# NEOPRISM-CRC

**NEO**adjuvant **P**emb**R**olizumab **I**n **S**tratified **M**edicine – **C**olo**R**ectal**C**ancer

Neoadjuvant Pembrolizumab stratified to tumour mutation burden for High Risk Stage 2 or Stage 3 MMR-deficient Colorectal Cancer

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| Name & Role: | Signature: | Date authorised: |
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**Please note:** This trial protocol must not be applied to patients outside the NEOPRISM-CRC trial. Cancer Research UK & UCL Cancer Trials Centre (UCL CTC) can only ensure that approved trial investigators are provided with amendments to the protocol.

**Acknowledgements:** Sandra Irvine is the patient representative on the Trial Management Group (TMG) and has contributed to the development of this trial and has reviewed the patient information documentation.

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# 1. PROTOCOL SUMMARY

## 1.1. Summary of Trial Design

| | |
|---|---|
| **Title:** | NEOadjuvantPembRolizumab In Stratified Medicine – ColoReCtal |
| **Short Title/acronym:** | **NEOPRISM-CRC** |
| **EudraCT no:** | 2020-000040-58 |
| **Sponsor name & reference:** | University College London<br>UCL/127464 |
| **Funder name & reference:** | MSD<br>MK-3475-B58; MISP 58807 |
| **Clinicaltrials.gov no:** | pending |
| **Design:** | Open label, 2 arm phase II trial |
| **Overall aim:** | To determine if neoadjuvant pembrolizumab improves pathological complete response (pCR) and relapse-free survival (RFS) in MSI-H/MMR-d CRC and to establish relationships of pCR and RFS to tumour mutation burden and other putative biomarkers of resistance and sensitivity to check point inhibition (CPI) |
| **Primary endpoint:** | Pathological complete response rate (pCR) assessed as per guidance provided in the Lab Manual |
| **Secondary endpoints:** | • 3 year relapse free survival<br>• 3 year overall survival (OS)<br>• Frequency and severity of adverse events recorded continuously in relation to each treatment cycle graded using CTCAE criteria<br>• Frequency and severity of post-operative surgical complications<br>• Rate of R0 resections and completed surgery<br>• Health-related Quality of Life (QoL) and functional outcome |
| **Exploratory Biological Studies:** | To explore the relationship between possible predictive novel biomarkers and response to pembrolizumab in blood, archival and fresh tumour tissue, oral and stool samples.<br>To explore bacterial and genomic changes in the microbiome in response to immunotherapy and surgery in oral and stool samples. |
| **Target accrual:** | 32 |
| **Inclusion & exclusion criteria:** | *Inclusion criteria:*<br>1. Histologically proven adenocarcinoma of the colon which is MMR-d by IHC or MSI-H by PCR (or microsatellite testing).<br>2. ECOG performance status 0-1 and patient eligible for planned curative surgery<br>a. Radiological node positive T1-4 CRC<br>OR<br>b. high risk T3 defined as EITHER ≥5mm of extramural depth of invasion OR unequivocal EMVI on imaging (regardless of depth)<br>OR |

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| | T4 disease<br>3. Patients with rectal cancer are eligible if neoadjuvant chemo-radiotherapy is not required to achieve a R0 resection.<br>4. Patients with acute colonic obstruction may enter the trial only after obstruction is relieved by a successful defunctioning stoma/stent<br>5. Adequate bone marrow function<br>6. Adequate renal function<br>7. Adequate liver function<br>8. Adequate coagulation<br>9. Aged ≥18 years<br>10. Able and willing to provide written informed consent<br>11. Willing to use highly effective contraception for the duration of trial treatment and for 120 days after the last dose of pembrolizumab<br>*Exclusion criteria:*<br>1. Any patient for whom radiotherapy is advised by the MDT<br>2. Strong evidence of distant metastases or peritoneal nodules (M1)<br>3. Prior therapy with an anti-PD-1, anti-PD-L1 or anti-PD-L2 agent<br>4. Any systemic anti-cancer therapy/investigational agents within 4 weeks prior to registration<br>5. Received a live vaccine or live-attenuated vaccine within 30 days prior to registration. Administration of killed vaccines is allowed<br>6. Any investigational agents or investigational devices within 4 weeks prior to registration<br>7. Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of pembrolizumab<br>8. Concurrent/previous malignancy that could compromise assessment of primary or secondary endpoints of the trial<br>9. Active CNS metastases and/or carcinomatous meningitis<br>10. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.<br>11. Previous severe/life-threatening skin adverse reaction with other immune-stimulatory anticancer agents<br>12. Active autoimmune disease that has required systemic treatment in past 2 years<br>13. History of (non-infectious) pneumonitis/interstitial lung disease that required steroids, or current pneumonitis/interstitial lung disease<br>14. Active infection requiring systemic therapy<br>15. Known history of HIV<br>16. Known hepatitis B or C infection<br>17. Known history of active TB (Mycobacterium tuberculosis)<br>18. Allogenic tissue/solid organ transplant.<br>19. Peritonitis (secondary to perforated tumour)<br>20. Has colonic obstruction that has not been defunctioned or stented<br>21. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's |

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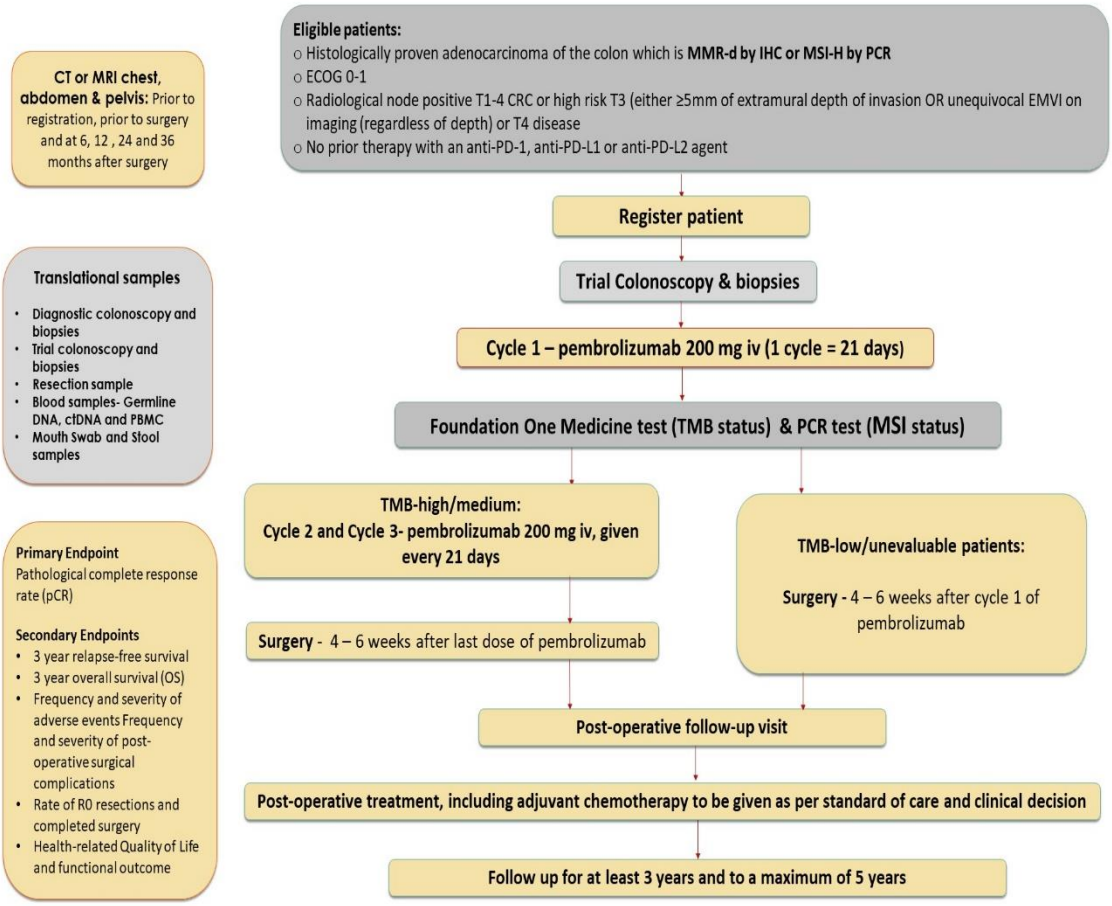
| | participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.<br>22. Known psychiatric or substance abuse disorder that would interfere with the patients ability to cooperate with the requirements of the study.<br>23. Women who are pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial<br>Refer to section 6.2 for full details of eligibility criteria |
| **Number of sites:** | **5** |
| **Treatment summary:** | All patients will receive one cycle of pembrolizumab 200 mg iv, then the following, according to TMB status:<br>TMB-high/medium:<br>• 2 further cycles of pembrolizumab 200 mg iv, given every 21 days<br>• Surgery 4 – 6 weeks after day 1 of the final cycle of pembrolizumab<br>TMB-low/unevaluable patients:<br>• Surgery 4 – 6 weeks after day 1 of the final cycle 1 of pembrolizumab<br>Post-operative treatment, including adjuvant chemotherapy to be given as per standard of care and clinical decision. |
| **Duration of recruitment:** | 2 years |
| **Duration of follow up:** | Patients will be followed up for at least 3 years from the date of surgery and to a maximum of 5 years |
| **Definition of end of trial:** | The study will end after the last patient on trial has completed 3 years of follow-up. |

## 1.2. Trial Schema



# 2. INTRODUCTION

## 2.1. Background

Colorectal cancer (CRC) is the 2nd to 3rd most common malignant disease in developed countries, with approximately 130,000/42,000 new cases and 50,000/16,000 deaths in the USA [1] and UK (CR UK 2016) respectively. There are one million new cases and 500,000 deaths worldwide each year. The primary treatment for early stage CRC is resectional surgery, which is possible in 80% of patients. Localised stage CRC is diagnosed in 39% of patients, for which the 5-year survival rate is 90%. The survival rate declines to 71% and 14% for patients diagnosed with regional lymph node and distant-stage disease, respectively. Even after curative intent surgery up to half of patients subsequently develop incurable recurrent disease. Adjuvant fluorouracil-based combination chemotherapy has been proven to produce a moderate but persistent improvement in survival for patients with stage III (node-positive) CRC as demonstrated in the MOSAIC (NCT00275210) and IDEA trials [2] . There is also good evidence from the QUASAR1+2 study meta-analysis [3] that chemotherapy in stage II (node-negative) disease reduces the risk of recurrence and death from CRC. Pooled analysis of 7 adjuvant chemotherapy studies (ACCENT) [4] showed that for patients with Stage 3 MMR-d CRC, there was significantly longer survival to first relapse. However, patients with tumours which were BRAF mutated and MMR-d, had T4/N2 disease or were poorly differentiated, did significantly worse [5].

### 2.1.1. MMR deficient Colorectal Cancer

15% of all colorectal cancer cases harbour mismatch repair deficiency (MMR-d) (comprising of 12% sporadic and 3% are hereditary cases). Amongst sporadic MMR-d colorectal cancer, the majority (~80%) are due to methylation of the MLH1 gene promoter. Sporadic MMR-d tumours are also often associated with BRAF gene mutations, reflecting their origin from sessile serrated polyps [6]. In early stage non-metastatic disease, MMR-d colorectal cancer is associated with reduced rates of recurrence and improved survival [7] [8]. Indeed ~4% of all metastatic colorectal cancer cases are MMR-d, but in metastatic disease MMR-d is, paradoxically, associated with poor survival, possibly driven by BRAF mutation [9].

Around 3% of MMR-d CRC are due to Lynch syndrome (previously known as hereditary non-polyposis colorectal cancer or HNPCC). In Lynch syndrome over 70% of cases are due to germline mutations in the genes MLH1 and MSH2 and the remainder occur in the genes PMS2 and MSH6 [10]. A small number of Lynch syndrome cases are due to mutations in the gene EPCAM which is immediately upstream of MSH2 and deletions in the 3' end of EPCAM results in epigenetic methylation of MSH2 [11] [12].

MMR-d tumours accumulate errors during DNA replication, in particular at repeat sequences called microsatellites which are prone to replication slippage. This leads to high microsatellite instability (MSI-H) and frequent indel (insertion deletion) mutations at microsatellite loci. Importantly, whilst microsatellite erosion within non-coding regions is generally silent and used only as a marker to detect the presence of MSI, indels at coding microsatellites result in frameshift mutations leading to generation of abnormal peptides. Some of these abnormal

peptides (neoantigens) will be processed and presented on HLA class I (human leucocyte antigen) molecules on the cancer cell surface leading to recognition and killing by T cells.

Intensive research is underway to understand the complex interplay between tumour, the immune system and host microenvironment. Such work has identified high tumour mutation burden [13] [14] and increased proportion of clonal neoantigens [15] as positive predictors of immunotherapy response. However, the molecular mechanisms of immune recognition and evasion in the context of an evolving tumour microenvironment are not fully understood. As MMR-d tumours evolve they continuously produce neoantigen peptides and the immune system may sculpt the tumour by removing clones recognised as foreign. The evolution of these tumours may therefore be a fine balance between selection of growth promoting and immune evasive mutations. A greater understanding of tumour-immune interactions at clonal resolution may lead to improved predictive biomarkers or therapeutic targets for immune based treatments.

### 2.1.2. The molecular heterogeneity of MMR-d/MSI-High CRC

The molecular landscape of MSI-H tumours has been analysed using whole exome and genome sequencing data from the TCGA (The Cancer Genome Atlas) [16] [17]. The heterogenous biology of cancers lead to a range of tumour mutation burden (TMB) [18], which may contribute to variable clinical benefit of Pembrolizumab. Less is known about mechanisms of resistance to Pembrolizumab in MSI-H CRC patients who have a high TMB due to defective mismatch repair [19] [20]. Amongst MSI-H colorectal cancers, exonic MSI events range from fewer than 10/MBp in some tumours to >100/MBp in others. MSI burden thus forms a continuous rather than discrete variable [17]. This leads to the possibility that additional secondary events may influence mutation burden and pattern in MSI-H tumours.

MSI event frequency has been found to correlate positively with microsatellite length, but even when microsatellite length is accounted for certain coding microsatellites are recurrently mutated [16]. This finding suggests positive selection at these loci. Previous work has identified recurrent frameshift mutations at coding microsatellites specific to each MSI tumour type. In MSI-H colorectal cancer recurrent microsatellite frameshift events occur in the genes ACVR2A, TGFBR2, JAK1, RNF43, MLL3, RPL22, APC, ASTE1, SLC22A9. Notably, frameshift inactivation of mismatch repair genes MSH6 (27%) and MSH3 (30%) are also frequently reported, as well as genes involved in other DNA repair pathways e.g. RAD50 and ATR. A further TCGA analysis focussing on immune evasion and recognition identified recurrent MSI events in genes involved in antigen presentation (B2M, TAP2, other HLA class I genes, NLRC5) and WNT signalling pathways [21]. Upregulation of WNT signalling (e.g. through APC mutations) was associated in this study with T-cell exclusion.

### 2.1.3. Immunotherapy for MMR-d/MSI-High Colorectal Cancer

Clinical trials using immune checkpoint inhibitors have demonstrated excellent results in advanced MMR-d/ MSI-H colorectal cancer. Single agent anti-PD1 therapy with either Pembrolizumab [22] [23] or Nivolumab +/- Ipilimumab [24] demonstrated response rates of between 30-40% in advanced pre-treated MSI-H colorectal cancer [25] [24]. The phase III KEYNOTE 177 trial [26] has recently showed Pembrolizumab provided a statistically significant and clinically meaningful improvement in progression-free-survival versus chemotherapy as

first-line therapy for MMR-d or MSI-H metastatic colorectal cancer. Combination immunotherapy with Ipilimumab (anti-CTLA4) and Nivolumab demonstrated a response rate of 55% and progression free survival rate of 71% at 12 months [24]. These data are clearly impressive, but there remains a significant proportion of patients (50-70%) with MMR-d tumours who do not appear to respond to immunotherapy. The reason for this heterogeneity of response urgently requires further investigation to understand the biology leading to resistance.

The benefits of neoadjuvant CPI are evident with enhanced local and systemic anti-tumour responses seen from neo-adjuvant CPI in both melanoma [27] [28] and in glioblastoma [29]. The Phase 3 FOXTROT [30] and Phase II PRODIGE 22 [31] trials have shown that neoadjuvant chemotherapy is safe and downstages radiologically determined High Risk Stage 2 and Stage 3 CRC. Preoperative compared to postoperative chemotherapy is more or equally effective in many other cancers, more tolerable, and has the potential to improve survival outcomes in colorectal cancer as well. However the benefits of neoadjuvant chemotherapy for MMR-d cancers may be limited. The FOXTROT trial [30] [32] showed no significant histopathological downstaging or difference in 2 year relapse free survival in 106 MMR-d tumours compared to 67 patients who had primary surgery. Although numbers are too small and follow up too short currently to determine differences in overall survival, there is not good evidence to offer neoadjuvant FOLFOX or CAPOX to patients with operable MMR-d bowel cancers. The NICHE trial [33] has recently demonstrated good downstaging and pathological complete response rate of operable stage 2 and 3 MSI-H bowel cancer with Nivolumab and Ipilimumab but long-term survival is unknown.

As evidenced above, the prognostic advantage of early stage MSI-H CRC is lost after recurrence or in *de novo* stage 4 CRC, so there is a pressing clinical need to maximize chance of cure in the earlier stages where prevalence of MMR-d is higher comprising approximately 12% of sporadic Stage 3 CRC and 20% of stage 2 CRC [34]. Although the ATOMIC (NCT02912559) and POLEM trials (NCT03827044) may demonstrate benefit of adjuvant checkpoint CPI, its efficacy is unclear in the context of micrometastatic disease without a supporting immune-competent microenvironment. Longitudinal studies especially in the neoadjuvant setting would be best to interrogate the changes seen after immunotherapy both in time and space.

### 2.1.4. Pembrolizumab – Pharmaceutical and Therapeutic background

Pembrolizumab is a potent humanised immunoglobulin G4 monoclonal antibody with high specificity of binding to the programmed cell death 1 (PD-1) immune checkpoint receptor thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® Pembrolizumab is indicated for the treatment of patients across a number of indications [35] [36] [37].

The PD-1/PDL-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-

lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [38] [39].

The structure of murine PD-1 has been resolved [40]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [39] [41] [42] [43]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [44] [45].

### 2.1.5. Rationale for the trial treatment arms

Pembrolizumab monotherapy has been rationally selected on the basis of early clinical data which demonstrates that CPI is clinically beneficial in terms of response rates in the metastatic setting [22] [26] [46] whether patients have a primary tumour *in situ* or not. Pembrolizumab monotherapy is less likely to cause significant early immunotherapy toxicity compared to CTLA-4 inhibitors and therefore safer to use in the neoadjuvant setting [27] [28]. Tumour mutation burden is an emerging biomarker for response and clinical benefit to immunotherapy but currently only based on phase 2 trials, or non randomised, retrospective studies. It remains a good biomarker to stratify therapy but remains exploratory especially in early stage MMR-d bowel cancer [47] [48].

The rationale behind giving only 1 cycle of Pembrolizumab to TMB low arm is based on data from the FOXTROT trial [30] which shows no clinical benefit of giving CAPOX or FOLFOX chemotherapy to MMR-d patients. There are no significant benefits of combining CAPOX with Pembrolizumab in a MSS mCRC patients regardless of TMB status. However as this population is a small cohort and the importance of TMB in operable CRC has not yet been proven, any benefits/changes due to Pembrolizumab would be safer and best explored with early surgery and provide cleaner translational data without additional chemotherapy effects.

### 2.1.6. The need for NEOPRISM-CRC trial

This is a Phase II Neoadjuvant Signal Seeking Stratified Trial of the efficacy of Pembrolizumab in MSI-H/MMR-d operable high risk Stage 2 or Stage 3 CRC to determine whether neoadjuvant Pembrolizumab improves pathological complete response rate and relapse-free survival. It has a comprehensive translational objective that runs in parallel. It will study the CRC genomic landscape, the evolutionary dynamics of intratumour heterogeneity over time combined with detailed clinical, histopathological and cancer phenotypic annotation for each patient, in order to significantly improve the outcomes of MSI-H CRC patients (e.g. reduce their chance of recurrence and improve survival). Biological samples will be taken at multiple time points during and following neoadjuvant treatment to understand the biology of CPI response of MSI-

H CRC and uncover clinically meaningful immunotherapy biomarkers in this patient population.

# 3. TRIAL DESIGN

This is a phase II neoadjuvant signal seeking, two-arm, non randomised and non blinded stratified trial of the efficacy of pembrolizumab in patients with MSI-H/MMR-d operable high risk Stage 2 or Stage 3 CRC.

## 3.1. Trial Objectives

### 3.1.1. Primary Objective

- To assess whether neoadjuvant pembrolizumab improves pathological complete response rate in patients with MSI-H/MMR-d, TMB high or medium with operable high risk Stage 2 or Stage 3 CRC.

### 3.1.2. Secondary Objectives

- To assess evidence of anti-tumour activity in terms of overall survival and relapse free survival
- To assess evidence of anti-tumour activity in terms of cancer-specific mortality and non-cancer specific mortality
- To assess the tolerability of the neoadjuvant therapies using NCI CTCAE v5.0 and patient-reported outcome measures
- To assess the nature and frequency of surgical complications
- To assess the rate of R0 resections and the rate of completed surgery at the planned timepoint
- To measure the impact of the treatments on patient's quality of life and resource usage

### 3.1.3. Exploratory Objectives

NEOPRISM-CRC is both an interventional trial and translational rich study in which a large amount of data are to be collected, covering personal and clinical characteristics, data throughout follow up from the time of baseline/surgery, genomics and all other laboratory results (using their blood and tissue samples), and data retrieved from patient medical records. This tissue resource will facilitate a wide range of subsidiary analyses using data that have already been collected from patients to link with translational studies.

Exploratory translational research objectives that may be included, but are not limited to:

- Does pembrolizumab significantly improve radiological and pathological downstaging compared to chemo for MSI-H/MMR-d High Risk Stage 2 or Stage 3 CRC, with a view to improved survival outcomes?
- Does pembrolizumab decrease perioperative toxicities by reducing the length and intensity of post-operative chemotherapy?
- Can there be optimal prediction of neoadjuvant CPI treatment response based on TMB patient stratification?
- Can CPI resistance mechanisms be revealed by exploring new somatic alterations and evolving microsatellite population diversity?

- Does detection of tumour-specific variants following CRC resection highlight patients at increased risk of reduced relapse-free survival (minimal residual disease biomarker)?
- Is ctDNA clearance following neoadjuvant treatment a surrogate biomarker of pCR response?
- Does non-invasive characterisation of immunotherapy resistance mechanisms and evolving microsatellite clonal diversity through tailored cell-free DNA enrichment strategies reveal tumour population dynamics in peripheral blood?
- Will Tracking T-cell receptor (TCR) evolution identify specific features of the tumour microenvironment (TME) associated with response and resistance
- Does blood TMB status accurately reflect tissue TMB status and associate with clinical outcome measures

Further examples of areas of research that may be explored include:

- Establishing the impact of neoadjuvant therapies on intratumour subclonal heterogeneity
- Determining the impact of evolving intratumour heterogeneity on treatment response and clinical outcome
- Assessing the relationship between genetic intratumour heterogeneity and the host immune response
- Developing analytical methods for determining phenotypic heterogeneity in relation to genomic heterogeneity
- Detection of active disease following neoadjuvant treatment through ctDNA and correlation with pathological measures of response for example complete pathological response in resection specimen (pharmacodynamic biomarker)
- Detection of minimal residual disease following resection of CRC as an indicator of reduced relapse free-survival (adjuvant biomarker).
- Establishing blood tumour mutation burden status and correlating to tissue tumour mutation burden status and clinical outcomes following PD1 therapy (therapeutic biomarker)
- Use of whole genome cell-free DNA sequencing coupled with multiplex-PCR enrichment strategies designed to identify novel somatic alterations and dynamic microsatellite clonal diversity occurring over time (population bottleneck followed by clonal expansion of resistant alleles)
- To track T-cell receptor evolution through therapy combined with high dimensional cytometry and unsupervised analysis
- Use of artificial intelligence image analysis techniques on histopathological and radiological material for development of predictive biomarkers

Samples will also be stored for use in future ethically and scientifically approved research in the UK or overseas. Optional consent will be taken from patients during informed consent.

## 3.2. Trial Endpoints

### 3.2.1. Primary Endpoint

- Pathological complete response rate (pCR) assessed as per guidance provided in the Lab Manual.

### 3.2.2. Secondary Endpoints

- 3 year relapse-free survival
- 3 year overall survival (OS)
- Frequency and severity of adverse events recorded continuously in relation to each treatment cycle graded using CTCAE criteria
- Frequency and severity of post-operative surgical complications
- Rate of R0 resections and completed surgery
- Health-related Quality of Life (QoL) and functional outcome

## 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(s), imaging, clinical care, follow up schedules and all requirements of the trial protocol
- Requirements of the UK Policy Framework for Health and Social Care Research, 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 eCRF completion timelines as per section 12.4 (Timelines for Data )
- Biological sample collection, processing and storage requirements
- Monitoring requirements, as outlined in protocol section 15 (Trial Monitoring and Oversight)

### 4.1.1. Selection of Principal Investigator and other investigators at sites

Each site must appoint an appropriate Principal Investigator (PI), i.e. a health care professional authorised by the site to lead and coordinate the work of the trial on behalf of a site. Co-investigators must be trained and approved by the PI. All PIs and co-investigators must be medical doctors and have experience of treating colorectal cancer (CRC). 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 plans to take a leave of absence UCL CTC **must be informed promptly.** For absences greater than three months, or where the PI is no longer able to perform his/her duties at the site, UCL CTC may terminate recruitment at the site. A new suitable replacement PI must be identified by the site and UCL CTC notified.

UCL CTC may terminate recruitment at a site where a suitable replacement PI has not been identified within three months.

### 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 two 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 on-site visit/ telephone or video conference. Re-initiating sites may be required where there has been a significant delay between initiation and enrolling the first patient.

### 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:

- 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)
- 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 a signed model Non-Commercial Agreement (mNCA) between the Sponsor and the relevant institution (usually an NHS Trust/Health Board) must be in place prior to site activation.

### 4.2.3. Site activation

Once the UCL CTC trial team has received all required documentation and the site has been initiated, notification of site activation 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 of eCRFs (including assessment of all adverse events)
- prompt notification and assessment of all serious adverse events
- 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 independent interpreter/NHS approved translator 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** must be allowed for the patient to consider and discuss participation in the trial.

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 medical 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 17 (Withdrawal of Patients).

# 6. SELECTION OF PATIENTS

## 6.1. Screening Log

A screening log must be maintained and appropriately filed at site. Sites should record each patient considered for the trial 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. 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' medical notes and on the registration CRF.

Patients must give written informed consent before any trial specific screening investigations may be carried out. Refer to section 9.1 (Pre-registration Assessments) for the list of assessments and procedures required to evaluate the suitability of patients prior to entry.

### 6.2.1. Inclusion criteria

1. Histologically proven adenocarcinoma of the colon or rectum which is MMR-d by IHC or MSI-H by PCR (or microsatellite testing).
2. Patient is fit (ECOG 0-1) and eligible for planned curative surgery in keeping with NICE guidelines and considered fit/suitable for adjuvant chemotherapy as per local site investigator's discretion based on:
   a) Radiological node positive T1-4 CRC

      or

   b) high risk T3 defined as EITHER ≥ 5mm of extramural depth of invasion OR unequivocal EMVI on imaging (regardless of depth)

      or

      T4 disease
3. Patients with rectal cancer are eligible if it is determined that neoadjuvant chemo-radiotherapy is not required to achieve a R0 resection.
4. Patients presenting with acute colonic obstruction may enter the trial only after obstruction is relieved by a successful defunctioning stoma/stent, and when recovered to a fitness level consistent with the other eligibility criteria
5. Adequate bone marrow function:
   - White Blood Cell >3.0 x $10^9$/L;
   - Absolute neutrophil count ≥1.5 x $10^9$/L

- Platelets ≥100 x $10^9$/L.
- Haemoglobin ≥90 g/L

  Note Anaemia (Hb <100 g/L) is not an exclusion, but should be corrected by transfusion prior to surgery and chemotherapy.

6. Adequate renal function:
   - GFR >50 mL/min estimated using validated creatinine clearance calculation (e.g. Cockroft-Gault)
   - **NB** If the calculated creatinine clearance is < 50 mL/min, a formal 24 hour urine collection or isotope clearance must be carried out demonstrating GFR ≥ 50 mL/min as per institutional standards
7. Adequate liver function:
   - Total bilirubin < 1.5 times Upper Limit of Normal (ULN) OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
   - AST and ALT ≤ 2.5 × ULN
8. Adequate coagulation:
   - International normalized ratio (INR) OR prothrombin time (PT) and Activated partial thromboplastin time (aPTT) ≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
9. Aged ≥18 years
10. Able and willing to provide written informed consent
11. Willing to use highly effective contraception for the duration of trial treatment and for 120 days after last dose of pembrolizumab

### 6.2.2. Exclusion criteria

1. Any patient for whom radiotherapy is advised by the MDT
2. Strong evidence of distant metastases or peritoneal nodules (M1)
3. 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 (e.g. CTLA-4, OX-40, CD137)
4. Prior systemic anti-cancer therapy including investigational agents within 4 weeks prior to registration.

   (NB: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline, with the exception of alopecia. Participants with ≤Grade 2 neuropathy may be eligible.)

   (NB: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.)
5. Has received a live vaccine or live-attenuated vaccine within 30 days prior to registration (seasonal flu vaccines that do not contain live virus are permitted). Administration of killed vaccines is allowed.

6. Any investigational agents or investigational devices within 4 weeks prior to registration

   Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

7. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (dosing exceeding 10mg daily of prednisone or equivalent), or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment

   Note: the use of physiologic doses of corticosteroids may be approved after consultation with UCL CTC.

8. Patients with concurrent or previous malignancy that could compromise assessment of the primary or secondary endpoints of the trial

9. Has known active CNS metastases and/or carcinomatous meningitis.

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

11. Has previous severe or life-threatening skin adverse reaction with other immune-stimulatory anticancer agents

12. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs).

    NB: Replacement therapy (e.g. levothyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is permitted.

13. History of (non-infectious) pneumonitis/interstitial lung disease that required steroids, or current pneumonitis/interstitial lung disease

14. Active infection requiring systemic therapy

15. Known history of Human Immunodeficiency Virus (HIV).

    NB: Testing for HIV for the NEOPRISM-CRC trial is not mandatory, however if this test has been done the result should be known prior to registration.

16. Known history of or is positive for hepatitis B (hepatitis B surface antigen [HBsAg] reactive) or known active hepatitis C (defined as hepatitis C virus [HCV] RNA [qualitative] is detected)

    Note: Without known history, testing is required to determine eligibility. Hepatitis C antibody testing is allowed for screening purposes in sites where HCV RNA is not part of standard of care.

17. Known history of active TB (Mycobacterium tuberculosis).

18. Has had an allogenic tissue/solid organ transplant.

19. Has peritonitis (secondary to perforated tumour)

20. Has a colonic obstruction that has not been defunctioned or stented

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

22. Known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.
23. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of pembrolizumab

## 6.3. Pregnancy and birth control

### 6.3.1. Definition of women of childbearing potential (WOCBP) and fertile men

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 or bilateral oophorectomy/salpingectomy
- Is not postmenopausal (a post-menopausal woman is a female who has not had menses at any time in the preceding 12 consecutive months without an alternative medical cause)
- Has not had premature ovarian failure confirmed by a specialist gynaecologist

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

### 6.3.2. Risk of exposure to trial treatment during pregnancy

The risk of exposure to trial treatment has been evaluated using the safety information available in the approved Investigator Brochure for pembrolizumab.

Overall, the trial treatment has been assessed as having an unknown risk of teratogenicity/fetotoxicity and genotoxicity. The current safety information for pembrolizumab states that no reproductive or developmental toxicity clinical studies have been conducted so far. The central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss. These results indicate a potential risk that administration of pembrolizumab during pregnancy could cause fetal harm, including increased rates of abortion or stillbirth. Therefore the trial treatment has been assessed as having a high risk of teratogenicity/fetotoxicity and genotoxicity. If any patient becomes pregnant during the study, pembrolizumab treatment must be discontinued and the clinician and patient should discuss the risks of continuing the pregnancy. Pregnant patients are excluded from the trial. If any patient or patient's partner becomes pregnant during the study, please refer to section 6.3.5.

### 6.3.3. Pregnancy testing

All female participants who are WOCBP must have a pregnancy test (serum or urine) within 7 days prior to registration. Repeat tests must be performed on cycle 1 day 1 and before each cycle of pembrolizumab, and during the pre-operative assessment. A final pregnancy test must be performed at the 3 month post-operative follow up assessment (120 days after last dose of pembrolizumab treatment administration). If a pregnancy urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

NB Additional pregnancy testing may be required for patients having adjuvant chemotherapy, which should be performed according to local site policy.

### 6.3.4. Contraceptive Advice

The method(s) of contraception used must be stated in the patient medical notes and eCRFs. The medical notes of male participants should include a statement that the female partner has been informed about contraception advice.

***Requirement for female patients:***

All female participants who are WOCBP must consent to use one of the following methods of highly effective contraception from the date of informed consent until 120 days from last treatment administration. Methods with low user dependency are preferable, particularly where introduced as a result of participation in the trial.

- combined (estrogen 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 subject.*

***Requirement for male patients:***

Due to the risk of genotoxicity and/or risk to the foetus from exposure to seminal fluid:

- Male patients (including those who have had vasectomies) must consent to use condoms with female partners who are WOCBP or are pregnant from informed consent until 120 days after last dose of pembrolizumab.

Male patients must also ensure that they advise their female partners who are WOCBP that they should in addition use a method of contraception as listed above for female patients.

### 6.3.5. Action to be taken in the event of a pregnancy

If a patient or the partner of a male trial patient becomes pregnant during the trial UCL CTC must be informed immediately (See section 13.6 Pregnancy for details on the reporting procedure). Trial treatment is strictly contraindicated in pregnant women.

***Female Patients:***

If a female patient becomes pregnant:

- 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).
- during treatment: the patient will be withdrawn from further treatment and, if they consent to pregnancy monitoring, followed up until 6 weeks after the end of the pregnancy.
- after the end of the treatment but during the pregnancy at-risk period: the patient will be followed up until 6 weeks after the end of the pregnancy if they consent to pregnancy monitoring.

***Male Patients:***

If a female partner of a male patient becomes pregnant or a pregnant female partner is exposed to trial treatment between the patient's informed consent and 120 days after the end of treatment, the male participant can continue with the trial whilst their female partner will be followed up if they have given consent to pregnancy monitoring.

### 6.3.6. Long Term Infertility

The effect of pembrolizumab on male and female fertility is unknown, therefore patients who wish to have children in the future should be given advice regarding sperm, oocyte and/or embryo cryo-conservation prior to treatment.

### 6.3.7. Lactation

It is not known whether pembrolizumab is excreted in human milk, therefore women who are breastfeeding are excluded from the trial.

# 7. REGISTRATION PROCEDURES

## 7.1. Registration

Patient registration will be undertaken by sites via a remote data capture system hosted by UCL CTC, 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 9.1 (Pre-registration Assessments).

Site staff responsible for patient registration must request access to the database by completing their contact details on the Database User Access Form and being assigned this responsibility on the site staff delegation log. Access to the database will be provided by UCL CTC.

Following pre-treatment evaluations, confirmation of eligibility and consent of a patient at a site, the registration form must be completed on the database. This will be used by UCL CTC to confirm patient eligibility. If further information is required UCL CTC will contact the person requesting registration to discuss the patient and request forms to be updated on the system.

Patients initials, age and sex are required to register a patient. Once eligibility has been confirmed the patient will be registered and a trial number will be assigned for the patient.

UCL CTC will e-mail confirmation of the patient's inclusion in the trial and their trial number to the PI, main contact and pharmacy. The trial number must be recorded in the patients notes.

Sites should contact UCL CTC if there are any difficulties in accessing the registration database.

| | |
|---|---|
| Trial Coordinator: | ctc.neoprism@ucl.ac.uk |
| Phone number: | 020 7679 9336 |
| 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
- Patient diary to record medications taken and side effects experienced. They must be reminded to bring this with them every time they visit the hospital

## 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

## 8.1. Investigational Medicinal Products (IMPs)

For the purpose of this protocol, the IMP for pre-operative neoadjuvant treatment:

- Pembrolizumab (provided free of charge for the trial)

### 8.1.1. Pembrolizumab

Pembrolizumab - 25 mg/mL vial; 100 mg vial

Dose: 200mg by IV infusion on Day 1 of each treatment cycle, every 3 weeks (Q3W).

Refer to Summary of Drug Arrangements for more details.

## 8.2. Treatment Summary

Patients should start treatment within 14 days of registration.

Patients will receive one of two pre-operative regimens depending upon their TMB status. All patients will have one cycle of pembrolizumab 200 mg IV (a cycle is 21 days).

Prior to cycle 2 the result of the FOUNDATIONONE®CDx test should be available and patients will continue their treatment as follows:

**TMB-high (defined as ≥20 mutations per Mb) or medium (defined as 6-19 mutations per Mb); FOUNDATIONONE®CDx (or MSI-H if FM1 test is not evaluable):**

- A further two cycles of pembrolizumab 200 mg IV every 21 days
- Planned surgery to remove the CRC 4 – 6 weeks after last dose of pembrolizumab

**TMB-low (defined as ≤5 mutations per Mb); FOUNDATIONONE®CDx (or if FM1 test and PCR are not evaluable)**

- Planned surgery to remove the CRC 4 – 6 weeks after last dose of pembrolizumab

Following surgical resection patients may receive post-operative chemotherapy in accordance with investigators clinical decision assessed on a case by case basis.

Figure 1: Pre-operative Trial Treatment Summary

| Pembrolizumab | | | | Surgery |
|---|---|---|---|---|
| Cycle | 1 | 2 | 3 | 4-6 weeks after last dose of pembrolizumab |
| Day | Day 1 | Day 22 | Day 43 | |
| TMB high/medium | x | x | x | x |
| TMB low patients/patients with non-evaluable PCR result | x | | | x |

## 8.3. Trial Treatment Details

### 8.3.1. Pembrolizumab

Pembrolizumab (MK-3475) vial (100mg/4ml per vial) sterile solution for IV infusion is manufactured by Merck Sharp & Dohme Ltd (MSD) and supplied for the NEOPRISM-CRC trial.

Pembrolizumab is currently licensed in the UK, but it is not licensed for the treatment of operable MSI High colorectal cancer.

Pembrolizumab 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.

**Pembrolizumab Drug Supply**

Pembrolizumab will be supplied for the NEOPRISM-CRC trial, via Sharp Clinical Services. Upon activation UCL CTC will arrange for an initial supply of pembrolizumab to be delivered to the pharmacy at Site. Re-ordering of pembrolizumab will be carried out by the Site by completing an order form, which should then be emailed directly to Sharp Clinical Services. **Sites should allow at least 5 working days from ordering to delivery of drug.** Further details on drug supply are available in the Summary of Drug Arrangements.

**Administration of pembrolizumab**

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Treatment may be administered up to 3 days before or after the scheduled day 1 of each cycle. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e. infusion time is 30 minutes: -5 min/+10 min).

## 8.4. Dose modifications

Pembrolizumab dose reductions are **not permitted**. Pembrolizumab treatment may be interrupted or discontinued due to toxicity.

A delay of pembrolizumab treatment of up to 3 weeks is acceptable in the case of medical/surgical events, or logistical reasons not related to trial treatment (e.g. elective surgery, unrelated medical events, patient holiday).

If pembrolizumab is delayed for more than 12 weeks for an adverse event, the patient should be withdrawn from treatment (unless clear clinical benefit is demonstrated; these cases must be discussed with UCL CTC).

## 8.5. Management of Adverse Events

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic aetiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment.

If a patient experiences an AE of Special Interest between informed consent and 30 days after the end of treatment, the site must inform UCL CTC immediately (see section 13 (Pharmacovigilance) for details on the reporting procedure).

Exceptional circumstances to following the dose modification tables below may be considered after consultation with UCL CTC.

The following general guidance should be followed for management of adverse events (AEs).

1. AEs should be graded according to the NCI Common Terminology Criteria for Adverse Events version 5 (CTCAE v5).
2. Dose reductions are not permitted for pembrolizumab however delays and discontinuations are required for management of adverse events (see table 1 below)
3. Treat each AE with maximum supportive care, including withholding administration of treatment where required.
4. Where several AEs with different grades or severity occur at the same time, the dose modifications applied should be the greatest applicable.
5. All treatment delays should be documented with clear reasoning in the medical notes.
6. A second occurrence of any grade 3 AE should result in the patient being withdrawn from treatment (unless clear clinical benefit is demonstrated; these cases must be discussed with the sponsor).
7. If pembrolizumab is delayed for more than 12 weeks for an adverse event, the patient should be withdrawn from treatment (unless clear clinical benefit is demonstrated; these cases must be discussed with the sponsor).
8. Severe life-threatening infusion related AEs (irAEs) should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if infusion related AEs are not controlled by corticosteroids.
9. 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.
10. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
11. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

**Table 1: Guidelines for withholding or discontinuation of pembrolizumab**

### 8.5.1. Management of Diarrhoea/Colitis

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

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

Corticosteroids should be administered for all grade ≥ 2 events.

| Grade | Management |
|---|---|
| 2 | Delay until recovery to grade 0/1<br>Administer oral corticosteroids; when symptoms ≤ grade 1 taper corticosteroid use over at least 4 weeks<br>**Discontinue treatment if:**<br>Grade 2 for >12 weeks<br>OR<br>Cannot reduce corticosteroid to ≤10mg daily of prednisolone or equivalent |
| 3 | Delay until recovery to grade 0/1<br>Administer intravenous corticosteroids followed by high dose oral corticosteroids; when symptoms ≤ grade 1 taper corticosteroid use over at least 4 weeks<br>**Discontinue treatment if:**<br>Grade ≥ 2 for >12 weeks<br>OR<br>Cannot reduce corticosteroid to ≤10mg daily of prednisolone or equivalent |
| 4 | **Discontinue treatment**<br>Administer intravenous corticosteroids followed by high dose oral corticosteroids |

| CTCAE Term | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Abdominal Pain | Mild pain | Moderate pain; limiting instrumental ADL | Severe pain; limiting self care ADL | - |
| Colitis | Asymptomatic; clinical or diagnostic observations only; intervention not indicated | Abdominal pain; mucus or blood in stool | Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs | Life-threatening consequences; urgent intervention indicated |
| Diarrhoea | Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline | Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline | Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL | Life-threatening consequences; urgent intervention indicated |

### 8.5.2. Management of Pneumonitis

Patients should be monitored for signs and symptoms of pneumonitis and if suspected, evaluation with radiographic imaging to exclude other causes is recommended. Corticosteroids should be administered for all grade ≥ 2 events.

Prophylactic antibiotics should be added for opportunistic infections in the case of prolonged corticosteroid administration.

| Grade | Management |
|---|---|
| 2 | *First occurrence:*<br>Delay until recovery to grade 0/1<br>Administer systemic corticosteroids; when symptoms ≤ grade 1 taper corticosteroid use over at least 4 weeks<br>**Discontinue treatment if:**<br>Grade 2 for >12 weeks<br>OR<br>Cannot reduce corticosteroid to ≤10mg daily of prednisolone or equivalent |
| 2 | *Second occurrence:*<br>**Discontinue treatment** |
| 3 or 4 | **Discontinue treatment**<br>Immediately treat with intravenous corticosteroids.<br>Administer additional anti-inflammatory measure as needed. |

| CTCAE Term | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Pneumonitis | Asymptomatic; clinical or diagnostic observations only; intervention not indicated | Symptomatic; medical intervention indicated; limiting instrumental ADL | Severe symptoms; limiting self care ADL; oxygen indicated | Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation) |

### 8.5.3. Management of immune related endocrinopathies

Hypophysitis, type 1 diabetes mellitus, diabetic ketoacidosis, hypothyroidism and hyperthyroidism may be observed in patients treated with pembrolizumab

***Type 1 diabetes mellitus or Hyperglycaemia***

Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria. Administer antihyperglycemic in participants with hyperglycemia

| Condition | Management |
|---|---|
| New onset type 1 diabetes mellitus (including diabetic ketoacidosis) | Delay until clinically and metabolically stable<br>Insulin replacement therapy recommended |
| Grade 3 or 4 hyperglycaemia, associated with ketosis or diabetic ketoacidosis | |

| | |
|---|---|
| | Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated haemoglobin, and C-peptide. Consider referral to endocrinologist. |

| CTCAE Term | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Hyperglycaemia | Abnormal glucose above baseline with no medical intervention | Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes | Insulin therapy initiated; hospitalization indicated | Life-threatening consequences; urgent intervention indicated |

***Hypophysitis***

Patients should be monitored for signs and symptoms of hypophysitis, including hypopituitarism and adrenal insufficiency and other causes excluded. Corticosteroids and other hormone replacement should be administered as clinically indicated.

| Grade | Management |
|---|---|
| 2 | Delay until recovery to grade 0/1<br>Treat with corticosteroids; when symptoms ≤ grade 1 taper corticosteroid use over at least 4 weeks; replace appropriate hormones as corticosteroid dose tapered<br>**Discontinue treatment if:**<br>Grade 2 for >12 weeks<br>OR<br>Cannot reduce corticosteroid to ≤10mg daily of prednisolone or equivalent |
| 3 or 4 | *Delay or discontinue (at the discretion of the treating investigator)*<br>*If delaying treatment:*<br>Delay until recovery to grade 0/1<br>Administer intravenous corticosteroids followed by oral corticosteroids; when symptoms ≤ grade 1 taper corticosteroid use over at least 4 weeks; replace appropriate hormones as corticosteroid dose tapered<br>**Discontinue treatment if:**<br>Grade ≥ 2 for >12 weeks<br>OR<br>Cannot reduce corticosteroid to ≤10mg daily of prednisolone or equivalent |

| CTCAE Term | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Adrenal insufficiency | Asymptomatic; clinical or diagnostic observations only; intervention not indicated | Moderate symptoms; medical intervention indicated | Severe symptoms; hospitalization indicated | Life-threatening consequences; urgent intervention indicated |

***Hyperthyroidism or Hypothyroidism***

Thyroid disorders can occur at any time during treatment. Patient should be monitored for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. Thyroid function and hormone levels should be monitored to ensure appropriate hormone replacement.

Hypothyroidism may be managed with replacement therapy without interrupting treatment with pembrolizumab.

**Hyperthyroidism**

| Grade | Management |
|---|---|
| 2 | Treat with nonselective beta-blockers (e.g. propranolol) or thionamides (e.g. carbimazole, propylthiouracil) as appropriate<br>**Continue treatment with pembrolizumab** |
| 3 | Delay until recovery to grade 0/1<br>Administer intravenous corticosteroids followed by oral corticosteroids; when symptoms ≤ grade 1 taper corticosteroid use over at least 4 weeks; replace appropriate hormones as corticosteroid dose tapered<br>**Discontinue treatment if:**<br>Grade ≥ 2 for >12 weeks<br>OR<br>Cannot reduce corticosteroid to ≤10mg daily of prednisolone or equivalent |
| 4 | **Discontinue treatment**<br>Administer intravenous corticosteroids followed by oral corticosteroids; when symptoms ≤ grade 1 taper corticosteroid use over at least 4 weeks; replace appropriate hormones as corticosteroid dose tapered |

**Hypothyroidism**

| Grade | Management |
|---|---|
| 2-4 | Treat with thyroid hormone replacement therapy, with levothyroxine or liothyronine as per standard of care. Monitor for signs and symptoms of thyroid disorders.<br>**Continue treatment with pembrolizumab** |

| CTCAE Term | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Hyperthyroidism | Asymptomatic; clinical or diagnostic observations only; intervention not indicated | Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL | Severe symptoms; limiting self care ADL; hospitalization indicated | Life-threatening consequences; urgent intervention indicated |
| Hypothyroidism | Asymptomatic; clinical or diagnostic observations only; intervention not indicated | Symptomatic; thyroid replacement indicated; limiting instrumental ADL | Severe symptoms; limiting self care ADL; hospitalization indicated | Life-threatening consequences; urgent intervention indicated |

### 8.5.4. Management of Deranged Liver Function

Patients should be monitored for changes in liver function, based on clinical evaluation and symptoms, and other causes excluded.

Corticosteroids should be administered for all grade ≥ 2 events, and based on severity of symptoms treatment with pembrolizumab withheld or discontinued.

| Grade | Management |
|---|---|
| 2 | Delay until recovery to grade 0/1<br>Treat with IV or oral corticosteroids; monitor liver function tests frequently (weekly or more frequently suggested) until returned to baseline values<br>**Discontinue treatment if:**<br>Grade 2 for >12 weeks<br>*Patients with liver metastases only:* ALT/AST grade 2 at baseline and ALT/AST increases by ≥ 50% relative to baseline for ≥ 1 week |
| 3 or 4 | **Discontinue treatment**<br>Treat with intravenous corticosteroids for 24 – 48 hours; when symptoms ≤ grade 1 taper corticosteroid use over at least 4 weeks |

| CTCAE Term | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Alanine aminotransferase increased | >ULN - 3.0 x ULN | >3.0 - 5.0 x ULN | >5.0 - 20.0 x ULN | >20.0 x ULN |
| Aspartate aminotransferase increased | >ULN - 3.0 x ULN | >3.0 - 5.0 x ULN | >5.0 - 20.0 x ULN | >20.0 x ULN |
| Blood bilirubin increased | >ULN - 1.5 x ULN | >1.5 - 3.0 x ULN | >3.0 - 10.0 x ULN | >10.0 x ULN |

### 8.5.5. Management of Nephritis/Renal Toxicity

Baseline GFR must be ≥50 mL/min for patients to be eligible for trial entry (estimated using validated creatinine clearance calculation e.g. Cockcroft-Gault or Wright formula).

Patients should be monitored for changes in renal function and other causes of renal dysfunction excluded. Consider referral to nephrology.

Corticosteroids should be administered for all grade ≥ 2 events, and based on severity of symptoms treatment with pembrolizumab withheld or discontinued.

| Grade | Management |
|---|---|
| 2 | Delay until recovery to grade 0/1<br>Treat with corticosteroids; when symptoms ≤ grade 1 taper corticosteroid use over at least 4 weeks<br>**Discontinue treatment if:**<br>Grade 2 for >12 weeks<br>OR<br>Cannot reduce corticosteroid to ≤10mg daily of prednisolone or equivalent |
| 3 or 4 | **Discontinue treatment** |

| | |
|---|---|
| | Treat with systemic corticosteroids; when symptoms ≤ grade 1 taper corticosteroid use over at least 4 weeks |

| CTCAE Term | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Creatinine increased | >1 - 1.5 x baseline; >ULN -1.5 x ULN | >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN | >3.0 baseline; >3.0 - 6.0 x ULN | >6.0 x ULN |

### 8.5.6. Management of Skin Reactions/ Exfoliative Dermatologic Conditions

Patients should be monitored for symptoms of severe skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) and other causes excluded. Corticosteroids should be administered based on the severity of symptoms and treatment with pembrolizumab withheld or discontinued as appropriate. Ensure adequate evaluation to confirm etiology or exclude other causes

| Grade | Management |
|---|---|
| Suspected SJS, TEN, or DRESS | Discontinue and refer to specialised unit for assessment and treatment.<br>Based on severity of AE administer corticosteroids. Ensure adequate evaluation to confirm etiology or exclude other causes |
| Confirmed SJS, TEN, or DRESS | Permanently discontinue<br>Based on severity of AE administer corticosteroids. Ensure adequate evaluation to confirm etiology or exclude other causes |

| CTCAE Term | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Stevens-Johnson syndrome | - | - | Skin sloughing covering <10% BSA with associated signs (e.g. erythema, purpura, epidermal detachment and mucous membrane detachment) | Skin sloughing covering 10 -30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment) |
| Toxic epidermal necrolysis | - | - | - | Skin sloughing covering ≥30% BSA with associated symptoms (e.g., erythema, purpura, or epidermal detachment) |

### 8.5.7. Management of Neurological Toxicities

Ensure adequate evaluation to confirm etiology and/or exclude other causes. Based on severity of AE administer corticosteroids

| Grade | Management |
|---|---|
| Grade 3 or 4 | Permanently discontinue |

### 8.5.8. Management of Infusion Reactions

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

In cases of suspected infusion related reactions patients should be evaluated to confirm aetiology and exclude other causes.

Corticosteroids should be administered based on the severity of symptoms and treatment with pembrolizumab withheld, dose reduced or discontinued as appropriate.

| Grade | Management |
|---|---|
| 1 | Increase monitoring of vital signs as medically indicated until medically stable in the opinion of the investigator |
| 2 | Stop infusion and monitor symptoms until recovery to grade 0/1; premedication required for next scheduled dose (e.g. Antihistamine and paracetamol, as per local practice)<br>Treat with corticosteroids and/or supportive care<br>**NB** if symptoms resolve within one hour of stopping infusion it may be restarted at 50% of original infusion rate.<br>**Discontinue treatment if:**<br>Toxicity persists despite adequate premedication |
| 3 | Withhold or discontinue based on the event.<br>Events that require discontinuation include, but are not limited to: encephalitis, other clinically important irAEs. |
| Recurrent 3 or 4 | **Discontinue treatment**<br>Treat with corticosteroids and/or supportive care |

| CTCAE Term | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Infusion related reaction | Mild transient reaction; infusion interruption not indicated; intervention not indicated | Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, opiates, IV fluids); prophylactic medications indicated for <=24 hrs | Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae | Life-threatening consequences; urgent intervention indicated |

### 8.5.9. Management of Myocarditis

In cases of myocarditis, corticosteroids should be administered based on the severity of symptoms and treatment with pembrolizumab withheld or discontinued as appropriate.

Ensure adequate evaluation to confirm etiology and/or exclude other causes. Consider referral to cardiology.

| Grade | Management |
|---|---|
| grade 1 | Delay until recovery to grade 0<br>Treat with corticosteroids |

| | |
|---|---|
| | **Discontinue treatment if:**<br>Grade 1 for >12 weeks<br>OR<br>Cannot reduce corticosteroid to ≤10mg daily of prednisolone or equivalent |
| grade 2, 3 or 4 | **Discontinue treatment**<br>Treat with corticosteroids and/or supportive care |

| CTCAE Term | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Myocarditis | | Symptoms with mild to moderate activity or exertion | Severe with symptoms at rest or with minimal activity or exertion; intervention indicated | Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support) |

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

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

| NCI CTCAE Grade | Treatment | Premedication at Subsequent Dosing |
|---|---|---|
| **Grade 1**<br>Mild reaction; infusion interruption not indicated; intervention not indicated | Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. | None |
| **Grade 2**<br>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.**<br>Additional appropriate medical therapy may include but is not limited to:<br>IV fluids<br>Antihistamines<br>NSAIDs<br>Paracetamol<br>Opiates<br>Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.<br>If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose.<br>**Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment** | Participant may be premedicated 1.5h (± 30 minutes) prior to infusion with:<br>Diphenhydramine 50 mg po (or equivalent dose of antihistamine).<br>Paracetamol 500-1000 mg po (or equivalent dose of analgesic). |
| **Grades 3 or 4**<br>Grade 3:<br>Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)<br>Grade 4:<br>Life-threatening; urgent intervention indicated | **Stop Infusion.**<br>Additional appropriate medical therapy may include but is not limited to:<br>Adrenaline**<br>IV fluids<br>Antihistamines<br>NSAIDs<br>Paracetamol<br>Opiates<br>Oxygen<br>Vasopressors<br>Corticosteroids<br>Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.<br>Hospitalization may be indicated.<br>**In cases of anaphylaxis, Adrenaline should be used immediately.<br>**Participant is permanently discontinued from further study drug treatment.** | No subsequent dosing |
| Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.<br>For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov | | |

## 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.

**Pembrolizumab**

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose).

Any overdose of pembrolizumab will be reported as follows:

- Any dose greater than 200 mg and less than 1000 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 13.4 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. Medication error/Investigational treatment error

A medication 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 medication error is an overdose, refer to section 8.6.1 Overdose above. Otherwise, medication errors should be reported on an incident report (see section 14.1). Any adverse events resulting from a trial treatment error should be reported as an SAE (see section 13.2.2 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 14.1).

## 8.7. Supportive Care

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 CRF.

NB Patients are permitted to receive COVID-19 vaccinations during treatment (these are not live vaccines), however, it is recommended patients should not receive pembrolizumab within 24 hours of having a COVID-19 vaccine.

## 8.8. Concomitant Medications

### 8.8.1. Medications/treatment NOT permitted

***Concurrent treatment with pembrolizumab***

Patients must not receive any chemotherapy, radiotherapy, biological therapy, immunotherapy or other investigational agents not specified in this protocol concurrently with pembrolizumab.

***Systemic glucocorticoids***

The use of systemic glucocorticoids should be avoided (see exclusion criteria 7 for those permitted), except in the management of adverse events described above (see section 8.4).

***Vaccines***

Vaccination with live vaccines, including measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG and typhoid must be avoided during treatment with pembrolizumab. 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.

NB. Patients are permitted to receive COVID-19 vaccinations during treatment (these are not live vaccines).

## 8.9. Pharmacy Responsibilities

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.

Refer to the Summary of Drug Arrangements document in the Pharmacy Site File for further details of pharmacy responsibilities, drug supply and drug accountability.

Pembrolizumab supplied for the Neoprism-CRC trial are for Neoprism-CRC patients only and must not be used outside the context of this protocol.

### 8.9.1. IMP accountability

The Pharmacy Lead must ensure that appropriate records are maintained.

These records must include accountability for pembrolizumab including: receipt, dispensing, returned medication, reconciliation and destruction of returned/unused medication (on sponsor authorisation). Accountability logs 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 15.2 (Centralised Monitoring).

### 8.9.2. Temperature Excursions

All temperature excursions at site outside the storage conditions specified in the IB/ Summary of Drug Arrangements document/labels 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 or faxed to +44 (0)20 7679 9871.

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

Please refer to Summary of Drug Arrangements document for information on reporting 'in-transit' temperature excursions.

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

| | | |
|---|---|---|
| **Pembrolizumab** | **Office hours**<br>09:00 to 17:00 Monday to Friday (excluding Bank Holidays)<br>**Contact**:<br>UCL CTC<br>020 7679 9241/9898 | **All other times**<br>Out of office hours<br><br>**Contact**:<br>MSD<br>0208 154 8000 |

Sites should use the out of office hours contact only once all other options have been explored (i.e. clinical management of emergency, following safety management guidance in protocol, IB, consulting with Chief Investigator, etc.). MSD cannot advise on clinical management of the patient but can only provide compound specific information.

## 8.11. Clinical Management after Treatment Discontinuation

If a patient discontinues trial treatment early, they will remain on trial for follow up purposes unless they explicitly withdraw consent. Also refer to sections 9 (Assessments) and 17 (Withdrawal of Patients) for further details regarding treatment discontinuation, patient withdrawal from trial treatment and withdrawal of consent to data collection.

# 9. ASSESSMENTS

| Schedule of assessments | Pre-operative Phase | | | | | | Resectional Surgery 4 – 6 weeks after last dose of pembrolizumab | Post-Operative phase | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening Phase (Before registration) Within 14- 21 days prior to registration | Pre-treatment | Trial Treatment period (Day 1 to Day 63) | | | Pre-op visit within 21 days prior to planned surgery | | Post-op Visit 28-35 days after surgery | Follow up 3 months after surgery (+/- 2 weeks) | Follow up[12] 6, 9, 12, 18, 24, 36 months after surgery (+/- 2 weeks) | Follow up after progression |
| | | | Cycle 1 Day 1 (+/- 3 days) | Cycle 2 Day 1 (+/- 3 days) | Cycle 3 Day 1 (+/- 3 days) | | | | | | |
| **Pembrolizumab (TMB high/medium patients)** | | | **X** | **X** | **X** | | | | | | |
| **Pembrolizumab (TMB low patients)** | | | **X** | | | | | | | | |
| **ADMINISTRATIVE PROCEDURES** | | | | | | | | | | | |
| **Informed Consent** | X | | | | | | | | | | |
| **Demographics and Medical History** | X | | | | | | | | | | |
| **Prior and Concomitant Medication Review (review patient diary)** | X | X[9] | | X | X | X | | X | X | | |
| **Survival Status** | | | | | | | | | X | X | X |
| **CLINICAL PROCEDURES** | | | | | | | | | | | |
| **Review Adverse Events(review patient diary[13])/ Adverse Reactions** | X | X[1] | | X | X | X | | X | X[7] | X | |
| **Quality of Life questionnaires** | X | | | | | X | | X | | | |
| **Full Physical Examination** | X | | | | | | | | | | |
| **Directed Physical Examination** | | X[1] | | X | X | X | | | X | X | |
| **Height (at screening only) and weight** | X | X[1] | | | X | X | | | X | X | |
| **12 Lead ECG** | X | X[1] | | | | X | | | | | |
| **ECOG Performance Status** | X | X[1] | | X | X | X | | X | | | |
| **Vital Signs (BP/HR/Temp)** | X | X[1] | | X | X | X | | | | | |
| **LOCAL LABORATORY ASSESSMENTS** | | | | | | | | | | | |
| **MMR/MSI status** | X | | | | | | | | | | |
| **FM1 TMB Status and PCR MSI status** | | | X | | | | | | | | |
| **Pregnancy Test – serum β-hcg** | X | X[9] | | X | X | X | | X | X | | |
| **coagulation** | X | X[1] | | | | | | | | | |
| **FBC with differential** | X | X[1] | | X | X | | | X | | | |
| **Biochemistry** | X | X[1] | | X | X | | | X | | | |
| **T3/FT3, FT4 and TSH** | X | X[1] | | X | | X | | X | | | |
| **CEA** | X | X[1] | | | X | X | | X | X | X | |
| **Urinalysis** | X | X[1] | | X | X | X | | | | | |
| **Virology (Hep B, Hep C, TB status)** | X | | | | | | | | | | |
| **CT Scan (+/-MRI)** | X | X[5] | | | | X | | | | X[4] | |

| Schedule of assessments | Pre-operative Phase | | | | | | Resectional Surgery 4 – 6 weeks after last dose of pembrolizumab | Post-Operative phase | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening Phase (Before registration) Within 14- 21 days prior to registration | Pre-treatment | Trial Treatment period (Day 1 to Day 63) | | | Pre-op visit within 21 days prior to planned surgery | | Post-op Visit 28-35 days after surgery | Follow up 3 months after surgery (+/- 2 weeks) | Follow up[12] 6, 9, 12, 18, 24, 36 months after surgery (+/- 2 weeks) | Follow up after progression |
| | | | Cycle 1 Day 1 (+/- 3 days) | Cycle 2 Day 1 (+/- 3 days) | Cycle 3 Day 1 (+/- 3 days) | | | | | | |
| **TNM8 staging** | | | | | | | | X | | | |
| **BLOOD AND TUMOUR COLLECTION** | | | | | | | | | | | |
| **Blood for Genetics (DNA and RNA)** | | X | | | | | | | | | |
| **Blood for ctDNA** | | X | | X | X | X | | X[11] | X | X | X |
| **Blood for PBMCs** | | X | | X | X | X | | X[11] | | | |
| **Oral swabs** | | X[10] | | X[8] | X[8] | X | | X | | | X |
| **Faecal samples** | | X[10] | | X[8] | X[8] | X | | X | | | X |
| **Diagnostic colonoscopy + biopsies** | X | | | | | | | | X[3] | X[3] | |
| **Trial Colonoscopy + biopsies** | | X | | | | | | | | | |
| **FM1 test (FFPE tumour biopsy)** | | X | | | | | | | | | |
| **PCR test to confirm MSI status (if not already done at screening)** | | X[6] | | | | | | | | | |
| **Tumour resection tissue** | | | | | | | X | | | | |
| **H&E slides** | | | | | | | | x | | | |
| **Tumour biopsy on progression**[2] | | | | | | | | | | | X[2] |

* Creatinine clearance or GFR calculated as per institutional standards

Notes:

[1] = pre-treatment assessments do not need to be repeated if done as part of the pre-registration assessments within 7 days of commencing C1D1.

[2] = Biopsy to be performed for consenting patients only and if there is accessible tumour. Biopsy should not be performed if thought not to be in the subject's best interest or if subject refuses.

[3] = Colonoscopy at 12 months and 36 months after surgery done as per site's local standard practice/patient individualised risk

[4] = Follow up CT scan or MRI (chest, abdomen & pelvis) should be done at 6, 12, 24 and 36 months post operatively. More frequent scanning can be done at PI discretion/institution guidelines or as per NICE guidance.

[5] = CT/ MRI repeated only if the pre-registration CT/MRI was performed >28 days prior to cycle 1 day 1 of pembrolizumab treatment.

[6] = PCR test to confirm MSI status to be done following trial colonoscopy only if PCR test not done at screening as part of diagnosis

[7] = Adverse events at 3 month follow up visit only, thereafter continue to assess adverse reactions for all follow up timepoints

[8] = Before day 1 of each cycle of pembrolizumab

[9] = Must be within 3 days prior to day 1 of each cycle of pembrolizumab

[10] = Must be collected prior to Trial colonoscopy

[11] = Blood samples for circulating biomarker analysis must be collected 4-6 weeks post-op visit

[12] = Patients should be followed up as per routine standard of care for additional 2 years after 36 months until the end of the trial

[13] = Patient diary should be reviewed at all visits up to 3 month follow up visit

## 9.1. Pre-registration Assessments

Patients must have histological confirmation of adenocarcinoma of the colon or rectum following diagnostic colonoscopy and biopsies, and confirmation of MMR-d status by IHC and/or MSI-H by PCR.

The following assessments or procedures are required to evaluate the suitability of patients for the trial. No trial-specific procedures or investigations may be performed prior to obtaining informed consent.

Within **21 days** prior to registration:

- CT or MRI chest, abdomen & pelvis confirming high risk T3N0M0, T4N0M0, or T1-4, node 1-2 M0 stage CRC

Within **14 days** prior to registration:

- Demographics, including family history of cancer
- Full medical history, including review of concomitant medications
- Quality of Life (QoL) questionnaires
- Full Physical examination, including height, weight and vital signs (blood pressure, pulse rate, temperature)
- 12 lead ECG
- Assessment of ECOG performance status (see Appendix 2)
- Haematology including Full Blood Count (with WBC differentials) and coagulation (PT/INR and APTT)
- Biochemistry: albumin, total bilirubin, calcium, creatinine, glucose, alkaline phosphatase, potassium, protein, sodium, ALT and/or AST, urea, magnesium
- Thyroid Function Tests (Free T3, Free T4, TSH)
- Serum CEA
- Urinalysis
- Renal function, estimated using a validated creatinine clearance calculation (e.g. Cockroft-Gault)

  **NB** If the calculated creatinine clearance is < 50 mL/min, a formal 24 hour urine collection or isotope clearance must be carried out demonstrating GFR ≥ 50 mL/min.
- Virology tests for hepatitis B & C (if not previously tested and results available)

Within **7 days** prior to registration:

- Pregnancy Test (urine or blood) in women of childbearing potential. **NB** If a urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required

## 9.2. Pre-treatment Assessments

The following samples should be collected as soon as possible after registration and prior to the Trial colonoscopy

- Oral swab for microbiome analysis (see section 11.3)

- Stool sample for microbiome analysis (see section 11.3)

The following samples should be collected within 14 days prior to start of pembrolizumab.

- Collection of biopsies via colonoscopy for FM1 test (FFPE Tumour biopsy)* and PCR test to confirm MSI status (if not already done)

*There is a 10 working day turnaround for TMB status (high/medium/low) result from the FM1 test so the result will be confirmed during cycle 1 of treatment.

The following samples for exploratory analysis should also be collected prior to cycle 1 day 1:

- Blood samples for circulating biomarker and germline analysis (see section 11.2)

## 9.3. Assessments during treatment (all patients)

**Patients must start treatment within 14 days after registration.** Any delay in starting treatment may be permitted under exceptional circumstances at the discretion of the treating investigator, but must be discussed with UCL CTC.

If the pre-registration CT/MRI was performed >28 days prior to cycle 1 day 1 of pembrolizumab treatment, the scan must be repeated.

The following assessments do not need to be repeated if they were done **within 7 days prior to start of pembrolizumab treatment** as part of the pre-registration assessments.

- Directed physical examination, including vital signs and weight
- 12 lead ECG
- ECOG performance status
- Haematology including Full Blood Count (with WBC differentials) and coagulation (PT/INR and APTT)
- Biochemistry: albumin, total bilirubin, calcium, creatinine, glucose, alkaline phosphatase, potassium, protein, sodium, ALT and/or AST, urea, magnesium
- Thyroid Function Tests (Free T3, Free T4, TSH)
- Urinalysis
- Renal function, estimated using a validated creatinine clearance calculation (e.g. Cockroft-Gault)

  **NB** If the calculated creatinine clearance is < 50 mL/min, a formal 24 hour urine collection or isotope clearance must be carried out demonstrating GFR ≥ 50 mL/min.
- Serum CEA
- Assessment of Adverse Events (review of patient diary)

Within **3 days prior** to start of pembrolizumab treatment:

- Concomitant medications (review of patient diary)
- Pregnancy test (urine or blood) in women of childbearing potential. **NB** If a urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Once the results of the FM1 test are available patients should be stratified accordingly. TMB high/medium patients will receive a further 2 cycles of pembrolizumab, TMB low patients will proceed directly to surgery.

NOTE: If FM1 test result fails patient will be stratified according to the result of the PCR test:

- PCR test for MSI shows patient is MSI-H - stratify as **TMB high/medium**
- PCR test for MSI shows patient is Microsatellite Stable (MSS) - stratify as **TMB low**

## 9.4. Assessments during treatment (TMB high/medium patients only)

The following assessments should be performed for TMB high/medium patients only **within 3 days** prior to Cycle 2 and Cycle 3 of pembrolizumab:

- Review of patient diary
- Review of concomitant medications
- Assessment of Adverse Events
- Directed physical examination, including vital signs (blood pressure, pulse rate, temperature) and weight (NB weight measured at cycle 3 only)
- ECOG Performance Status
- Pregnancy test (urine or blood) in women of childbearing potential. **NB** If a urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required
- Haematology including Full Blood Count (with WBC differentials)
- Biochemistry: albumin, total bilirubin, calcium, creatinine, glucose, alkaline phosphatase, potassium, protein, sodium, ALT and/or AST, urea, magnesium
- Thyroid Function Tests (Free T3, Free T4, TSH) (pre-cycle 2 only)
- Urinalysis
- Serum CEA (cycle 3 only)

The following research samples should be collected prior to cycle 2 and cycle 3 of pembrolizumab:

- Blood samples for circulating biomarker analysis (see section 11.2)
- Oral swab for microbiome analysis (see section 11.3)
- Stool sample for microbiome analysis (see section 11.3)

## 9.5. Pre-operative Assessments

The following assessments should be performed for all patients within 21 days prior to planned surgery:

- Review of patient diary
- Review of concomitant medications
- Assessment of Adverse Events
- Directed physical examination, including vital signs (blood pressure, pulse rate, temperature) and weight

- Quality of life (QoL) questionnaires
- 12 Lead ECG
- ECOG Performance
- Serum CEA
- Urinalysis
- Thyroid Function Tests (Free T3, Free T4, TSH)
- Pregnancy test (urine or blood) in women of childbearing potential. **NB** If a urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required
- CT or MRI scan (chest, abdomen & pelvis)

The following research samples should be collected prior to surgery (ideally aligned with the CT/MRI scan:

- Blood samples for circulating biomarker analysis (see section 11.2)
- Oral swab for microbiome analysis (see section 11.3)
- Stool sample for microbiome analysis (see section 11.3)

## 9.6. Surgery

Surgery is recommended to take place 4 – 6 weeks after day 1 of the final cycle of pembrolizumab.

The decision to proceed to surgical resection, is based on MDT review of the cross-sectional imaging before and after pembrolizumab treatment and clinical assessment.

The decisions concerning the planned surgical procedure should be made in keeping with standard practice and there are no prescriptive criteria for surgical resection of the primary tumour in this trial. It is however expected that resection of the tumour will be undertaken in the elective setting by a colorectal specialist.

The Surgery CRF will record the details of primary colorectal tumour resection including the type of surgical resection, method used, plane of surgical excision and whether there was macroscopic clearance of the tumour. Surgical and/or post-operative complications and length of hospital stay will also be recorded.

Any macroscopic residual primary colorectal tumour or equivocal areas should be both biopsied and recorded.

Post-operative morbidity will be assessed at the follow up time points.

## 9.7. Histopathology

### 9.7.1. Diagnostic colonic biopsy

Primary tissue will be obtained by colonoscopy. Multiple core biopsies will be obtained. At least 1 is required for confirmation of the MMR-d status. Any remaining diagnostic cores may be requested from sites for exploratory biological studies if there is sufficient tissue remaining.

### 9.7.2. Trial colonic biopsy

Primary tissue will be obtained by colonoscopy. Multiple core biopsies will be obtained. Four cores will be processed as per the Neoprism-CRC trial lab manual document and sent for FoundationOneCDx testing and MSI testing by PCR for stratification purposes. Please see section 10.2 of the protocol for more details. Remaining cores will be processed according to the Neoprism-CRC trial lab manual document for use in Exploratory research. In addition, diagnostic core biopsies collected at the time of diagnostic colonic biopsy and processed as per the Neoprism-CRC trial lab manual document should also be provided for use in exploratory research.

### 9.7.3. Resection specimen

Colonic resection specimens will be processed by the local pathologist to obtain sufficient material for routine diagnostic purposes. Separate multiple samples will be taken from the tumour and surrounding normal colon for translational research studies. These samples will be processed according to the lab manual.

H&E slides (usually 4-5 per patient) used to make the histological diagnosis of the primary tumour will be requested. See section 11.1.3 of the protocol and Neoprism-CRC trial lab manual document for more details.

### 9.7.4. Tumour biopsy at relapse

Biopsy to be performed if there is accessible tumour. Biopsy should not be performed if thought not to be in the subject's best interest or if subject refuses.

Detailed instructions on sample collection, processing, labelling and storage are provided in the Neoprism-CRC laboratory manual document and should be referred to in conjunction to this protocol.

## 9.8. Post-operative follow-up

The following assessments should be performed 28-35 days after surgery:

- Review of patient diary
- Review of concomitant medications
- Assessment of Adverse Events

- Quality of life (QoL) questionnaires
- ECOG performance status
- Haematology including Full Blood Count (with WBC differentials)
- Biochemistry: albumin, total bilirubin, calcium, creatinine, glucose, alkaline phosphatase, potassium, protein, sodium, ALT and/or AST, urea, ,magnesium
- Thyroid Function Tests (Free T3, Free T4, TSH)
- Serum CEA
- Pregnancy test (urine or blood) in women of childbearing potential. **NB** If a urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required
- Tumour Assessment by TNM8 Staging

The following research samples should be collected 4- 6 weeks following surgery:

- Blood samples for circulating biomarker analysis (see section 11.2)
- Oral swab for microbiome analysis (see section 11.3)
- Stool sample for microbiome analysis (see section 11.3)

## 9.9. Post-operative Chemotherapy

Patients may receive post-operative chemotherapy in accordance with investigators clinical decision, assessed on a case by case basis. Adjuvant chemotherapy should ideally start within 12 weeks after surgery, but patients with ongoing surgical complications requiring a longer recovery period may, start later at the discretion of the treating investigator.

Information on the type of chemotherapy, total number of cycles received, start and end dates will be collected in the electronic case report forms.

## 9.10. Assessments During Follow Up

Patients should be seen at 3, 6, 9, 12, 18, 24 and 36 months (+/- 2 weeks) after surgery. The following assessments should be performed:

- Review of patient diary (3 month follow up visit only)
- Review of concomitant medications (3 month follow up visit only)
- Assessment of Adverse Events (3 month follow up visit only)
- Assessments of Adverse Reactions (from 6 monthly follow up visit)
- Survival Status
- Directed physical examination
- Weight
- Serum CEA

- Pregnancy test (urine or blood) in women of childbearing potential (3 month follow up visit only (up to **120 days** after last dose of pembrolizumab)).
- CT scan or MRI (chest, abdomen & pelvis) should be done at 6, 12, 24 and 36 months post operatively. More frequent scanning can be done at PI discretion/institution guidelines or as per NICE guidance.
- Colonoscopy at 12 months and 36 months post surgery and/or as per standard practice

The following research samples should be collected at all follow-up visits:

- Blood samples for circulating biomarker analysis (see section 11.2)

For patients who received adjuvant chemotherapy, information on the type of chemotherapy, total number of cycles received and details of dose modifications and delays will be collected at the end of chemotherapy.

## 9.11. Follow up after 36 months

Once patients have completed follow up assessments in accordance with section 9.10 above, and in the absence of progression, they should continue to be followed up according to routine standard of care. An eCRF capturing routine data about the patient's health status and survival information should be completed annually.

## 9.12. Assessments after Disease Progression

- If disease relapse is confirmed, patients should continue to be followed up as per standard oncological care for patients with colorectal cancer.
- Patients should be re-consented if necessary to have access to tissue for exploratory analyses for the trial.
- Blood samples for circulating biomarker analysis (see section 11.2)
- Oral swab for microbiome analysis (see section 11.3)
- Stool sample for microbiome analysis (see section 11.3)

After documentation of disease progression patients should be followed up as per standard of care. A eCRF should be completed at 6 monthly intervals to capture survival information.

# 10. TISSUE SAMPLES FOR STRATIFICATION

## 10.1. Diagnostic colonic biopsy

At least one biopsy core should be obtained during the diagnostic colonoscopy for confirmation of MMR-d status by IHC. Additional tissue should be obtained for MSI test by PCR, if this is routinely performed at site.

## 10.2. Pre-treatment

### 10.2.1. FOUNDATIONONE®CDx test

The FOUNDATIONONE®CDx test will be taken from the trial colonic biopsy tissue following patient registration to the trial and prior to commencing cycle 1 of pembrolizumab. Molecular profiling with TMB read out (TMB high/medium/low) will be obtained within 10 working days of receipt of sample at the Foundation Medicine laboratory in Germany or United States. Results will be available prior to start of cycle 2 of pembrolizumab. Please refer to the Neoprism-CRC trial lab manual document for more details on sample collection, processing, storage and shipment of samples.

UCL CTC will email the site informing them of the patient's FOUNDATIONONE®CDx TMB result.

If there are any delays UCL CTC will contact the site to inform them of this.

If the FOUNDATIONONE®CDx fails or a result is not obtained and PCR test result for MSI shows tumour is MSI-H patients will be allocated the TMB high/medium arm; if PCR test results shows tumour is Microsatellite Stable (MSS) patients will be allocated to the TMB low arm.

Additionally if any mutations are detected that are deemed clinically relevant (e.g. BRCA 1 or 2 which could potentially be germline mutations), this information will be fed back to the Investigator at Site who should inform the patient of this in line with local policies and procedures, and according to the wishes expressed by the patient on the consent form.

### 10.2.2. MSI status on PCR

If sites do not routinely perform MSI tests using PCR biopsy tissue should be obtained and sent to UCLH laboratory according to the instructions in the Neoprism-CRC trial lab manual document .

# 11. EXPLORATORY BIOLOGICAL STUDIES

At the time of trial entry, patients will be consented to donate tissue, blood, oral and stool samples for exploratory biological studies. Consent for this will be mandatory for all patients.

Refer to the NEOPRISM-CRC laboratory manual in the Investigator Site File (ISF) for more details on sample collection, processing, storage and shipment of samples.

Samples will include the following.

## 11.1. Tissue sample collection

### 11.1.1. Archival Tumour Tissue

Tumour tissue obtained from the diagnostic colonoscopy may be requested from sites for exploratory biological studies, including multiregional sampling and genomic analysis of tumour heterogeneity.

### 11.1.2. New Tumour Tissue

**Pre-treatment**
Collection of fresh and FFPE tissue from colonic biopsies for FM1/TMB status as well as exploratory biological studies should be performed as per Lab Manual.
**Surgical resection**
Tumour tissue and normal tissue collected at surgical resection will be requested for multiregional sampling and genomic analysis of tumour heterogeneity.
**Disease relapse**
If a tissue biopsy of a local recurrent or metastatic site is collected, this should be provided for genomic analysis.

All tissue should be stored at site until requested.

### 11.1.3. H & E slides

All of the H&E slides (usually 4-5 per patient) used to make the histological diagnosis of the primary tumour will be requested, scanned into a digital archive at UCLH and then returned to sites. If preferred by the local pathology team, slides can be scanned at 40x to ndpi file format at site and the image files transferred to UCLH.

## 11.2. Blood samples

All patients will have blood taken for circulating biomarker assessment and germline analysis. This will include up to 590 mL of blood for the analysis of germline DNA (10 mL), ctDNA (up to 480 mL) and immunological analyses (up to 100 mL).

The following will be collected:

**Germline DNA**

10 mL blood to be collected at baseline only.

**Blood for ctDNA analysis**

40 mL blood to be collected at the each of the following timepoints:

- At baseline
- Pre cycle 2 (TMB high/medium patients only)
- Pre cycle 3 (TMB high/medium patients only)
- Pre-operative follow-up
- Post-operative follow-up
- All follow up timepoints to be taken alongside routine serum CEA
- At relapse

**Blood for immunological analysis**

20 mL blood to be collected at the each of the following timepoints:

- At baseline
- Pre cycle 2 (TMB high/medium patients only)
- Pre cycle 3 (TMB high/medium patients only)
- Pre-operative follow-up
- Post-operative follow-up

## 11.3. Tongue swabs/faecal sample for microbiome analysis

All patients will have oral swabs and stool samples obtained to examine the microbiome and evaluate its value for predicting treatment response.

For oral samples, patients should be asked to provide an oral sample using the tongue swap self collection kit provided. For stool samples, patients should be asked to provide a stool sample on Faecal Occult Blood (FOB) cards. Please refer to the NEOPRISM-CRC laboratory manual in the Investigator Site File (ISF) for more details on sample storage and shipment of samples.

Oral swab samples will be collected at the following timepoints:

- At baseline (prior to Trial colonoscopy)
- Pre cycle 2 (TMB high/medium patients only)
- Pre cycle 3 (TMB high/medium patients only)
- Pre-operative follow-up
- Post-operative follow-up
- Relapse

Stool samples will be collected at the following timepoints:

- At baseline (prior to Trial colonoscopy)
- Pre cycle 2 (TMB high/medium patients only)

- Pre cycle 3 (TMB high/medium patients only)
- Pre-operative follow-up
- Post-operative follow-up
- Relapse

# 12. DATA MANAGEMENT AND DATA HANDLING GUIDELINES

Data will be collected from sites using an eCRF (electronic case report form) created and maintained by UCL CTC. Data entered onto the eCRF must be verifiable from source data at site. Examples of source documents are hospital records, which include patient's medical notes, laboratory and other clinical reports etc.
An exception to source data requirements are AE causalities. AE causality can be entered directly on to the eCRF without any associated source data, provided the instructions on the eCRF are followed.

## 12.1.Entering data into the eCRF

The eCRF must be completed by site staff who have been appropriately trained, are listed on the site staff delegation log and authorised by the PI to perform this duty. Each authorised staff member will be issued 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.

The use of abbreviations and acronyms must be avoided.

## 12.2.Corrections to eCRF Forms

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.

## 12.3. Missing Data

To avoid the need for unnecessary data queries fields should not be left blank on the eCRF. If data is unavailable, please refer to the CTC eCRF Manual for Sites for information on how to indicate that data is "Not Done", Not Applicable", "Not Available" or "Not Known" (only use if every effort has been made to obtain the data).

## 12.4. Timelines for Data Entry

eCRF forms must be completed as soon as possible after a patient's visit. Eligibility and Registration forms must be completed for a patient to be registered onto the study. All other forms must be completed within **5 working days** of the patient being seen.

Sites that persistently do not return data within the required timelines may be suspended from recruiting further patients into the trial by UCL CTC and this may trigger a 'Triggered' monitoring visit. See section 15.3 (' 'Triggered' On-Site/Remote Monitoring) for details.

## 12.5. 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 at UCL CTC and queries raised where necessary. Further guidance on the process for handling data queries can be found in the CTC eCRF Manual for Sites.

# 13. PHARMACOVIGILANCE

## 13.1. 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 an IMP. 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 IMPs whether or not related to that IMPs. See section 13.2.1 for AE reporting procedures.

***Adverse Reaction (AR)***

All untoward and unintended responses to an IMPs related to any dose administered. A causal relationship between an IMPs 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 13.2.2 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 that meets all 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

See section 13.3 for reporting procedures for these events.

***Adverse Event of Special Interest (AESI)***

An AE that is of scientific and medical concern to the 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 13.4. See section 13.4 for reporting procedures for these events.

***Overdose, IMP or Occupational exposure***

Refer to section 8.6 for details on reporting of these events.

## 13.2. 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 pembrolizumab or surgery.

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

NB Events will be classified as related to pembrolizumab if evaluated as possibly, probably or definitely related by the investigator or sponsor.

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

### 13.2.1. Reporting of Adverse Events (AEs) and Adverse Reactions (ARs)

All adverse events that occur between informed consent and 3 months post surgery must be recorded in the patient medical notes and the trial CRFs.

All adverse reactions (i.e. related to pembrolizumab or surgery) that occur between start of treatment and the end of trial (see section 18.1 (End of Trial) for end of trial definition) must be recorded in the patient medical notes and the trial CRFs.

Those meeting the definition of a Serious Adverse Event (SAE) or Adverse Events of Special Interest must also be reported to UCL CTC using the trial specific SAE Report. Also see section 13.2.2 (Reporting of Serious Adverse Events (SAEs) and section 13.4 (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.

### 13.2.2. Reporting of Serious Adverse Events (SAEs) and Serious Adverse Reactions (SARs)

All SAEs that occur between the signing of informed consent and 3 months post surgery must be submitted to UCL CTC by email within **24 hours** of observing or learning of the event, using the trial specific SAE Report.

In addition, all SARs i.e. serious events the site investigator feel is related to pembrolizumab or surgery that occur between the start of treatment and the end of trial (see section 18.1 (End of Trial) for end of trial definition) 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 to UCL CTC within 24 hours**, 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 not related to pembrolizumab or surgery that occur more than **3 months** post surgery

  Note: this does not include pregnancy related events (see section 13.6)

- events that are only related to adjuvant chemotherapy
- disease progression (including disease related deaths)
- 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.neoprism@ucl.ac.uk**

***SAE Follow-Up Reports***

UCL CTC will follow up all SAE/SARs until resolution and until there are no further queries.

Sites must ensure any new and relevant information is provided to UCL CTC promptly. If an 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 the delay must be detailed in the SAE/SAR Report to avoid unnecessary queries.

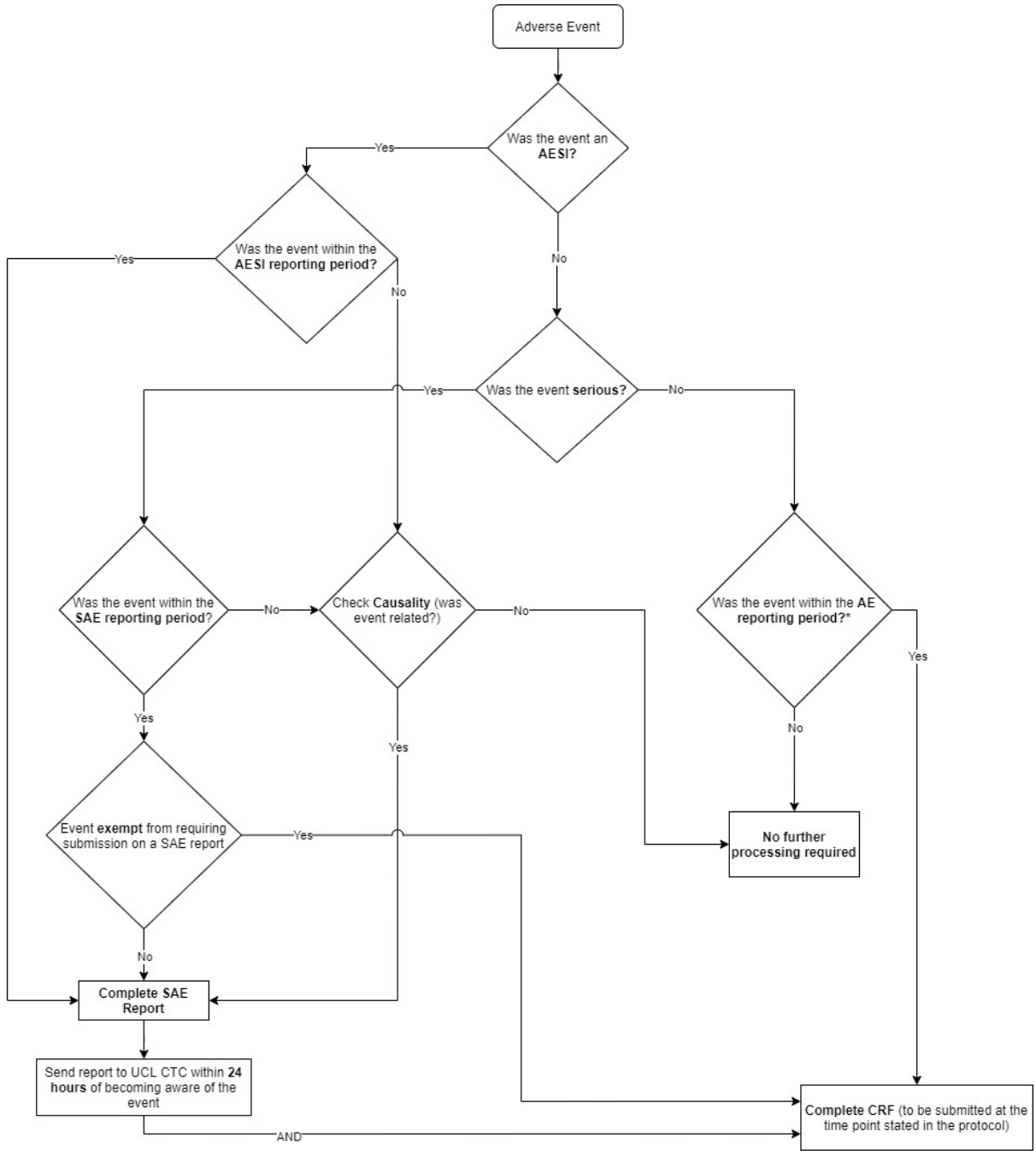
***SAE Processing at UCL CTC***

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 i.e. the list of expected adverse events in the IB for pembrolizumab.

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

UCL CTC will submit all SAE Reports to MSD according to the timelines outlined in the agreement between UCL and MSD.

### *SAE, AE and AESI Reporting Flowchart*




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

## 13.3. SUSARs

If an event related to pembrolizumab is evaluated as a Suspected Unexpected Serious Adverse Reaction (SUSAR), i.e. an unexpected event that is related (reasonable possibility) to pembrolizumab, 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 UK sites of any SUSARs that occur on the trial. Sites 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 PIs. These must be processed according to local requirements and filed with the applicable IB.

## 13.4. Adverse Events of Special Interest

An AE of Special Interest (AESI) is an event that is of particular interest to MSD, even if it does not meet the standard criteria for seriousness or it occurs outside the standard AE reporting timeframes for the trial. AESIs must be reported as SAEs (see section 13.2.2). Please note, if the event does not meet any seriousness criteria, please tick "Other medically significant" and state "AESI". The following adverse events of special interest for pembrolizumab must be reported from start of treatment to the end of the trial (see section 18.1 for end of trial definition). They must be reported on an SAE report within **24 hours of becoming aware of the event**.

- An overdose of pembrolizumab of ≥ 1000 mg (see also section 9.3.1)
- ALT/AST ≥ 3 x ULN **AND** bilirubin ≥ 2 x ULN **AND** alkaline phosphatase ≤ 2 x ULN

UCL CTC will process these reports in a similarly way to other SAE reports. However, it is only possible for AESIs that are serious to meet the criteria of SUSARs. Serious AESIs should therefore also be evaluated for a possible SUSAR as previously described.

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

**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.neoprism@ucl.ac.uk**

## 13.5. 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.

The IDMC will review the following trial safety data:

- Disease-related events (exempt from SAE reporting as per section 13.2.2) according to treatment allocation to identify whether disease-related events appear to be enhanced by pembrolizumab
- Line listing of adverse reactions to pembrolizumab to identify new adverse reactions;
- Incidence of AESIs as outlined in section 13.4 of the protocol

The IDMC and TMG will review trial safety data to identify:

- A higher incidence of rare serious adverse reactions than is stated in the RSI for pembrolizumab
- Trial related events or incidents that may lead to changes to the trial documents.

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.

## 13.6. Pregnancy

***Reporting Period***

For any pregnancy exposure to trial treatment, the site must submit a trial specific Pregnancy Report to UCL CTC by email within **24 hours of learning of its occurrence**.

A pregnancy exposure to trial treatment includes:

- Pregnancy in a trial patient
- Pregnancy in a partner of a male trial patient
- Exposure to treatment in a partner of a male trial patient who was pregnant at the start of the trial occurring between start of trial treatment and 120 days after last dose of pembrolizumab.

The site must request consent from the pregnant trial patient or pregnant female partner of a male patient to report information regarding a pregnancy using:

- For female patients: the trial-specific Informed Consent Form and Patient Information Sheet/the trial-specific Pregnancy Monitoring Information Sheet and Informed Consent Form for trial patients
- For female partners of male patients: the trial specific Pregnancy Monitoring Information Sheet and Informed Consent Form for partners of 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.neoprism@ucl.ac.uk**

***Pregnancy Follow-Up Reports***

For pregnant patients or partners who consent, their pregnancies must be followed-up **at least monthly** for up to 6 weeks after the end of the pregnancy (or later if there are ongoing issues) to collect information on any ante- and post-natal problems for both mother and child. If significant new information is received, follow-up Pregnancy Reports must be submitted to UCL CTC by email within **24 hours** of learning of the new information. In case of adverse outcome to the pregnancy 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 pregnancy SAE Report, according to SAE reporting procedures. Refer to section 13.2.2 (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 13.3 (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.

## 13.7. 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.

# 14. INCIDENT REPORTING AND SERIOUS BREACHES

## 14.1. Incident Reporting

Organisations must notify UCL CTC of all deviations from the protocol or GCP immediately. When an incident report is requested by UCL CTC, this should 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.

## 14.2. 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 subjects, 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).

# 15. 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 staff or its representatives will conduct all monitoring in compliance with the participant 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 to sites during initiation. The trial monitoring plan will be kept under review during the trial and updated information provided to sites as necessary.

## 15.1. 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 routine monitoring 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 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 12 Data Management and Data Handling Guidelines for details of how source documentation may 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.

## 15.2. 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 log, sample worksheets, sample inventory log and accountability logs. 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 determined for the trial. Checklists detailing the current version/date of version controlled documents will be provided by UCL CTC for this purpose.

## 15.3. '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 reasons 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.

## 15.4. 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, indication that dose interruption rules for pembrolizumab were not observed following an adverse reaction, etc.), 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 14 (Incident Reporting and Serious breaches) and 15.3 ( 'Triggered' On-Site/Remote Monitoring) for further details.

# 16. OVERSIGHT COMMITTEES

### 16.1.1. Trial Management Group (TMG)

The TMG will include the Chief Investigator, clinicians and experts from relevant specialties and NEOPRISM-CRC trial staff from UCL CTC. The TMG will be responsible for overseeing the trial. The group will meet regularly (up to 4 times per year) and will send updates to PIs (via newsletters or at Investigator meetings) and to the NCRI Colorectal Groups.

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.

A TMG charter, which outlines the responsibilities of the committee for the NEOPRISM-CRC trial, must be signed by members prior to their first meeting.

### 16.1.2. 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 and the Sponsor.

The NEOPRISM-CRC Trial will be reviewed by an established UCL CTC TSC that has oversight of a number of trials. All member have signed a TSC charter.

### 16.1.3. 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 periodically 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.

An IDMC charter, which outlines the responsibilities for the NEOPRISM-CRC trial, will be signed by all members prior to their first meeting.

### 16.1.4. 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 13 (Pharmacovigilance).

# 17. WITHDRAWAL OF PATIENTS

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

## 17.1. 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 medical notes and on the relevant Case Report Form(s). Reasons that a patient may not start treatment include:

- Deterioration in health
- Patient decision
- No longer eligible

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

## 17.2. Discontinuation of Trial Treatment

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

- Disease progression whilst on trial treatment
- Unacceptable toxicity
- Intercurrent illness that prevents further treatment
- Patient decision not to continue with trial treatment
- Any alterations in the patient's condition that justifies the discontinuation of treatment in the site investigator's opinion
- Non-compliance with the trial treatment and/or procedures
- If a female patient becomes pregnant or male/female fails to use adequate birth control (for patients of childbearing potential)

In these cases patients will remain on the trial for the purposes of follow-up and will be included in appropriate data analysis unless they explicitly withdraw consent to this.

If a patient expresses their wish to discontinue trial treatment, sites should explain the importance of remaining on trial follow-up, or of at least allowing routine follow-up data and data already collected to be used for trial purposes. If the patient gives a reason for wishing to discontinue trial treatment, this should be recorded.

The following eCRFs/data must be entered if a patient discontinues trial treatment early:

- Treatment Summary

- All CRFs up to an including the date of treatment discontinuation

Thereafter, unless the patient has withdrawn consent for data collection, the following should continue to be submitted:

- SAE reports
- Adverse event form(s)
- Follow up forms

## 17.3. Withdrawal of Consent

If a patient withdraws consent for any aspect of the study, UCL CTC should be notified and the Change of Status form should be entered on the trial database.

### 17.3.1. Withdrawal of consent for follow up

If a patient withdraws consent for trial follow up, but is happy to continue with future data Collection from hospital medical notes:

- They will remain on trial for follow up.
- The patient will no longer have trial-specific visits and assessments. Follow up forms should be completed based on the routine visit nearest the due date for the follow up form.
- The following CRFs/data must be entered at time of withdrawal:
  - Change of Status
  - All CRFs up to and including the date of withdrawal of consent
- Thereafter, the site should report AEs/SAEs as per section 12.2 and follow up forms, including notifications of relapse, death and second malignancy

### 17.3.2. Withdrawal of consent for data collection

If a patient explicitly states they do not wish to contribute further data to the trial their decision must be respected. The following CRFs must be entered at the time of withdrawal of consent:

- Change of Status
- All eCRFs up to and including the date of withdrawal of consent

Thereafter, no further data should be submitted, with the exception of SAE reports as per section 13.2 (due to the regulatory requirement for oversight of IMP safety)

### 17.3.3. Withdrawal of consent for use of samples

If a patient withdraws consent for the use of some, or all, of their samples in the trial, or for future research, this should be entered on the Change of Status form. Unless the patient has also withdrawn from trial treatment/follow up, management and data collection should continue as per protocol.

## 17.4. 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 the patient to be followed-up via the patient's 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 another participating site, the registering site remains responsible for submission of eCRFs.

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

At the time of loss to follow up, the following eCRFs should be entered:

- Change of Status
- All CRFs due up to and including the date of loss to follow up

If contact is re-established with the patient, further follow up forms should be sent, including notifications of relapse and second malignancy. A death form should also be submitted if the site becomes aware that the patient has died.

Prior to primary analysis and presentation/publication of the primary endpoint data, UCL CTC may/will ask sites to attempt to re-establish contact with patients who were lost to follow up and/or check hospital records for evidence of when the patient was last known to be alive and evidence of death, disease progression or second malignancies.

## 17.5. Loss of Capacity

Patients who lose capacity during the trial would continue in the trial for the purposes of data collection, if appropriate. If the patient regained capacity, an Investigator would discuss with the patient their continued participation in the trial and together, the patient and Investigator would decide what action, if any, to take.

# 18. TRIAL CLOSURE

## 18.1. End of Trial

For regulatory purposes the end of the trial will be after the last patient on trial has completed 3 years of follow-up. At this 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.

## 18.2. 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.

## 18.3. 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 16.1.2 Trial Steering Committee (TSC) and 16.1.3 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.

## 18.4. 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.

# 19. STATISTICS

## 19.1. Sample Size Calculation

In a population of 99 high risk Stage 2 or stage 3 CRC patients in the Phase 2 component of the Phase 3 FOXTROT trial [30], the observed complete pathological response rate with 3 cycles (6 weeks) of FOLFOX chemotherapy was 2% (2/99) and another 2% had marked tumour regression (2/99). Interim outcomes were reported at ASCO 2019 J Clin Oncol 37, 2019 (suppl; abstr 3504). In the Phase 2 NICHE trial of 7 MMR-d stage 2 or 3 CRC patients, the complete response rate with 2 cycles of Nivolumab and 1 cycle of Ipilimumab was 4/7 (57%). This trial is ongoing aiming to recruit 30 patients in the MMR-d arm NCT03026140.

In the NEOPRISM-CRC trial we assume that the complete pathological response rate with 3 cycles of pembrolizumab will be ≥ 33% for patients with high or medium TMB, and intend to rule out a percentage ≤10%. This would represent a clinically-relevant improvement compared to the pathological complete response rate observed from the interim Phase 2 data from the Phase 3 FOXTROT trial [30]. Using A'Hern's single-stage phase II design, with a one-sided 5% significance level and 80% power,19 patients are required in the high/medium TMB arm. The trial will be considered a success if at least 5 patients out of 19 have a complete pathological response rate after 3 cycles of pembrolizumab. It is therefore possible that the primary endpoint is reached before last patient out date.

At UCLH, we recently analysed the tumour mutation burden in a sample of 14 MMR-deficient mCRC patients using the FOUNDATIONONE® or FOUNDATIONONE®CDX profile. Of these patients, 12/14 (86%) had a high or medium TMB.

Using a conservative 70%/30% split in high/medium vs low/unknown TMB patients, and including an allowance for patient drop-off rate of 15% before reaching the primary endpoint (due to patient withdrawal of consent), 32 patients will need to be recruited into NEOPRISM-CRC.

While the trial is not powered to detect a specific response rate in the TMB low patients, their data will be reported descriptively for all endpoints and will add to the limited pool of information regarding the use of neoadjuvant immunotherapy in patients with low TMB.

## 19.2. Statistical Analysis

### 19.2.1. Analysis of main endpoint

All patients who receive at least one dose of pembrolizumab in Experimental Arm 1 (TMB high or medium) will be included in the safety population, which will be used for the analysis of the

primary (main) endpoint. Patients who do not proceed to surgery for reasons other than progression or complications on neoadjuvant therapy will be considered unevaluable for primary endpoint.

A pCR will be defined as having no residual cancer cells in the resected specimen. Patients who do not achieve pCR or who do not proceed to resectional surgery for any reason will be counted as non-responders.

The number and percentage of patients with pathological complete response will be presented with a 90% two-sided confidence interval.

### 19.2.2. Analysis of secondary endpoints and secondary analyses

The safety population defined for the primary endpoint will also be used for the analyses of the secondary endpoints.

Overall- and relapse-free survival

Overall survival (OS) is defined as the time from start of treatment to time of death from any cause. For patients who have not died, overall survival will be censored at the date of last contact. Relapse-free Survival (RFS) is defined as time from start of treatment to time of any signs or symptoms of the cancer or time of death from any cause. For patients who have not died or progressed, relapse-free survival will be censored at the date of last patient contact. OS and RFS will be presented using KM plots and 3-month, 6-month, 1-year, 2-year and 3-year OS and RFS rates will be estimated (with 95% confidence intervals). Median OS and RFS will also be reported with corresponding 95% confidence intervals if these are reached.

R0 resections

The incidence of resection types (R0, R1 and R2) will be presented in tables using frequencies, as well as the rate of surgery completed.

Surgical complications

The incidence of surgical complications will be described in tables by complication type/grade using frequencies. The Clavien-Dindo grading system will be used: https://www.baus.org.uk/patients/surgical_outcomes/grading_of_surgical_complications.aspx

Quality of Life

The EORTC QLQ-C30 and EuroQoL EQ-5D will be used.

Quality of Life (QoL) data will be analysed using methods for repeated measures (ANCOVA for analysis of change from baseline, and hierarchical models for more than two time points). Mean scores will be presented at each time point, as well as changes from baseline, for each category and overall.

Safety Reporting

All patients who received at least one dose of pembrolizumab will be included in the safety analysis. Adverse events (AEs) will be monitored on an ongoing basis and their frequencies reported. AEs will be categorized using the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. The worst event for each patient will be described. Both events related and unrelated to treatment will be captured and part of the reporting.

## 19.3. Interim Analyses

The study will be regularly monitored by UCL CTC, 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 received surgery following their treatment with pembrolizumab (at least one dose), 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 recommendation to stop the trial will be communicated to Trial Steering Committee (TSC).

# 20. ETHICAL AND REGULATORY CONSIDERATIONS

This trial will adhere to the conditions and principles of GCP as outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), as amended.

In conducting the trial, the Sponsor, UCL CTC and sites shall comply 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 Authority
- Human 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 Act 1968
- Medicines for Human Use (Clinical Trials) UK Regulations SI 2004/1031, and subsequent amendments
- Good Manufacturing Practice

## 20.1. 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 Yorkshire and the Humber – Leeds East 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.

## 20.2. 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.

## 20.3. 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.

## 20.4. Protocol Amendments

UCL CTC will be responsible for gaining ethical and regulatory approval, 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.

## 20.5. Patient Confidentiality & Data Protection

Patient identifiable data, including initials and age will be required for the registration process. 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 General Data Protection Regulation (EU)2016/679 (GDPR), with the Data Protection Officer at UCL.

Patient identifiable data, including initials will be provided to the central laboratories listed in section 11 in order to process and store the samples. All laboratories will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified.

# 21. SPONSORSHIP AND INDEMNITY

## 21.1. Sponsor Details

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

## 21.2. 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 not.

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.

# 22. FUNDING

MSD is supporting the central coordination of the trial through UCL CTC.

Research A and B costs will be reimbursed to sites as per the finance section of the site agreement .

# 23. PUBLICATION POLICY

All publications and presentations relating to the trial will be authorised by the TMG. Publication of the trial results will include named members of the TMG, meeting the three criteria of i) scholarship (contribution to the design execution and/or analysis and interpretation of the data, ii) authorship (participation in the drafting, reviewing and revising of the manuscript and iii) approval (approve the manuscript to be published). It is anticipated that this will include the Chief Investigator, Trial Coordinator, and Statistician involved in the trial. The TMG will form the basis of the writing committee and advise on the nature of publications. Data from all sites will be analysed together and published as soon as possible. Participating centres may not publish trial results prior to the first publication by the TMG or without prior written consent from the TMG. The trial data is owned by the TMG. The ISRCTN number allocated to this trial will be quoted in any publications resulting from this trial.

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# APPENDIX 1: ABBREVIATIONS

| | |
|---|---|
| **AE** | Adverse Event |
| **AESI** | Adverse Event of Special Interest |
| **ALT** | Alanine transaminase |
| **ANC** | Absolute Neutrophil Count |
| **AR** | Adverse Reaction |
| **AST** | Aspartate aminotransferase |
| **CEA** | Carcinoembryonic Antigen |
| **CI** | Chief Investigator |
| **CPI** | Checkpoint inhibition |
| **CR** | Complete Response |
| **CRC** | Colorectal Cancer |
| **CRF** | Case Report Form |
| **CT** | Computerised Tomography |
| **CTA** | Clinical Trial Authorisation |
| **CTCAE** | Common Terminology Criteria for Adverse Events |
| **DPA** | Data Protection Act |
| **DSUR** | Development Safety Update Report |
| **ECOG** | Eastern Cooperative Oncology Group |
| **EEA** | European Economic Area |
| **EMA** | European Medicines Agency |
| **EudraCT** | European Clinical Trials Database |
| **FBC** | Full Blood Count |
| **GDPR** | General Data Protection Regulation (EU)2016/679 |
| **GFR** | Glomerular Filtration Rate |
| **Hb** | Haemoglobin |
| **H&E** | Hematoxylin and eosin stain |
| **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 |
| **ISRCTN** | International Standard Randomised Controlled Trial Number |
| **IV** | Intravenous |
| **MMR-d** | Mismatch repair deficiency |
| **MRI** | Magnetic Resonance Image |
| **MHRA** | Medicines and Healthcare products Regulatory Agency |
| **MSI-H** | Microsatellite Instability High |
| **NCRI** | National Cancer Research Institute |
| **OS** | Overall Survival |
| **PD** | Progressive Disease |
| **PFS** | Progression Free Survival |
| **PI** | Principal Investigator |

| | |
|---|---|
| **REC** | Research Ethics Committee |
| **RFS** | Relapse free survival |
| **SAE** | Serious Adverse Event |
| **SAR** | Serious Adverse Reaction |
| **SD** | Stable Disease |
| **SPC** | Summary of Product Characteristics |
| **SUSAR** | Suspected Unexpected Serious Adverse Reaction |
| **TCR** | T-cell Receptor |
| **TMF** | Trial Master File |
| **TMG** | Trial Management Group |
| **TSC** | Trial Steering Committee |
| **UCL CTC** | CR UK and UCL Cancer Trials Centre |
| **U&E** | Urea and Electrolytes |
| **ULN** | Upper Limit of Normal |
| **WBC** | White Blood Cells |

# APPENDIX 2: EASTERN COOPERATIVE ONCOLOGY GROUP SCALE [49]

| ECOG Grade | ECOG Status |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair |

# APPENDIX 3: EXPECTED SURGERY RELATED ADVERSE EVENTS

**THE FOLLOWING AES ARE COMMONLY ASSOCIATED WITH SURGERY AND WILL BE CONSIDERED EXPECTED FOR THIS TREATMENT [50] [51]**

| Adverse Events | | |
|---|---|---|
| **GI motility complication**<br>Prolonged ileus<br>Bowel obstruction | Pneumonia | Anastomotic leak |
| Cardiorespiratory | Urinary | Venous thromboembolism |
| Readmission | Haemorrhage | Re-operation |
| **Infectious**: wound infection | | Mortality |

# APPENDIX 4: CLAVIEN-DINDO CLASSIFICATION

### Table 1: CLAVIEN-DINDO Classification of Surgical Complications

| Grade | Definition |
|---|---|
| Grade I | Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions.<br>Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside. |
| Grade II | Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included. |
| Grade III | Requiring surgical, endoscopic or radiological intervention. |
| Grade IIIa | Intervention not under general anaesthesia required. |
| Grade IIIb | Intervention under general anaesthesia required. |
| Grade IV | Life-threatening complications (including CNS complications)[1] requiring IC/ICU[2] management. |
| Grade IVa | Single organ dysfunction (including dialysis). |
| Grade IVb | Multi-organ dysfunction. |
| Grade V | Death of a patient. |
| Suffix "d" | If patient suffers from a complication at the time of discharge (see examples in Table 2). The suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication. |

[1] Brain haemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.

[2] CNS, central nervous system; IC, intermediate care: ICU, intensive care unit.

### Table 2: Clinical Examples of Complication Grades

| Grade | Organ System | Examples |
|---|---|---|
| Grade I | Cardiac | Atrial fibrillation converting after correction of $K^+$-levels |
| | Respiratory | Atelectasis requiring physiotherapy |
| | Neurological | Transient confusion not requiring therapy |
| | Gastrointestinal | Non-infectious diarrhoea |
| | Renal | Transient elevation of serum creatinine |
| | Other | Wound infection treated by opening of the wound at the bedside |
| Grade II | Cardiac | Tachyarrythmia requiring β-receptor antagonists for heart rate control |
| | Respiratory | Pneumonia treated with antibiotics on the ward |
| | Neurological | TIA[3] requiring treatment with anticoagulants |
| | Gastrointestinal | Infectious diarrhoea requiring antibiotics |
| | Renal | Urinary tract infection requiring antibiotics |
| | Other | Same as for Grade I but followed by treatment with antibiotics because of additional phlegmonous infection |
| Grade IIIa | Cardiac | Bradyarrhythmia requiring pacemaker implantation in local anaesthesia |
| | Neurological | See Grade IV |
| | Gastrointestinal | Biloma after liver resection requiring percutaneous drainage |

| Grade | Organ System | Examples |
|---|---|---|
| | Renal | Stenosis of the ureter after kidney transplantation treated by stenting |
| | Other | Closure of dehiscent non-infected wound in the OR[3] under local anaesthesia |
| Grade IIIb | Cardiac | Cardiac tamponade after thoracic surgery requiring fenestration |
| | Respiratory | Bronchopleural fistulas after thoracic surgery requiring surgical closure |
| | Neurological | See Grade IV |
| | Gastrointestinal | Anastomotic leakage after descendorectostomy requiring relaparotomy |
| | Renal | Stenosis of the ureter after kidney transplantation treated by surgery |
| | Other | Wound infection leading to eventration of small bowel |
| Grade IVa | Cardiac | Heart failure leading to low-output syndrome |
| | Respiratory | Lung failure requiring intubation |
| | Neurological | Ischemic stroke/brain hemorrhage |
| | Gastrointestinal | Necrotizing pancreatitis |
| | Renal | Renal insufficiency requiring dialysis |
| Grade IVb | Cardiac | Same as for IVa but in combination with renal failure |
| | Respiratory | Same as for IVa but in combination with renal failure |
| | Gastrointestinal | Same as for IVa but in combination with hemodynamic instability |
| | Neurological | Ischemic stroke/brain hemorrhage with respiratory failure |
| | Renal | Same as for IVa but in combination with hemodynamic instability |
| Suffix “d” | Cardiac | Cardiac insufficiency after myocardial infarction (IVa–d) |
| | Respiratory | Dyspnoea after pneumonectomy for severe bleeding after chest tube placement (IIIb–d) |
| | Gastrointestinal | Residual faecal incontinence after abscess following decendorectostomy with surgical evacuation (IIIb–d) |
| | Neurological | Stroke with sensorimotor hemisyndrome (IVa–d) |
| | Renal | Residual renal insufficiency after sepsis with multiorgan dysfunction (IVb–d) |
| | Other | Hoarseness after thyroid surgery (I–d) |

[3] TIA, transient ischemic attached; OR, operating room

# APPENDIX 5: PROTOCOL VERSION HISTORY

| **Protocol:** | | **Amendments:** | | |
|---|---|---|---|---|
| **Version no.** | **Date** | **Amendment no.** | **Protocol Section (no./title)** | **Summary of main changes from previous version.** |
| 1 | 30/07/2021 | N/A | N/A | N/A |
| 2 | 04/10/2021 | N/A | 9. Assessments | Clarified timeframe for patient diary collection in the schedule of assessments table, section 9.3 and section 9.10.<br><br>Clarified in the schedule of assessments table and section 9.11 that data collected for an additional 2 years after 36 months follow up will be routine data about patient's health status, collected during standard of care clinic visits. |
| | | | 20.1 Ethical Approval | REC name added |