-mucinous recurrent ovarian/fallopian tube or primary non-mucinous peritoneal cancer who have had up to 3 lines of previous platinum treatment and the reasons why they were not registered in the trial if this is the case. The log must be sent to UCL CTC when requested.

6.2. Identifying potential patients

Those patients who may meet the eligibility criteria will be approached during routine outpatient clinics by the Principal Investigator, or a delegated member of the PI's research team (e.g. Co-investigator or research nurse) and will be given the patient information sheet. The details of the trial will be discussed with the patient, including what will be required of them.

6.3. Patient Eligibility

There will be no exception to the eligibility requirements at the time of registration. Queries in relation to the eligibility criteria must be addressed prior to registration. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria applies.

Patients' eligibility must be confirmed by an investigator who is suitably qualified and who has been allocated this duty, as documented on the site staff delegation log, prior to registering the patient. Confirmation of eligibility must be documented in the patients' notes and on the registration eCRF.

Patients must give written informed consent before any trial specific screening investigations may be carried out. Refer to section 9 (Assessment/Trial Procedures).

6.3.1. **Inclusion criteria**

1. Patients must have a diagnosis of high grade recurrent ovarian/fallopian tube or primary non-mucinous peritoneal cancer

2. Be willing and able to provide written informed consent for the trial, indicating that the patient has been informed of and understands the experimental nature of the study, possible risks and benefits, trial procedures, and alternative options

3. Be ≥ 18 years of age on day of signing informed consent

4. Patients should be treated with a minimum of 4 cycles of weekly paclitaxel for recurrent disease. [Non-platinum-based therapy given for CT/MR documented recurrence where further platinum therapy considered unsuitable]. If a good interim response is recorded, patients could discontinue chemotherapy after 4 cycles and be considered for trial treatment.

5. Patients can have had up to 3 prior lines of platinum-based chemotherapy for ovarian cancer before starting weekly paclitaxel

6. Patients must have achieved at least stable disease or response following a minimum of four cycles of weekly paclitaxel (measured by CT/MR)

7. Trial treatment with pembrolizumab must start within 8 weeks after last paclitaxel dose

8. Availability of archival tissue

9. Fresh tumour biopsy should be taken at baseline if this is judged by radiological assessment to be technically feasible. If a biopsy is taken at baseline, then a second biopsy should be taken, if feasible before the start of cycle 4.

10. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

11. Willing and able to comply with the protocol for the duration of the study, including the treatment plan, investigations required and follow up visits

12. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Haematological	
Absolute neutrophil count (ANC)	≥1.5 x10^9/l
Platelets	≥ 100 x10^9/l
Haemoglobin	≥90 g/l
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance (CrCl) Glomerular filtration rate (GFR) can also be used in place of creatinine or CrCl	≤1.5 X upper limit of normal (ULN) **OR** ≥30 mL/min for patient with creatinine levels > 1.5 X institutional ULN
Hepatic	
Total bilirubin	≤ 1.5 X ULN **OR** Direct bilirubin ≤ ULN for patients with total bilirubin levels > x 1.5 ULN
Aspartate aminotransferase [AST (SGOT)] and/or alanine aminotransferase [ALT (SGPT)]	≤2.5X ULN
Albumin	>30 g/l
Lactate Dehydrogenase (LDH)	<2.5 X ULN
[a]Creatinine clearance should be calculated per institutional standard.	

13. Patients of childbearing potential should have a negative urine or serum pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required

14. Patients of childbearing potential (defined in Section 6.4.1) must be willing to use an adequate method of contraception as outlined in Section 6.4.4 from the start of treatment through to 4 months after the last dose of study medication

6.3.2. **Exclusion criteria**

1. Prior therapy with an anti-PD-1, anti-PD-L1 or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137)

2. Has a diagnosis of low grade or mucinous ovarian cancer

3. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (dose exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment (n.b. the use of physiologic doses of corticosteroids may be approved after consultation with UCL CTC). Use of inhaled steroids is permitted.

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

5. Has known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known Hepatitis C virus (defined as HCV RNA [qualitative] is detected)*

6. Has a known history of Human Immunodeficiency Virus (HIV). *

7. Patients may be registered for the trial after 4 cycles of chemotherapy with paclitaxel but may not start pembrolizumab until 4 weeks has elapsed from the last dose of paclitaxel and toxicity. All patients must start pembrolizumab within 8 weeks of last dose of paclitaxel.

   Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible. Participants with endocrine-related AEs Grade ≤2 requiring treatment or hormone replacement may be eligible

   Note: If participant required major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.

8. Has received 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 (a maximum of 2 weeks radiotherapy is allowed) to non-CNS disease.

9. Patients with concurrent or previous malignancy within the last 5 years (except Stage I grade 1 endometrial cancer; in situ cervical cancer; DCIS of the breast) that could compromise assessment of the primary or secondary endpoints of the trial

10. Active central nervous system (CNS) metastases and/or carcinomatous meningitis; patients with previously treated brain metastases may participate provided they are:

    a) radiologically stable

b) without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening)
c) clinically stable
d) without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.

11. Has active autoimmune disease that required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids (at doses >10mg prednisolone daily or equivalent) or immunosuppressive drugs) except vitiligo or resolved childhood asthma/atopy. Replacement hormone therapy (e.g. levothyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is permitted

12. Has a corrected serum calcium of >1.5 x ULN despite maximal anti-hypercalcaemic therapy

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

14. Has a newly diagnosed venous thrombotic event (e.g. PE, DVT) untreated with anticoagulation. Patients must have received at least 14 days of anticoagulation for a new thrombotic event and be suitable for continued therapeutic anticoagulation during trial participation. Patients are excluded if they have a history of arterial thrombosis

15. Has an active infection requiring systemic therapy

16. Has symptoms of bowel obstruction in the past three months

17. Any serious and/or unstable pre-existing medical, psychiatric or other condition that, in the treating clinician's judgement could interfere with patient safety or obtaining informed consent

18. Has known psychiatric or substance abuse disorders that would interfere with co-operation with the requirements of the trial

19. Is pregnant or breastfeeding, or expecting to conceive children within the projected duration of the trial, starting with the screening visit through to 4 months after the last dose of trial treatment

20. Has received a live vaccine or live attenuated vaccine within 30 days prior to the first dose of study treatment. Administration of killed vaccines is allowed.

*Testing for Hepatitis and HIV is not required unless mandated by local health authority.

6.4. Pregnancy and birth control

6.4.1. Pregnancy and birth control

Definition of women of childbearing potential (WOCBP)

A woman of childbearing potential (WOCBP) is a sexually mature woman (i.e. any female who has experienced menstrual bleeding) who has not:

- undergone a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion;
- been postmenopausal for 12 consecutive months (i.e. who has had menses at any time in the preceding 12 consecutive months without an alternative medical cause). In women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- had premature ovarian failure confirmed by a specialist gynaecologist;
- had a congenital or acquired condition that prevents childbearing.

6.4.2. Risks of exposure to trial treatment during pregnancy

Pembrolizumab may have adverse effects on a foetus in utero.

WOCBP must agree to avoid becoming pregnant whilst receiving study drug and for 4 months after the last dose of study drug by complying with highly effective contraception during heterosexual activity as per section 6.4.4.

6.4.3. Pregnancy testing

WOCBP must undergo urine or serum pregnancy testing pre-registration, on the first day of each cycle, prior to treatment and at the end of treatment. Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

6.4.4. Contraceptive advice

All WOCBP must consent to use one of the following methods of highly effective contraception from the start of treatment for a minimum of 4 months post last treatment administration. The method(s) of contraception used must be stated in the patient medical notes and eCRF:

- combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
    - oral (e.g. desogestrel)
    - injectable
    - implantable[1]

- intrauterine device (IUD)[1]
- intrauterine hormone-releasing system (IUS)[1]
- bilateral tubal occlusion[1]
- vasectomised partner[1,2]
- sexual abstinence[3]

1. Contraception methods that are considered to have low user dependency.

2. Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

3. 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 treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

6.4.5. **Action to be taken in the event of a pregnancy**

If a patient inadvertently becomes pregnant while on treatment with pembrolizumab:

- prior to initiating treatment, the patient will not receive trial treatment unless they elect to have a termination (please note, in such instances, termination must be the patient's own choice)
- while on treatment with pembrolizumab, the patient will immediately be withdrawn from the study treatment.
- after the end of the treatment, but during the pregnancy at-risk period (4 months after last treatment)

The site will contact the patient at least monthly and document the patients status until six weeks after the pregnancy has been completed or terminated, if the patient consents to pregnancy monitoring. The outcome of the pregnancy will be reported without delay and **within 24 hours** to the Sponsor (See also section 12.6 for pregnancy reporting). The sponsor will forward the report to MSD, in accordance to the timelines stated in the contract.

6.4.6. **Long Term Infertility**

No clinical data are available on the possible effects of pembrolizumab on fertility. Although reproductive and developmental toxicity studies have not been conducted with pembrolizumab, there were no notable effects in the male and female reproductive organs in monkeys based on 1-month and 6-month repeat dose toxicity studies.

6.4.7. **Lactation**

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

7. REGISTRATION PROCEDURES

7.1. Registration

Patient registration will be undertaken centrally at UCL CTC or remotely and this must be performed prior to commencement of any trial treatment. Pre-registration evaluations should be carried out at sites as detailed in section 9 (Assessments/Trial Procedures)

7.1.1. Pre-registration Assessments

Following pre-treatment evaluations, confirmation of eligibility and consent of a patient at a site, the registration eligibility checklist must be fully completed and the information entered onto the registration database (MACRO 4 online). UCL CTC will then be notified of the registration data entry and the PROMPT trial team will check the eligibility data fulfil the protocol requirements. If further information is required, UCL CTC will contact the site to discuss further.

Once eligibility has been checked, the PROMPT trial team will confirm the patient's registration and trial number with the site. UCL CTC will send an email confirmation to the PI/treating clinician, main research team contact and pharmacy (please see Patient Registration Procedure for site in Investigator site File).

UCL CTC Telephone number for queries relating to PROMPT Registrations and email:	+44 (0)20 7679 9010 ctc.prompt@ucl.ac.uk
Access to PROMPT Registration database https://rde.ctc.ucl.ac.uk/	
UCL CTC Office hours:	09:00 to 17:00 Monday to Friday, excluding Bank Holidays

Once a patient has been registered onto the trial they must be provided with the following:

- A copy of their signed consent form and patient information sheet
- A patient contact card. Site contact details for 24 hour medical care must be added to this card and patients advised to carry this with them at all times while participating in the trial

7.2. Initial Trial Drug Supply

Refer to Summary of Drug Arrangements document for details of initial supply of pembrolizumab for the trial.

8. TRIAL TREATMENT

Investigational Medicinal Products (IMPs)

For the purpose of this protocol, the IMP is Pembrolizumab (MK-3475).

8.1. Investigational Medicinal Products

Pembrolizumab (MK-3475) is currently not licensed in this disease area. It is manufactured and supplied by MSD for the PROMPT trial.

Trial supplies of pembrolizumab (MK-3475) must not be used outside the context of this trial. Under no circumstances should the site investigator or other site personnel supply trial drug to other investigators, patients or clinics, or allow supplies to be used other than directed by this protocol without prior authorisation from the Supplier and notification to the Sponsor.

Please refer to the Summary of Drug Arrangements document (SoDA) for full arrangements for the trial.

8.1.1. Packaging and Labelling Information

Clinical Supplies will be provided by MSD as summarized in Table 2.

Table 2 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab (MK-3475) 100 mg/ 4mL	Solution for Injection

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

8.1.2. Clinical Supplies Disclosure

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

8.2. Treatment Summary

The treatment to be used in this trial is outlined below in Table 3.

Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Summary of Drug Arrangements document.

Table 3 Trial Treatment

Drug	Dose	Dose Frequency	Route of administration	Treatment period Day 1 (±3 days)	Use
Pembrolizumab (MK-3475)	200mg	Q3 weekly	IV infusion	Day 1 of each 3 week cycle	Investigational

Trial treatment is outlined in Table 3 and should begin within 8 weeks after the last dose of paclitaxel chemotherapy.

8.3. Trial Treatment Details

8.3.1 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 Schedule of Procedures/Assessments (Appendix 1). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab (MK-3475) 200mg will be administered as a 30 minute IV infusion every 3 weeks. 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: - 5min/+10 min).

Patients will remain on treatment for a maximum of 24 months, if pembrolizumab is tolerable and there is no evidence of disease progression.

The Summary of Drug Arrangements document (SoDA) contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution. It is the responsibility of the Pharmacy Lead to maintain drug accountability records for pembrolizumab (MK-3475). The Pharmacy Lead (or appropriate delegate) must record the receipt and dispensing of pembrolizumab (MK-3475) on the appropriate Accountability Log found in the Pharmacy Site File.

8.4. Dose Delays

Adverse events (both serious and non-serious) associated with pembrolizumab exposure may represent an immunologic aetiology. These immune-related AEs (irAEs) may occur shortly after the first dose or up to a year after the last dose of treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complication. 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 and exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on severity of irAEs, withhold or permanently discontinue

pembrolizumab and administer corticosteroids. Dose delay and toxicity management guidelines for irAEs associated with pembrolizumab are provided in table 4.

If a dose of pembrolizumab is withheld for toxicity, then patients may resume dosing, if appropriate at their next scheduled appointment or when toxicity has improved as per Table 4. Patients should be placed back on study treatment within 12 weeks of the scheduled interruption, unless otherwise discussed with UCL CTC. The reason for interruption should be documented in the patient's case report form.

Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 4 below. See Section 8.7 for supportive care guidelines, including use of corticosteroids.

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

Patients may receive any concomitant therapy deemed to be necessary for their welfare at the investigator's discretion, if believed to provide appropriate supportive care and not to interfere with trial medication (see section 8.8 for details of contraindicated medication).

All medications or other treatments taken by the patient during the trial (including those initiated prior to the start of the trial) must be recorded in the patient's clinical notes and the case report form.

Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid 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.

If after the evaluation the event is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance outlined below.

Dose modifications will not be permitted.

8.5. Management of Adverse Events

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

General instructions:

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

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 • Add prophylactic antibiotics for opportunistic infections	• Monitor patients for signs and symptoms of pneumonitis • Evaluate patients with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment •
	Recurrent Grade 2, 3 or 4	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 patients for signs and symptoms of enterocolitis (ie, diarrhoea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Patients with ≥ Grade 2 diarrhoea suspecting colitis should consider GI referral and performing endoscopy to rule out colitis. • Patients 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.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST / ALT elevation or	Grade 2[a]	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable).

Increased bilirubin			prednisolone or equivalent) followed by taper	
	Grade 3[b] or 4[c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisolone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[d]	• Initiate insulin replacement therapy for patients with T1DM • Administer anti-hyperglycemic in patients with hyperglycemia	• Monitor patients for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis 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		
Neurological Toxicities	Grade 2 Grade 3 or 4	Withhold Permanently discontinue	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm aetiology and/or exclude other causes

Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS Confirmed SJS, TEN, or DRESS	Withhold Permanently discontinue	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm aetiology or exclude other causes
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm aetiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
All other AEs	Persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the event[e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

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

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

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

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

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

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs.

Dose delay and toxicity management of infusion-reactions related to pembrolizumab
Pembrolizumab (MK-3475) 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. Table 5 below shows treatment guidelines for patients who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 5 Pembrolizumab Infusion reaction Dose delay and treatment guidelines

NCI CTCAE Grade V5.0	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 patient is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, opiates, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Paracetamol Opiates Increase monitoring of vital signs as medically indicated until the patient 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 patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Patient may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: chlorphenamine 10mg IV (or equivalent dose of antihistamine). paracetamol 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalisation indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; antihypotensive or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Adrenaline ** IV fluids Antihistamines NSAIDs Paracetamol Opiates Oxygen Vasopressors/inotropes drugs Corticosteroids Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. Hospitalisation may be indicated. **In cases of anaphylaxis, adrenaline should be used immediately. **Patient is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a doctor readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf		

8.6. Management of Overdoses, Trial treatment error, or Occupational Exposure

8.6.1. Overdose

Overdose is administration of a quantity of a trial treatment, either per administration or cumulatively, which is in excess of the protocol specified dose. The dose can either be evaluated as overdose by the trial team at site or by UCL CTC upon review.

For purposes of this trial, an overdose of pembrolizumab will be reported as follows:

- Any dose greater than 200 mg and less than 1,000 mg – to be reported on an incident report
- Any dose of 1,000 mg or greater (≥5 times the indicated dose) – to be reported as an Adverse Event of Special Interest (see section 12.4 for reporting procedures).

No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.6.2. Trial treatment error

A trial treatment error is any unintentional error in prescribing, dispensing, or administration of a trial treatment while in the control of a healthcare professional or consumer. The error can be identified either by the trial team at site or by UCL CTC upon review.

If the trial treatment error is an overdose of 1,000 mg or greater, refer to section 8.6.1 (Overdose) above. Otherwise, trial treatment errors should be reported on an incident report (see section 13.1). Any adverse events resulting from a trial treatment error should be reported as an SAE (see section 12.2.3 for reporting procedures).

8.6.3. Occupational exposure

Exposure to a trial treatment as a result of one's professional or non-professional occupation. Occupational exposure should be reported on an incident report form (see section 13.1).

8.7. Supportive Care

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator in keeping with the standards of care. Suggested supportive care measures for the management of adverse events with potential immunologic aetiology are outlined in table 4. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The management guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

COVID-19 Vaccinations

Even though no interaction studies have been performed, patients are permitted to receive COVID-19 vaccinations that are not live vaccines during treatment. The timing of COVID-19 vaccine administration and Trial treatment should be determined by the Principal Investigator or a Co-investigator at site in the best interests of the patient, however it is recommended patients should not receive pembrolizumab within 24 hours of having a COVID-19 vaccine.

Details of vaccine administration should be added to the Concomitant Medication eCRF and medical records.

8.8. Contraindications

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 treatment may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive treatment or vaccination rests with the investigator.

8.8.1. **Acceptable Concomitant Medications**

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

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and AESIs as defined in Section 12.

8.8.2. **Prohibited Concomitant Medications**

Patients are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy except for treatment to manage hypercalcaemia of malignancy (for example bisphosphonates, denosumab)
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. 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 event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids at daily doses equivalent to or less than 10mg prednisolone.

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

The Exclusion Criteria describes other medications which are prohibited in this trial.

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

8.9. Pharmacy Responsibilities

Oversight of all pharmacy aspects of the trial at participating sites are the responsibility of the PI, who may delegate this responsibility to the local pharmacist or other appropriately qualified personnel, who will be the Pharmacy Lead. The delegation of duties must be recorded on the site staff delegation log.

Pembrolizumab supplied for the PROMPT trial is for PROMPT trial patients only and must not be used outside the context of this protocol.

8.9.1. **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.

8.9.2. **Temperature Excursions**

All temperature excursions outside the storage conditions specified in the IB must be reported to UCL CTC as per the 'Pharmacy Procedure for Reporting Temperature Excursions' (see Pharmacy Site File).

Upon identifying an excursion:

- all affected trial stock must be quarantined IMMEDIATELY
- the 'Notification of Temperature Excursion' form must be completed and e-mailed to ctc.excursions@ucl.ac.uk.

Please note that UCL CTC must be informed immediately if a patient has been administered drug affected by a temperature excursion.

8.9.3. **Study IMP Accountability**

The Pharmacy Lead must ensure that appropriate records are maintained.

These records must include accountability for each drug including: receipt, dispensing, reconciliation and destruction of unused medication (on sponsor authorisation). Accountability forms will be supplied, and must be used, unless there is prior agreement from UCL CTC to use alternative in-house records.

Copies of completed drug accountability logs must be submitted to UCL CTC for all trial patients upon request. Also refer to section 14.2 (Centralised Monitoring).

8.9.4. **Returns and Reconciliation**

The investigator or pharmacy lead is responsible for keeping accurate records of the clinical trial supplies received from MSD, the amount dispensed to the patients and the amount remaining in stock throughout the trial.

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

8.10. 24 Hour/Out-of-Office Hours Emergency Drug-Specific Advice

Pembrolizumab	**Office hours** 09:00 to 17:00 Monday to Friday, excluding Bank Holidays Contact UCL CTC 0207 679 9284	**All other times** 24 Hour/Out-of-Office Hours Emergency Drug-Specific Contact MSD 0208 154 8000

8.11. Clinical Management after Treatment Discontinuation

If a patient discontinues trial treatment early, they will remain on the trial for follow up purposes unless they explicitly withdraw consent. Also refer to sections 9 (Assessments) and 15 (Withdrawal of Patients) for further details regarding treatment discontinuation, patient withdrawal from trial treatment and withdrawal of consent to data collection.

8.12. Drug Provision During the Trial

Pembrolizumab will be provided to patients for a maximum of two years whilst the trial is on-going (unless the trial closes early).

8.13. Drug Supply

Please see Summary of Drug Arrangements for further details on drug supply.

9. ASSESSMENTS/TRIAL PROCEDURES

Please also see Schedule of Procedures/Assessments table in Appendix 1.

9.1. Pre-registration Assessments/Procedures

Patients must give written informed consent **before** any trial specific screening investigations may be carried out. The following assessments or procedures are required to evaluate the suitability of patients for the trial:

- Fulfill the eligibility criteria outlined in Section 6

Within 28 days prior to registration-

- **Imaging (CT) of chest-abdomen-pelvis** to document baseline local disease status and response to the last chemotherapy, measured using RECIST criteria for patients with measurable disease
- **Full medical history**, including review of concomitant medications
- **Baseline symptoms**
- **Full physical examination**, including weight and vital signs (temperature, pulse rate, blood pressure)
- **Assessment of ECOG performance status**
- **Haematology** including Full Blood Count (with WBC differentials) Table 6 outlines the laboratory tests required; these should be performed within 10 days prior to the first dose of treatment.
- **Biochemistry** including urea, creatinine (or creatinine clearance) and electrolytes (sodium, potassium). Liver function test: albumin, serum bilirubin, AST or ALT, alkaline phosphatase and glucose (refer to Table 6); these should be performed within 10 days prior to the first dose of treatment.
- **Thyroid function tests** (TSH, T3 and FT4)
- **CA125**
- **Urinalysis**
- **Urine or serum pregnancy test** (if applicable)
- **Blood sample** (PT/INR and aPTT) to assess clotting factors – only for patients undergoing a biopsy (*this must be completed within 7 days prior to biopsy*)

After registration and prior to treatment-

- Blood sample for immunology
- **Immunological tumour biopsy if feasible** (blood sample to assess clotting factors before biopsy sample)
- **Archival tissue** sites will send archival tissue to a central laboratory.

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below in Table 6.

Table 6 Laboratory Tests

Haematology	Chemistry	Urinalysis	Other
Haematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin (β-hCG)†
Haemoglobin	Alkaline phosphatase	Glucose	
Platelet count	Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST)	Protein	Total triiodothyronine (T3)
WBC (total and differential)		Microscopic exam (If abnormal results are noted)	Free thyroxine (T4)
Absolute Neutrophil Count	Lactate dehydrogenase (LDH)		Thyroid stimulating hormone (TSH)
Absolute Lymphocyte Count	Uric Acid		CA125
	Calcium		
	Glucose		Clotting (PT/INR and aPTT) required if patient proceeding with a biopsy
	Phosphate		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Creatinine		
† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required			

9.2. Assessments During Treatment

During treatment patients should be seen every 3 weeks and the following assessments/investigations/procedures should be performed:

At every cycle to be performed before each dose of trial treatment:

- **Prior and concomitant medication review**
- **Urine or serum pregnancy test (if applicable)**
- **Review of adverse events** The investigator or qualified designee will assess each patient to evaluate for potential new or worsening AEs as specified in Appendix 1 and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0 (see Section 12.2) Toxicities will be characterised in terms of seriousness, causality, toxicity grading, and action taken with regard to trial treatment. Please refer to Section 12.2 for detailed information regarding the assessment and recording of AEs.
- **Vital signs and weight (**temperature, pulse, respiratory rate and blood pressure)
- **ECOG performance status**
- **Haematology** including Full Blood Count (with WBC differentials) after Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. The laboratory tests are outlined in table 6. Results of these tests must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.
- **Biochemistry** including liver function tests after Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. The laboratory tests are outlined in table 6. Results of these tests must be reviewed by the investigator

or qualified designee and found to be acceptable prior to each dose of trial treatment.

- **CA125**
- **Urinalysis**
- **Trial treatment administration**

Assessments at specific time points

- **Physical examination** to be carried out at cycle 1 and then every second cycle prior to administration of treatment dose.
- **Thyroid function tests (T3, FT4 and TSH)** to be carried out at cycle 1 and then every second cycle prior to administration of treatment dose.
- **CT scan chest, abdomen and pelvis** Imaging should be performed before cycles 4 and 7 of pembrolizumab and then every 12 weeks (approximately every 4 cycles) during treatment. Response will be assessed according to RECIST v1.1.
- **Blood sample (PT/INR and aPTT) to assess clotting factors** for patients undergoing a biopsy (this must be completed within 7 days prior to tumour biopsy (before cycle 4)
- **Immunological tumour biopsy** before cycle 4 (if biopsy taken pre-treatment)
- **Immunological bloods** (post registration, before cycle 4 and upon progression).

9.3. Tumour Imaging and assessment of disease

All eligible patients will be included in the progression free survival analysis.

9.3.1. Evaluation of Efficacy

Tumour assessments will be based on RECIST v1.1. Tumour assessments will be performed at baseline, before cycle 4 and cycle 7 and thereafter after every 4 cycles (12 weekly) until progression.

Progression must be confirmed with another CT scan at 6 weeks if patient is still taking study medication . See section 15.2.2 – Treatment beyond Progression.

RECIST v1.1 will be used as the primary measure for assessment of tumour response. Elevation in CA125 should not be used to determine progression.

9.3.2. Tumour Assessment

Tumour assessments will include cross-sectional imaging using CT scan of the chest, abdomen, and pelvis; CT scan of the brain will be performed at screening for any symptomatic patient. Post- baseline brain imaging will be performed for all patients with brain metastases at baseline or if the patient develops neurological symptoms. The preferred method of disease assessment is CT with contrast. If CT with contrast is contraindicated, CT without contrast. The same method is required for all subsequent tumour assessments.

9.3.3. CT scans of the chest, abdomen and pelvis with contrast

CT scans should be performed with contiguous cuts in slice thickness of 5 mm or less. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.

9.4. Assessments on Completion of Trial Treatment

When a patient completes all scheduled doses of pembrolizumab, or discontinues/withdraws before completing all scheduled doses, the end of treatment visit should be conducted at Day 30 ± 7 days from the time of discontinuation.

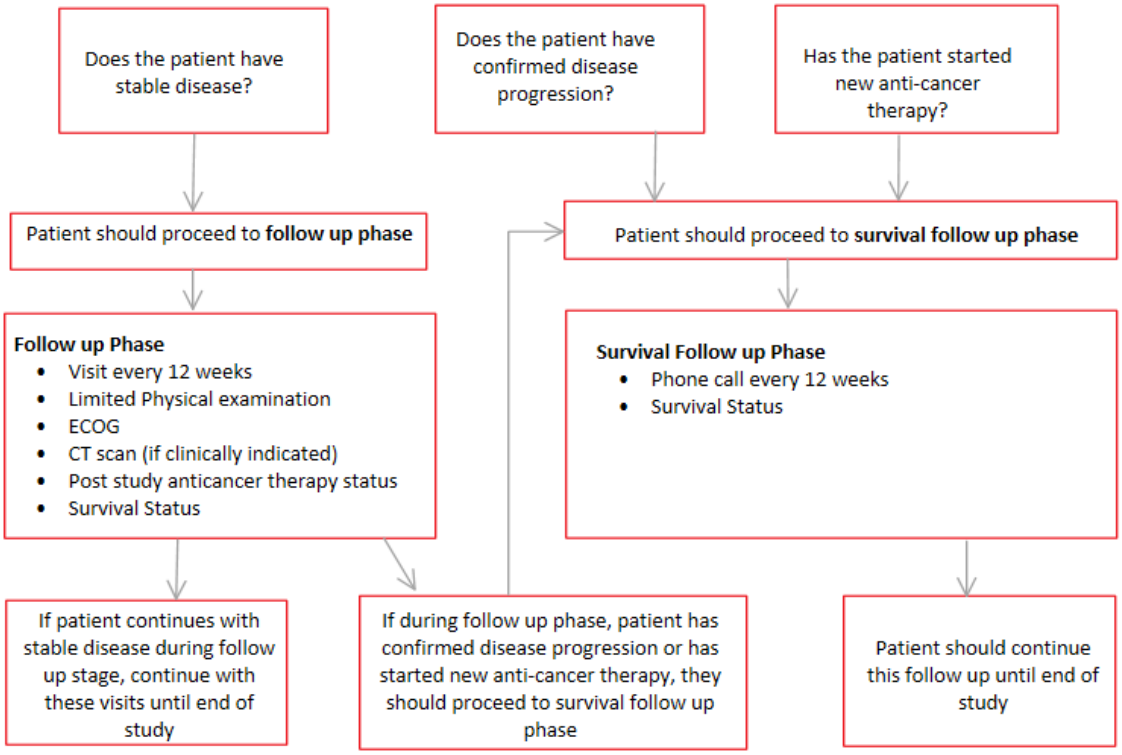
At the End of treatment visit, the following procedures should be performed (outlined in Appendix 1):

- **Review of adverse events**
- **Review of concomitant medication**
- **Physical examination** including vital signs and weight
- **ECOG performance status**
- **Haematology** including Full Blood Count (with WBC differentials). The laboratory tests are outlined in table 6.
- **Biochemistry** including liver function tests. The laboratory tests are outlined in table 6.
- **Thyroid function tests** (TSH, T3 and FT4)
- **CA125**
- **Urinalysis**
- **Post-study anticancer therapy status**
- **Survival status**

If a patient fails to attend a clinic or cannot be followed up at site, all efforts should be made by the Site to contact the patient's GP to assess their condition.

9.5. Assessments During Follow Up

Figure 3: Overview of follow up schedules



9.5.1. Follow up phase

Patients with stable disease after 24 months of Pembrolizumab, and patients who discontinue (for reasons other than progression, e.g. adverse events) will be assessed every 12 weeks from end of treatment visit until the end of the study (or until death, withdrawing consent or becoming lost to follow up). The assessment will include:

- **Limited physical examination**
- **ECOG performance status**
- **CT scan (only if clinically indicated)**
- **Post study anticancer therapy status**
- **Survival status**

Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

9.5.2. Survival Follow-up phase

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

10. IMMUNOLOGICAL AND BIOLOGICAL STUDIES

FFPE tumour samples available from primary diagnosis and subsequent biopsies and exploratory blood samples will be requested, in order to understand the changes in the immune landscape over time. For details on sample collection, processing, shipment and analysis please refer to the PROMPT lab manual.

10.1 Archival tissue collection

Sites will send archival FFPE tissue to a central laboratory once a patient has been registered into the trial.

10.2 Tumour Biopsies

If feasible, fresh tumour biopsies will be obtained prior to administration of the first dose of pembrolizumab. In addition, fresh tumour biopsies will be obtained prior to cycle 4 of pembrolizumab. If clinically practical, at each fresh biopsy time point, patients will undergo three core biopsies.

10.3 Blood sample collection

For each patient, exploratory blood samples will be collected, at baseline and prior to cycle 4, and upon progression. 20ml of whole blood will be collected in 2 x EDTA tubes for immunological analysis, 3ml of whole blood will be collected in 1 x tempus tube for T-cell Receptor analysis and 10ml whole blood taken in 1 x EDTA tube for circulating tumour DNA extraction.

10.4 Proposed analysis

The below analysis planned to be performed on the archival, tumour biopsy and blood samples, may include:

- Analysis of FFPE tissue
- Isolation of Tumour infiltrating lymphocytes (TILS)
- Multi-Parametric flow cytometry (FACS) and time of flight mass cytometry (CyTOF)
- Assessment of T cell repertoire and clonality
- Identification of candidate neoantigens and assessment of T cell specificity
- Analysis of circulating tumour DNA
- Studies on live cells isolated from patients
- RNA analysis

11 DATA MANAGEMENT AND DATA HANDLING GUIDELINES

Data will be collected from sites on electronic case report forms (eCRFs) designed for the trial and supplied by UCL CTC. SAEs and AESIs will be reported on paper reports. Data must be accurately entered/transcribed onto trial forms/reports and must be verifiable from source data at site. Examples of source documents are hospital records which include patient's notes, laboratory and other clinical reports etc.

Where copies of supporting source documentation (e.g. autopsy reports, pathology reports, CT scan images etc.) are being submitted to UCL CTC, the patient's trial number must be clearly indicated on all material and any patient identifiers removed/blacked out prior to sending to maintain confidentiality.

11.1 Completing Electronic Case Report Forms (eCRFs)

All eCRFs must be entered by staff who are appropriately trained, listed on the site staff delegation log and authorised by the PI to perform this duty. Each authorised staff member will be issued with their own unique login details for the eCRF by UCL CTC, and a list of current users at each site will be maintained by UCL CTC. Site staff must never share their login details with other staff as the eCRF audit trail will record all entries/changes made by each user. The PI is responsible for the accuracy of all data reported in the eCRF and paper SAE/AESI reports.

Where necessary, corrections can be made by site staff to data on the eCRF, as long as the eCRF has not been locked/frozen by UCL CTC. The eCRF audit trail will record the original data, the change made, the user making the change and the date and time. Site staff should contact UCL CTC if changes need to be made to a locked/frozen eCRF.

For paper SAE/AESI reports, all entries must be clear, legible and written in ball point pen. Any corrections made to a paper SAE/AESI report at site must be made by drawing a single line through the incorrect item ensuring that the previous entry is not obscured. Each correction must be dated and initialed. Correction fluid must not be used.

The use of abbreviations and acronyms should be avoided.

Originals of the paper SAE/AESI reports must be sent to UCL CTC and a copy kept at site.

11.2 Missing Data

To avoid the need for unnecessary data queries, eCRFs must be checked at site to ensure there are no blank mandatory fields that require completion (unless it is specifically stated that a field may be left blank). For paper SAE/AESI reports, when data are unavailable because a measure has not been taken or test not performed, enter "ND" for not done. If an item was not required at the particular time the form relates to, enter "NA" for not applicable. When data are unknown enter the value "NK" (only use if every effort has been made to obtain the data). For eCRF data guidance, please refer to the PROMPT eCRF manual for sites which can be found in the ISF.

11.3 Timelines for Data Completion

Electronic CRFs must be completed at site as soon as possible after the relevant visit and within one month of the patient being seen.

Sites that persistently do not complete data items within the required timelines may be suspended from recruiting further patients into the trial by UCL CTC and subject to a 'Triggered' monitoring visit. See section 14.3 ('Triggered' On-Site/Remote Monitoring) for details. Please refer to section 12, for the reporting timeframes required for SAEs/AESI and AEs.

11.4 Data Queries

Data entered onto the eCRF will be subject to some basic checks at the time of entry, and any discrepancies will be flagged to the user in the form of a warning. The data can be corrected immediately, or where this is not possible, the warning can be saved and the data amended at a later stage.

Further data review will be carried out by UCL CTC, with regular reports to sites, listing any overdue forms that require completion. Repeated failure to complete data queries/complete eCRFs within the required timeframes, will result in an escalation procedure that may involve suspension to recruitment at the trial site. Sites should inform UCL CTC as soon as possible of any issues they may experience that affects completion of the data required.

12 PHARMACOVIGILANCE REPORTING

12.1 Definitions

The following definitions have been adapted from Directive 2001/20/EC, ICH E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" and ICH GCP E6.

Adverse Event (AE)

Any untoward medical occurrence in a patient treated on a trial protocol, which does not necessarily have a causal relationship with a trial treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a trial treatment, whether or not related to that trial treatment. See section 12.2.1 for AE reporting procedures.

Adverse Reaction (AR)

All untoward and unintended responses to a trial treatment related to any dose administered. A causal relationship between a trial treatment and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

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

An adverse event or adverse reaction that at any dose:

- Results in death
- Is life threatening (the term "life-threatening" 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 that hypothetically might have caused death if it were more severe)
- Requires in-patient hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is otherwise medically significant (e.g. important medical events 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 above)

See section 12.2.2 for SAE reporting procedures.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature or severity of which is not consistent with the applicable reference safety information.

i.e. an adverse event meeting the following criteria:

- Serious – meets one or more of the serious criteria, listed under the definition of SAE above
- Related – assessed by the local PI or designee or Sponsor as causally related to one or more elements of the trial treatment

- Unexpected – the event is not consistent with the applicable reference safety information (RSI)

See section 12.3 for reporting procedures for these events.

Adverse event of special interest (AESI)

An AE that is of scientific and medical concern to the Trial Management Group and MSD for which rapid communication is required. The AESI may not meet the standard criteria for seriousness and it may occur outside the standard AE reporting timeframes for the trial. The AEs of special interest for this trial are listed in section 12.4. See section 12.4 for reporting procedures for these events.

12.2 Reporting Procedures

Adverse Event Term

An adverse event term must be provided for each adverse event. Wherever possible a valid term listed in the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 should be used. This is available online at:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Severity grade

Severity grade of each adverse event must be determined by using CTCAE v5.0

Causality

The relationship between the treatment and an adverse event will be assessed.

For AEs (including SAEs), the local PI or designee will assess whether the event is causally related to trial treatment.

For SAEs, a review will also be carried out by the Sponsor's delegate.

Causal relationship to each trial treatment must be determined as follows:

- Related (reasonable possibility) to a trial treatment
- Not related (no reasonable possibility) to a trial treatment

UCL CTC will consider events evaluated as related to be adverse reactions.

12.2.1 Reporting of Adverse Events (AEs)

All adverse events that occur between informed consent and 30 calendar days (or 16 weeks for AESIs) post last trial treatment administration (see section 16.1 for end of trial definition) must be recorded in the patient's medical notes and the trial CRFs.

Those meeting the definition of a SAE or AESI must also be reported to UCL CTC using the trial specific SAE Report. Also refer to section 12.2.2 (Reporting of Serious Adverse Events (SAEs) and section 12.4 (Adverse Events of Special Interest)).

Pre-existing conditions (i.e. conditions present at informed consent) do not qualify as adverse events unless they worsen or recur (i.e. improves/resolves and then worsens/reappears again).

E.g. an AE could be an exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition (worsening of the event). Another example of an AE is when a pre-existing condition improves during the trial (e.g. from grade 3 to grade 1) and then it worsens again (e.g. from grade 1 to grade 2), even if the event is of severity equal or lower to the original condition (improvement and recurrence of the event).
NB the disease(s) under study and its anticipated day-to-day fluctuations would not be an AE.

12.2.2 Reporting of Serious Adverse Events (SAEs)

All SAEs including AESIs that occur between the signing of informed consent and 16 weeks post last trial treatment administration **(or after this date if the site investigator feels the event is related to the trial treatment)** must be submitted to UCL CTC by email within **24 hours** of observing or learning of the event, using the trial specific SAE Report.

All sections on the SAE Report must be completed. If the event is **not being reported within 24 hours** to UCL CTC, the circumstances that led to this must be detailed in the SAE Report to avoid unnecessary queries.

Exemptions from SAE Report submission

For this trial, the following events are exempt from requiring submission on an SAE Report. However, the events must be recorded in the relevant section(s) of the trial CRFs:

- events that occur more than 16 weeks post last trial treatment administration unless:
  - considered to be a late effect of the trial treatment
  - it is a pregnancy related event (see section 12.6)
- disease progression (including disease progression related deaths) unless considered related to the IMP

Please note that hospitalisation for elective treatment, palliative care, socio-economic or logistic reasons does not qualify as an SAE.

Completed SAE Reports must be emailed to UCL CTC within 24 hours of becoming aware of the event

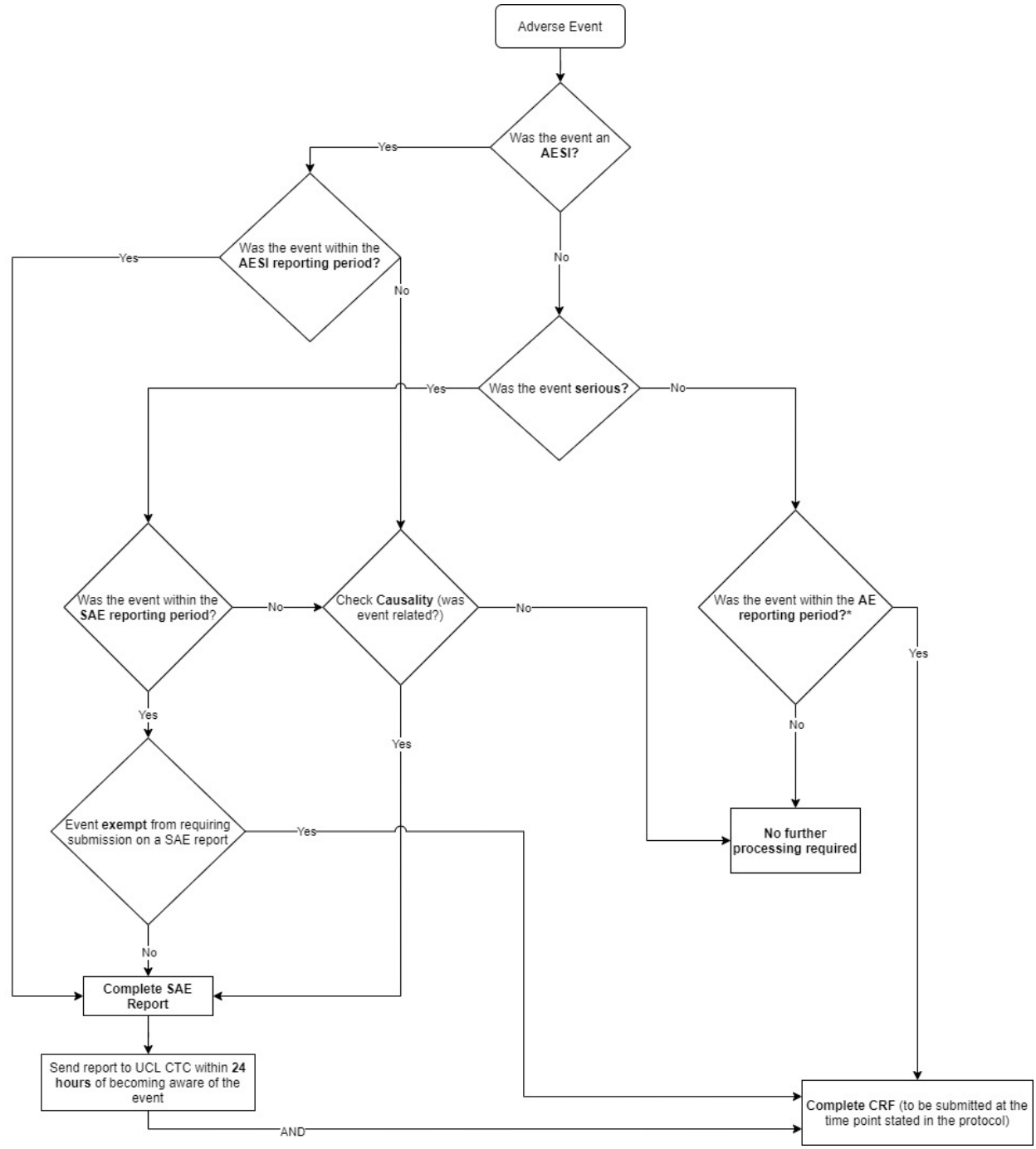
Email: ctc.prompt@ucl.ac.uk

SAE Follow-Up Reports

UCL CTC will follow up all SAEs until resolution and until there are no further queries.

Sites must ensure any new and relevant information is provided to UCL CTC promptly. If the event term changes or a new event is added, the causality must be re-assessed by an Investigator. If the event is not being reported to UCL CTC within 24 hours, the circumstances that led to this must be detailed in the SAE Report to avoid unnecessary queries.

Figure 4: Adverse Event Reporting Flowchart



**This applies if AE, SAE and AESI reporting period differs*

SAE Processing at UCL CTC

On receipt of the SAE Report, UCL CTC will check for legibility, completeness, accuracy and consistency. Expectedness will be evaluated, to determine whether or not the case qualifies for expedited reporting, using the approved RSI (the list of expected adverse reactions in the IB for pembrolizumab).

The CI, or their delegate (e.g. a clinical member of the TMG), will be contacted to review the SAE and to perform an evaluation of causality on behalf of the sponsor. If UCL CTC has considered expectedness difficult to determine, the CI, or their delegate, will be consulted for their opinion at this time.

UCL CTC will submit all SAE Reports and SUSAR Reports concerning patients who have received pembrolizumab to MSD according to the timelines outlined in the agreement between UCL and MSD.

UCL CTC will provide MSD with quarterly line listings of SAEs concerning patients who have received pembrolizumab.

12.3 SUSARs

If the event is evaluated as a SUSAR, i.e. an unexpected event that is related (reasonable possibility) to the investigational drug, UCL CTC will submit a report to the MHRA and the REC within 7 calendar days for initial reports of fatal/life threatening events (with a follow-up report within a further 8 calendar days) and 15 calendar days for all other events.

Wherever possible, evaluations of causal relationship by both the site and the Sponsor's clinical reviewer will be reported.

UCL CTC will submit all SUSAR reports relating to pembrolizumab to MSD according to the timelines outlined in the agreement between UCL and MSD.

Informing Sites of SUSARs

UCL CTC will inform all sites of any SUSARs that occur on the trial. PIs will receive a quarterly line listing which must be processed according to local requirements.

UCL CTC will forward reports received from MSD regarding SUSARs that have occurred on other trials using pembrolizumab to all sites. These must be processed according to local requirements and filed with the applicable IB.

12.4 Adverse events of special interest

All SAEs, including AESIs that occur between the signing of informed consent and 16 weeks post last trial treatment administration **(or after this date if the site investigator feels the event is related to the trial treatment)** must be submitted to UCL CTC by email within **24 hours** of observing or learning of the event, using the trial specific SAE Report.

The following adverse events of special interest for the study treatment must be collected between informed consent and16 weeks post last trial treatment administration. They must be reported on an SAE report regardless of their seriousness within **24 hours of becoming aware of the event.** All sections of the SAE report must be completed. In terms of causality and expectedness, these reports will be processed as other SAE reports.

- An overdose of pembrolizumab as defined in section 8.6
- Abnormal liver function tests meeting ALL the following criteria:

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

All AEs of special interest must be reported by emailing a completed SAE report to UCL CTC within 24 hours of becoming aware of the event

Email: ctc.prompt@ucl.ac.uk

UCL CTC will submit SAE reports relating to AESIs in patients who have received study treatment to MSD according to the timelines in the agreement between UCL and MSD.

12.5 Safety Monitoring

UCL CTC will provide safety information to the Trial Management Group (TMG) and the Independent Data Monitoring Committee (IDMC) on a periodic basis for review.

Trial safety data will be monitored to identify:

- Whether disease-related events (exempt from SAE reporting as per section 12.2.2) appear to be enhanced by study treatment(s)
- new adverse reactions to the trial treatment regimen
- a higher incidence in rare adverse events than is stated in the IB for a trial treatment
- trial related events that are not considered related to the trial treatment, but may lead to changes to the trial documents
- review of AESIs as outlines in section 12.4 of the protocol

If UCL CTC identifies or suspects any issues concerning patient safety at any point during the trial, the CI or TMG will be consulted for their opinion, and if necessary the issue will be referred to the IDMC.

12.6 Pregnancy

Reporting Period

If a patient becomes pregnant between the start of trial treatment and 4 months after last trial treatment administration (or 30 days following cessation of treatment if the patient initiates new anticancer therapy, whichever is earlier), the site must submit a trial specific Pregnancy Report to UCL CTC by email within 24 hours of learning of its occurrence.

The site must request consent from the pregnant trial patient to report information regarding a pregnancy using the trial-specific Pregnancy Monitoring Information Sheet and Informed Consent Form for trial patients

If consent is not given, the notification that a pregnancy has occurred will be retained by UCL CTC, however no further action will be taken on the information detailed in the report.

All pregnancies must be reported by emailing a completed Pregnancy Report to UCL CTC within 24 hours of becoming aware of the pregnancy

Email: ctc.prompt@ucl.ac.uk

Pregnancy Follow-Up Reports

For pregnant patients or partners who consent, their pregnancies must be followed -up at least monthly until an outcome is determined. Follow-up Pregnancy Reports must be submitted to UCL CTC by fax and email within **24 hours** of learning of the outcome. Reports must include an evaluation of the possible relationship of each trial treatment to the pregnancy outcome.

SAEs during Pregnancy

Any SAE occurring in a pregnant patient must be reported using the trial specific SAE Report, according to SAE reporting procedures. Refer to section 12.2.2 (Reporting of Serious Adverse Events (SAEs)) for details.

Pregnancy Report processing at UCL CTC

UCL CTC will submit a report to the MHRA and the REC if the pregnancy outcome meets the definition of a SUSAR. Refer to section 12.3 (SUSARs) for details.

UCL CTC will submit all Pregnancy Reports concerning exposure to pembrolizumab to MSD according to the timelines outlined in the agreement between UCL and MSD.

12.7 Development Safety Update Reports (DSURs)

Safety data obtained from the trial will be included in DSURs that UCL CTC will submit to the MHRA and the REC.

UCL CTC will provide MSD with DSURs that include information regarding pembrolizumab.

13 INCIDENT REPORTING AND SERIOUS BREACHES

13.1 Incident Reporting

Organisations must notify UCL CTC of all deviations from the protocol or GCP immediately. An incident report may be requested and will be provided, but an equivalent document (e.g. Trust Incident form) is acceptable where already completed.

If site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the UCL CTC trial team can be contacted immediately to discuss.

UCL CTC will use an organisation's history of non-compliance to make decisions on future collaborations.

UCL CTC will assess all incidents to see if they meet the definition of a serious breach.

13.2 Serious Breaches

A "serious breach" is defined as a breach of the protocol or of the conditions or principles of Good Clinical Practice (or equivalent standards for conduct of non-CTIMPs) which is likely to affect to a significant degree the safety or physical or mental integrity of the trial patients, or the scientific value of the research.

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

In cases where a serious breach has been identified, UCL CTC will inform the MHRA and REC within 7 calendar days of becoming aware of the breach.

Sites must have written procedures for notifying the sponsor of serious breaches (MHRA Guidance on the Notification of Serious Breaches).

14 TRIAL MONITORING AND OVERSIGHT

Participating sites and PIs must agree to allow trial-related on-site monitoring, Sponsor audits and regulatory inspections by providing direct access to source data/documents as required. Where permitted by site policy, remote access to source data/documents may also be provided by participating sites for remote monitoring by UCL CTC or its representatives.

Patients are informed of this in the patient information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the consent form. UCL CTC or its representatives will conduct all monitoring in compliance with the particular consent, site policy and data protection requirements.

UCL CTC will determine the appropriate level and nature of monitoring required based on the objective, purpose, phase, design, size, complexity, endpoints and risks associated with the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

Details of monitoring activities will be included in the trial monitoring plan and conveyed top sites during initiation. The Monitoring Plan will be under review throughout the trial and updated information provided to sites as necessary.

14.1 On-Site and Remote Monitoring

On-Site Monitoring

Sites will be sent an email in advance of any on-site monitoring visits, confirming when a visit is scheduled to take place. The email will include a list of the documents to be reviewed, interviews that will be conducted, planned inspections of the facilities and who will be performing the visit.

Remote Monitoring

UCL CTC defines remote monitoring as activities conducted at a location remote from the research site which replicate some on-site activities e.g. source data review. Remote monitoring may be conducted in response to exceptional circumstances preventing access to participating sites (e.g. global pandemic) or conducted routinely. Details of remote monitoring will be agreed with participating sites, conducted in accordance with site policy and documented in the monitoring plan.

Sites will be sent an email in advance, confirming when remote monitoring is scheduled to take place and how the source documents will be remotely accessed. The email will include a list of the documents to be reviewed, interviews that will be conducted via telephone/videoconference and who will be performing the remote monitoring.

Remote monitoring will be conducted by UCL CTC or its representatives via a device with adequate security. Patient confidentiality will be maintained at all times, and monitoring activities will be conducted in an appropriate environment where no unauthorised viewing or overhearing of conversations is possible by third parties. Refer to section 11 Data Management and Data Handling Guidelines for details of how source documentation should be submitted to UCL CTC.

Monitoring Follow Up

Following on-site/remote monitoring, the Trial Monitor/Trial Coordinator will provide a follow up email to the site, which will summarise the documents reviewed and a statement of findings, incidents, deficiencies, conclusions, actions taken and/or actions

required. The PI at each site will be responsible for ensuring that monitoring findings are addressed in a timely manner, and by the deadline specified.

14.2 Centralised Monitoring

UCL CTC performs centralised monitoring, which requires the submission of the following documents by sites to UCL CTC for review: screening logs, staff delegation logs, Principal Investigator CV and GCP, drug accountability logs and site laboratory normal ranges. Expectations for document submission will be explained during site initiation and UCL CTC or its representatives will send emails to sites requesting the documents when required.

Sites will be requested to conduct quality control checks of documentation held within the Investigator Site File and Pharmacy Site File at the frequency required for the trial. Checklists detailing the current version/date of version controlled documents will be provided for this purpose.

14.3 'Triggered' On-Site/Remote Monitoring

Additional on-site/remote monitoring visits may be scheduled following UCL CTC review and/or where there is evidence or suspicion of non-compliance at a site with important aspect(s) of the trial protocol/GCP requirements.

On-site Monitoring

Sites will be sent an email in advance outlining the reason(s) for the visit and confirming when it will take place. The email will include a list of the documents that are to be reviewed, interviews that will be conducted, planned inspections of the facilities and who will be performing the visit.

Remote Monitoring

Sites will be sent an email in advance, confirming when remote monitoring is scheduled to take place and how the source documents will be remotely accessed. The email will include a list of the documents to be reviewed, interviews that will be conducted via telephone/videoconference and who will be performing remote monitoring.

14.4 Escalation of monitoring issues

Where monitoring indicates that a patient may have been placed at risk (e.g. evidence of an overdose having been administered), the matter will be raised urgently with site staff and escalated as appropriate.

UCL CTC will assess whether it is appropriate for the site to continue participation in the trial and whether the incident(s) constitute a serious breach. Refer to section 13 (Incident Reporting and Serious Breaches) for details.

14.5 Oversight Committees

14.5.1 Trial Management Group (TMG)

The TMG will include the Chief Investigator, clinicians and experts from relevant specialities and PROMPT trial staff from UCL CTC (see page 2). The TMG will be responsible for overseeing the trial. The group will meet regularly and will send updates to PIs (via newsletters or at Investigator meetings) and to the NCRI Gynaecological Clinical Studies Group.

The TMG will review substantial amendments to the protocol prior to submission to the REC and MHRA. All PIs will be kept informed of substantial amendments through their nominated responsible individual and are responsible for their prompt implementation.

All TMG members will be required to sign a UCL CTC TMG Charter.

14.5.2 Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial. The TSC will review the recommendations of the Independent Data Monitoring Committee and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the funder(s) and the Sponsor.

All TSC members will be required to sign a UCL CTC TSC Charter.

14.5.3 Independent Data Monitoring Committee (IDMC)

The role of the IDMC is to provide independent advice on data and safety aspects of the trial. Meetings of the Committee will be held at least once a year to review interim analyses, or as necessary to address any issues. The IDMC is advisory to the TSC and can recommend premature closure of the trial to the TSC.

All IDMC members will be required to sign a UCL CTC IDMC Charter.

14.5.4 Role of UCL CTC

UCL CTC will be responsible for the day to day coordination and management of the trial and will act as custodian of the data generated in the trial (on behalf of UCL). UCL CTC is responsible for all duties relating to pharmacovigilance which are conducted in accordance with section 12 (Pharmacovigilance Reporting).

15 WITHDRAWAL OF PATIENTS

In consenting to the trial, patients are consenting to trial treatment, assessments, collection of biological samples, follow-up and data collection.

15.1 Patients who do not start Trial Treatment

If a patient does not start treatment, the reasons for this must be recorded in the patient's notes and on the relevant Case Report Form(s). Reasons that a patient may not start treatment include:

- Deterioration in health
- Patient decision

If a patient does not start treatment, then the patient should be withdrawn from the trial. Data collected will be used in the trial analysis. Biological samples collected may still be used unless the patient explicitly withdraws consent to this.

15.2 Discontinuation of Trial Treatment

A patient may be withdrawn from trial treatment whenever such treatment is no longer in the patient's best interests, but the reasons for doing so must be recorded in the patient's notes and on the relevant Case Report Form(s). Reasons for discontinuing treatment may include:

- Confirmed radiographic disease progression

  Note: For unconfirmed radiographic disease progression, please see Section 15.2.2
- Unacceptable toxicity
- Intercurrent illness which prevents further treatment
- Patient decision not to continue with trial treatment
- Any alterations in the patient's condition which justifies the discontinuation of treatment in the site investigators opinion
- The patient has confirmed positive serum pregnancy test or fails to use adequate birth control (for patients of childbearing potential)
- Non-compliance with the trial treatment or procedure requirements
- The patient is lost to follow up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.
- *Note: 24 months of study medication is calculated from the date of first dose.*

The End of Treatment and Follow-up visit procedures are listed in Appendix 1 (Trial Schedule of Procedures/Assessments) and Section 9 (Assessments/Trial Procedures)). After the end of treatment, each patient will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 16 weeks after the end of treatment as described in Section 12.2.2).

Patients who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented

disease progression each patient will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

If a patient expresses their wish to withdraw from trial treatment, sites 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 and for allowing existing collected data to be used. If the patient gives a reason for wishing to discontinue trial treatment, this should be recorded.

15.2.1 Discontinuation of Study treatment after CR

Discontinuation of treatment may be considered for patients who have attained a confirmed CR that have been treated for at least 6 cycles of pembrolizumab and had at least 2 additional cycles of pembrolizumab beyond the date when the initial CR was declared.

15.2.2 Treatment beyond Progression

If progressive disease (PD; based on RECIST) occurs before completion of the 24-month treatment period, the patient may continue to be treated until one of the following criteria is met:

- Confirmed PD: The assessment of PD by RECIST v1.1 (baseline PD assessment) will be confirmed by a repeat evaluation 6 weeks later (after 2 further cycles of pembrolizumab), but no sooner than 4 weeks later. If any subsequent tumour assessment time point shows ≥ 20% increase in the overall tumour burden (the sum of diameters of target lesions and new lesions), when compared to the baseline PD assessment (the sum of diameters of target lesions and new lesions), the patient would be deemed as having confirmed PD and must be discontinued.

- Meets any of the investigational product discontinuation criteria (Section 15.1)

- Clinical symptoms or signs indicating clinically significant PD such as the benefit-risk ratio of continuing treatment is no longer justified.

- Decline in Eastern Cooperative Oncology Group (ECOG) performance status compared to baseline.

- Rapid PD or threat to vital organs/critical anatomical sites (e.g. spinal cord compression) requiring urgent alternative medical intervention, and/or continuation of study treatment would prevent institution of such intervention.

Patients will be made aware of the potential benefits and risks of continuing the study regimens in the setting of PD as this will be included in the written consent form.

15.3 Future Data Collection

If a patient explicitly states they do not wish to contribute further data to the trial their decision must be respected, with the exception of essential safety data, and recorded on the relevant eCRF. In this event data due up to the date of withdrawal must be submitted but no further data, other than essential safety data, sent to UCL CTC.

15.4 Losses to Follow-Up

If a patient moves from the area, every effort should be made for the patient to be followed up at another participating trial site and for this new site to take over the responsibility for the patient, or for follow-up via GP. Details of participating trial sites can be obtained from the UCL CTC trial team, who must be informed of the transfer of care and follow up arrangements. If it is not possible to transfer to a participating site, the registering site remains responsible for submission of forms.

If a patient is lost to follow-up at a site every effort should be made to contact the patient's GP to obtain information on the patient's status.

16 TRIAL CLOSURE

16.1 End of Trial

For regulatory purposes the end of the trial will be two years following registration of the last patient and when laboratory sample analysis of human tissue collected for relevant protocol translational research is complete.at which point the 'declaration of end of trial' form will be submitted to the MHRA and Ethics Committee, as required.

Following this, UCL CTC will advise sites on the procedure for closing the trial at the site.

Once the end of trial has been declared, no more prospective patient data will be collected but sites must co-operate with any data queries regarding existing data to allow for analysis and publication of results.

16.2 Archiving of Trial Documentation

At the end of the trial, UCL CTC will archive securely all centrally held trial related documentation for a minimum of 5 years. Arrangements for confidential destruction will then be made. It is the responsibility of PIs to ensure data and all essential documents relating to the trial held at site are retained securely for a minimum of 5 years after the end of the trial, and in accordance with national legislation.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of GCP and all applicable regulatory requirements.

UCL CTC will notify sites when trial documentation held at sites may be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

16.3 Early Discontinuation of Trial

The trial may be stopped before completion as an Urgent Safety Measure on the recommendation of the TSC or IDMC (see section 14.5.2 Trial Steering Committee (TSC) and 14.5.3 Independent Data Monitoring Committee (IDMC)). Sites will be informed in writing by UCL CTC of reasons for early closure and the actions to be taken with regards the treatment and follow up of patients.

16.4 Withdrawal from Trial Participation by a Site

Should a site choose to close to recruitment the PI must inform UCL CTC in writing. Follow up as per protocol must continue for any patients recruited into the trial at that site and other responsibilities continue as per the site agreement.

17 STATISTICS

17.1 Sample Size Calculation

The primary outcome measure of the study is progression-free survival (PFS) rate at 6 months from the start of maintenance pembrolizumab. From previous trials with weekly paclitaxel, 6-month PFS is expected to be around 30% from the start of chemotherapy (McNeish et al 2014; Poveda et al 2015), but this includes patients who progressed. Therefore, excluding these patients, there will be no further interest in using maintenance pembrolizumab if the 6-month PFS rate is <40%. If it is to be clinically worthwhile, we aim to detect an increase in the 6-month PFS rate to 65% (based on the AURELIA trial, Poveda et al 2015).

Using A'Hern's single-stage phase II design (Sample Size Tables for Clinical Studies Software Program), with a one-sided 5% significance level and 80% power, a sample size of 28 patients is required and ≥16 need to be alive and progression-free at 6 months to warrant further investigation. We aim to recruit 28 patients over 18 months, any patient who becomes ineligible will be replaced.

17.2 Statistical analysis

17.2.1 Analysis of main endpoint

The primary endpoint of the study is progression-free survival (PFS) rate at 6 months from the start of maintenance pembrolizumab.

Kaplan-Meier estimates will be used to analyse PFS, defined as the time from the start of maintenance pembrolizumab to the date of first progression or death from any cause, censoring will occur on the date of last study assessment. The number and percentage of patients who are progression-free and alive at 6 months will be presented with both one-sided (lower confidence limit) and two-sided 95% confidence intervals. Analysis will be on an intention-to-treat (ITT) basis for all eligible patients.

No statistical methods will be used to impute missing data.

17.2.2 Analysis of secondary endpoints and exploratory analyses

Kaplan-Meier estimates will be used to analyse PFS from the start of weekly dose-dense paclitaxel to the date of first progression or death from any cause, censoring will occur on the date of last study assessment. The number and percentage of patients who are progression-free and alive at 6 months will be presented with the 95% confidence interval.

Kaplan-Meier estimates will be used to analyse overall survival from the start of maintenance pembrolizumab and from the start of weekly dose-dense paclitaxel to the date of death from any cause, censoring will occur on the date of last study assessment.

The number and percentage of patients achieved disease response (RECIST) to trial treatment will be presented, with two-sided 95% confidence intervals constructed using exact methods based on the binomial distribution.

Of patients who start trial treatment, compliance to trial treatment and the number and percentage of patients who suffer a grade 3 or 4 toxicity at any time will be presented. The maximum grade of toxicity will also be tabulated for each adverse event. Two-sided

95% confidence intervals will be constructed using exact methods based on the binomial distribution.

Further treatment of patients who progress will also be described, this will include the time-until the next treatment, the treatment received and patient outcomes for these.

17.3 Interim analyses

The study will be regularly monitored by trials unit staff, with input from members of the Trial Management Group. A report will be provided to the Independent Data Monitoring Committee (IDMC), who will review accrual, compliance, safety and efficacy. The first review by the IDMC will be triggered after 10 patients have completed four cycles of pembrolizumab, and at least once each year thereafter. The IDMC will make recommendations on whether the trial should continue or stop recruitment, or the protocol modified. Any decision to stop the trial will be communicated to the Trial Steering Committee (TSC).

18 ETHICAL AND REGULATORY CONSIDERATIONS

In conducting the trial, the Sponsor, UCL CTC and sites shall comply with the protocol and with all relevant guidance, laws and statutes, as amended applicable to the performance of clinical trials and research including, but not limited to:

- UK Policy Framework for Health and Social Care Research, issued by the Health Research AuthorityHuman Rights Act 1998
- Data Protection Act 2018
- General Data Protection Regulation (EU 2016/679) (GDPR)
- Freedom of Information Act 2000
- Human Tissue Act 2004
- Medicines for Human Use (Clinical Trials) UK Regulations 2004 (SI 2004/1031)
- Medicines Act 1968
- Good Manufacturing Practice

18.1 Ethical Approval

The trial will be conducted in accordance with the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (1996 version) and in accordance with the terms and conditions of the ethical approval given to the trial.

The trial has received a favourable opinion from the Cambridge and Hertfordshire Research Ethics Committee (REC) and Health Research Authority (HRA) approval for conduct in the UK.

UCL CTC will submit Annual Progress Reports to the REC, commencing one year from the date of ethical approval for the trial.

18.2 Regulatory Approval

A Clinical Trial Authorisation (CTA) has been granted for the trial.

The trial will be conducted at approved trial sites in accordance with the trial protocol and the terms of the CTA granted by the MHRA.

18.3 Site Approvals

Evidence of assessment of capability and capacity by the Trust/Health Board R&D for a trial site must be provided to UCL CTC. Sites will only be activated when all necessary local approvals for the trial have been obtained.

18.4 Protocol Amendments

UCL CTC will be responsible for gaining ethical and regulatory ***approvals***, as appropriate, for amendments made to the protocol and other trial-related documents. Once approved, UCL CTC will ensure that all amended documents are distributed to sites as appropriate.

Site staff will be responsible for acknowledging receipt of documents and for implementing all amendments promptly.

18.5 Patient Confidentiality & Data Protection

Patient identifiable data, including initials and date of birth (or equivalent) will be required for the registration process and will be provided to UCL CTC. UCL CTC will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Data will be stored in a secure manner and UCL CTC trials are registered in accordance with the Data Protection Act 2018 and GDPR, with the Data Protection Officer at UCL.

Patient identifiable data, including initials and date of birth will be provided to UCL Cancer Institute and Health Services Laboratories at UCLH in order to process the immunological tissue and blood samples. The UCL Cancer Institute and Health Services Laboratories will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified.

19 SPONSORSHIP AND INDEMNITY

19.1 Sponsor Details

Sponsor Name:	University College London
Address:	Joint Research Office Gower Street London WC1E 6BT
Contact:	Managing Director, UCLH/UCL Research
Tel:	020 3447 9995/2178 (unit admin)
Fax:	020 3447 9937

19.2 Indemnity

University College London holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

20 FUNDING

MSD are supporting the central coordination of the trial in the UK through UCL CTC and providing the study IMP, pembrolizumab.

There is a contribution for Research A and B costs which will be reimbursed to sites as per the finance section of the site agreement.

21 PUBLICATION POLICY

All publications and presentations relating to the trial will be authorised by the Trial Management Group. The first publication of the trial results will be in the name of the Trial Management Group. Members of the TMG and other investigators that the TMG deem appropriate will be included as named authors. Data from all sites will be analysed together and published as soon as possible. Authorship will be agreed in advance between the investigators, based on the number of patients recruited at each centre and contribution to the initiation and conduct of the trial and analysis of data. Participating sites may not publish trial results prior to the first publication by the TMG or without prior written consent from the TMG. The trial data are owned by UCL as the Sponsor. The ClinicalTrials.gov number NCT NCT03430700 and funder reference will be quoted in any publications resulting from this trial.

Abstracts and papers will be reviewed by MSD prior to submission in accordance with the requirements of the Trial Drug Supply Agreement.

22 REFERENCES

1) The National Cancer Registration Service, Eastern Office on request. Similar data can be found here: http://www.ncras.nhs.uk/ncrs-east/

2) Pujade-Lauraine, E et al. Bevacizumab Combined With Chemotherapy for Platinum-Resistant Recurrent Ovarian Cancer: The AURELIA Open-Label Randomized Phase III Trial, Journal of Clinical Oncology 32, no. 13 (May 2014) 1302-1308.

3) Poveda, AM et al. Bevacizumab Combined With Weekly Paclitaxel, Pegylated Liposomal Doxorubicin, or Topotecan in Platinum-Resistant Recurrent Ovarian Cancer: Analysis by Chemotherapy Cohort of the Randomized Phase III AURELIA Trial. Journal of Clinical Oncology 33, no. 32 (November 2015) 3836-3838.

4) Varga, A et al. Antitumour activity and safety of pembrolizumab in patients with PD-L1 positive advanced ovarian cancer: Interim results from a phase Ib study. Journal of Clinical Oncology 33, no. 15_suppl (May 2015) 5510-5510.

5) Matulonis et al. Final results from the KEYNOTE-100 trial of pembrolizumab in patients with recurrent ovarian cancer. J Clin Oncol [Internet]. 2020 May 20;38(15_suppl):6005. Available from: https://doi.org/10.1200/JCO.2020.38.15_suppl.6005

6) Bohm, S et al. Neoadjuvant chemotherapy modulates the immune microenvironment in metastases of tubo-ovarian high grade serous carcinoma. Clinical Cancer Research 22, no. 12 (June 2016) 3025–3036.

7) Robert, C et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab In ipilimumab refractory advanced melanoma. Lancet 384, no. 9948 (September 2014) 1109-1117.

APPENDIX 1: SUMMARY SCHEDULE OF PROCEDURES/ASSESSMENTS

Procedure	Screening See section 9.1		Cycle 1 See 9.1	Cycle 2 See 9.2	Cycle 3 See 9.2	Cycle 4 See 9.2	Cycle 5 See 9.2	Cycle 6 (& all subsequent cycles until discontinuation/progression)	End of treatment visit	Follow up
Day/week	Day -28 to -1	Day 0	Day 1	Wk 3 (±3days)	Wk 6 (±3days)	Wk 9 (±3days)	Wk 12 (±3days)	Wk 15 and then 3 weekly (±3 days)	30 days (±7 days) post discontinuation/progression	Every 12 weeks (±7 days)
Written informed consent	X									
Determine eligibility	X									
Medical history	X									
Registration		X								
Prior and concomitant medication review	X		X	X	X	X	X	X	X	
Pregnancy test (if applicable)	X		X	X	X	X	X	X	X	
Review adverse events			X	X	X	X	X	X	X	
Physical examination	X		X		X		X[a]		X	X[b]
Vital signs and weight	X		X	X	X	X	X	X	X	
Performance status (ECOG)	X		X	X	X	X	X	X	X	X
PT/INR and aPTT		X[c]			X[c]					
FBC with differential	X		X	X	X	X	X	X	X	
Comprehensive serum chemistry panel	X		X	X	X	X	X	X	X	
CA 125	X		X	X	X	X	X	X	X	
Urinalysis	X		X	X	X	X	X	X	X	
T3, FT4 and TSH	X		X		X		X[a]		X	
CT scan chest, abdomen and pelvis*	X					X[d]		X[d]		X[e]
Tumour biopsy (if possible) and immunological blood collection		X[f]			X[g]				X[h]	
Trial treatment administration			X	X	X	X	X	X		
Post study anticancer therapy status									X	X
Survival status									X	X

[a] Procedure should be carried out every second cycle from this point [b] limited physical examination [c] Clotting factors are required ≤ 7days pre-biopsy [d] CT scan before cycle 4, before cycle 7 and then every fourth cycle (approximately every 12 weeks) [e] CT only if clinically indicated [f] Biopsy (if possible) and exploratory blood sample only to be collected after patient has been registered [g] Biopsy (if possible) and exploratory blood sample to be performed before cycle 4 [h] No biopsy at this visit, and immunological blood samples to only be taken if patient has progressed. * Please refer to section 9.3

APPENDIX 3: ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine transaminase
AR	Adverse Reaction
AST	Aspartate aminotransferase
CI	Chief Investigator
CR	Complete Response
CT	Computerised Tomography
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
DPA	Data Protection Act
DSUR	Development Safety Update Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EudraCT	European Clinical Trials Database
FBC	Full Blood Count
GFR	Glomerular Filtration Rate
HRA	Health Research Authority
IB	Investigator's Brochure
ICH GCP	International Conference of Harmonisation-Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
irAE	Immune-related Adverse Events
ISRCTN	International Standard Randomised Controlled Trial Number
IV	Intravenous
LCRN	Local Clinical Research Network
LDH	Lactate Dehydrogenase
LFT	Liver Function Tests
LLN	Lower Limit of Normal
MRC	Medical Research Council
MHRA	Medicines and Healthcare products Regulatory Agency
NCRI	National Cancer Research Institute
OS	Overall Survival
PD	Progressive Disease
PFI	Platinum-Free Intervals
PFS	Progression Free Survival
PI	Principal Investigator
PR	Partial Response
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Stable Disease

SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UCL CTC	CR UK and UCL Cancer Trials Centre
ULN	Upper Limit of Normal
WBC	White Blood Cells

APPENDIX 4: PROTOCOL VERSION HISTORY

Protocol:		**Amendments:**		
Version no.	**Date**	**Amend no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version.**
1		N/A	N/A	N/A
1.1	02/10/18	N/A	6.4.4- Contraceptive advice 8.8.2	Following wording removed '(or 30 days following cessation of treatment if the patient initiates new anticancer therapy, whichever is earlier).' Updated to include live vaccines are prohibited until 4 months post last trial treatment
2.0	03/01/19	1	Throughout 6.3.1- Inclusion criteria 10. Immunological and Biological Samples 10.3 Blood sample collection	Administrative changes throughout Updated to remove criteria- CT chest, abdominal and pelvic scan within 28 days of registration. Addition of criteria- Patient has measurable disease based on RECIST v1.1 Additional lab added- Cellular Pathology at Shropshire House Immunological blood samples now collected in EDTA tube. Circulating tumour DNA sample now 10ml in EDTA tube.
2.1	30/04/19	2	10. Immunological and biological samples 10.4 Proposed analyses	Laboratory added: Health Services Laboratories Removed Laboratory 'Cellular Pathology at the Rockefeller' Added RNA as a proposed analysis
2.2	26/07/19	3	1.1 Summary of Trial Design 6.1- Screening Log 6.3.1- Inclusion criteria	Inclusion criteria amended to 3 prior lines of platinum-based chemotherapy Instructions updated to include patients who have had 3 prior lines of platinum-based chemotherapy Inclusion criteria amended to 3 prior lines of platinum-based chemotherapy

3.0	18/08/21	12	Page 1 Page 2 1.1 Summary of Trial Design 1.2 Trial Schema 2.1 Background 3.0 Trial Design 3.1 Trial Objectives 6.3.1 Inclusion Criteria 6.3.2 Exclusion Criteria 6.4 Pregnancy and Birth Control 7.1.1 Pre-Registration 8.5 Management of Adverse Events 8.7 Supportive Care 8.8.2 Prohibited Con-Meds 9.0 Assessments 9.3.1 Evaluation of Efficacy 10.0 Biological Studies	Only one sponsor sign off required by Trials Group Lead TMG updates. -Protocol changes outlined below added to summary. -Tumour biopsy 'if feasible' added to schema. -Literature updated. -Tumour biopsy 'if feasible' added. -Immune objectives clarified. -Patients to be considered after 4 lines of chemo if good response. -Biopsy to be taken if feasible. -Measurable disease deleted. -Vaccine criteria updated. -Clotting factors removed from eligibility bloods Table1. -Clarification that patient can be registered for trial after cycle 4 of paclitaxel. Treatment with pembrolizumab must start between 4 and 8 weeks post last paclitaxel dose. -CTC template updates -Procedure updated and clarified. -Updated guidance added from MSD core protocol. -COVID vaccine guidance added. -Vaccine clarifications. -Clarifications of above changes. -Confirmation that 2nd progression scan only required if patient continues on trial treatment. -Clarification sample shipping details provided in Lab Manual. -CTC template updates incorporating eCRFs. -CTC template updates.

Protocol:		Amendments:		
Version no.	**Date**	**Amend no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version.**
			11.0 Data Management 12.0 Pharma-covigilance 14. Monitoring 16.0 Trial Closure 17.2.2 Statistics 18.0 Ethics and Regulatory 18.5 Patient Confidentiality 22 References	-CTC template updates incorporating remote monitoring. -Archiving requirement reduced from 25 to 5 years. -RECIST analysis clarified. -CTC template updates. -Laboratory names updated. -Updated. Minor administrative updates and clarifications throughout protocol.
4	05/11/24	15	1.1 'Summary of Trial Design'	Change to end of trial definition to factor in completion of the laboratory sample work for translational research.
			10 'Proposed Analysis'	Minor adjustments applied to description of work.
			16.1'End of Trial'	Change to end of trial definition to factor in completion of the laboratory sample work for translational research.