

**Avelumab and hypofractionated Palliative radiotherapy in
metastatic soft-tissue sarcoma**

Short title:	APPLE study
Sponsor:	Royal Marsden NHS Foundation Trust
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PROTOCOL SIGNATURES

Investigator Signature:

I have read and agree to the protocol, as detailed in this document. I am aware of my responsibilities as an Investigator under the UK Clinical Trials Regulations¹, the guidelines of Good Clinical Practice (GCP) the Declaration of Helsinki (Appendix 2), the applicable regulations of the relevant NHS Trusts and the trial protocol. I agree to conduct the trial according to these regulations and guidelines and to appropriately direct and assist the staff under my control who will be involved in the trial, and ensure that all staff members are aware of their clinical trial responsibilities.

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¹The Medicines for Human Use (Clinical Trials) Regulations (S.I. 2004/1031) and any subsequent amendments to it.

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Role of Study Sponsor and Funder

For this trial some of the duties of the Sponsor have been delegated to the Chief Investigator (CI), for example the CI has overall responsibility for the design and development of the protocol. The sponsorship agreement describes the allocation of such responsibilities, and a summary of this can be provided by the Sponsor upon request. The funder of this trial will not be involved in trial design, conduct, data analysis and interpretation, manuscript writing, or dissemination of results.

Role of Other Protocol Contributors

All key contributors to the protocol including the PI and Trial Coordinator are involved in study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results. Neither the Sponsor nor the funder controls the final publication of the trial. An Independent Cancer Patients' Voice representative is involved in the protocol design including methodology, sample collection, patient information and consent forms.

Roles and Responsibilities of Trial Management Committees/ Groups & Individuals

Trial Management Group/Trial Steering Committee/ Safety Review Committee
Please see section 12 Trial Summary

Trial Title	Avelumab and hypofractionated Palliative radiotherapy in metastatic soft-tissue sarcoma (APPLE)
Clinical Phase	Phase I
Summarised Trial Design	Interventional single arm study
Summarised Eligibility Criteria	<ul style="list-style-type: none"> • Have measurable (RECIST v1.1) metastatic soft-tissue sarcoma disease; requiring palliative radiotherapy for which no curative therapy exists will be recruited into the trial. Patients are permitted to have disease that will not be encompassed within the radiotherapy field (radiation tumour target volume above diaphragm) and will allow assessment for abscopal response. • At least one site of accessible disease for pre- and post-treatment core biopsies. • Patients ≥ 18 years of age with ECOG performance status ≤ 1. • Tolerate a 2.5 week course of palliative radiotherapy and life expectancy of >12 weeks. • Include but not limited to the following soft-tissue sarcoma

	<p>histological sub-types: leiomyosarcoma, myxoid liposarcoma, liposarcoma, undifferentiated pleomorphic sarcoma, fibrosarcoma, epithelioid, clear cell, and synovial sarcoma.</p> <ul style="list-style-type: none"> • Patients that have had no previous chemotherapy treatment or have received ≥ 1 or more lines chemotherapy therapies • Male patients and women of childbearing potential (WOCBP) and their male partners must agree to use 1 highly effective methods of contraception and a condom during the screening period (i.e. for a period of 35 days after giving informed consent prior to starting avelumab) throughout treatment with avelumab and for at least 60 days after Avelumab treatment. Women of childbearing potential include pre-menopausal women and women within the first 2 years of the onset of menopause. Women of childbearing potential must have a negative pregnancy test ≤ 72 hours prior to Day 1 of study as defined in section 7.3.7 and following this initial test must agree to monthly pregnancy tests whilst receiving avelumab and at the end of avelumab treatment. • If the patient has symptoms, that these, when assessed using CTCAE v.4.0, are of grade 0 or 1 severity only.
Summary of Main Exclusion Criteria	<ul style="list-style-type: none"> • Prior systemic therapy targeting PD-1: PD-L1 axis. • Patients who are curable by conventional multidisciplinary management. • Patients with known central nervous system metastatic disease are ineligible for enrolment. • Patients with severe and/or uncontrolled concurrent medical disease that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol. • Patients who have received radiotherapy ≤ 4 weeks prior to Day 1 of study or who have not recovered adequately from side effects. • Previous radiotherapy within the treatment area. • Patients who have active infections requiring therapy.

- Patients with a history of Human Immunodeficiency Virus (HIV), Hepatitis B or Hepatitis C. Positive test for HBV surface antigen and / or confirmatory HCV RNA (if anti-HCV antibody tested positive).
- Patients that have a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the trial.
- Patients who received systemic anti-cancer treatment prior to the first dose of study drug within the following time frames:
- Patients who have received biologic therapy (e.g., antibodies) within 4 weeks.
- Patients who have undergone major surgery \leq 2 weeks prior to starting study drug
- Patients with active autoimmune disease or a documented history of autoimmune disease or syndrome that requires systemic steroids or immunosuppressive agents. Patients with vitiligo or resolved childhood asthma/atopy would be exception to this rule. Patients that require inhaled steroids or local steroid injections would not be excluded from the study. Patients with hypothyroidism not from autoimmune disease that is stable on hormone replacement will not be excluded from the study.
- Women who are pregnant or nursing/breastfeeding.
- Known hypersensitivity to avelumab or another mAb.
- Patients with a history of non-infectious pneumonitis that has required a course of oral or intravenous steroids to assist with recovery, or interstitial lung disease.
- Immunosuppressants: Current use of immunosuppressive medication, EXCEPT for the following: a. intranasal, inhaled, topical steroids, or local steroid injection (eg, intra-articular injection); b. Systemic corticosteroids at physiologic doses \leq 10 mg/day of prednisone or equivalent; c. Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).
- Patients with the risk factors for bowel obstruction or bowel

	<p>perforation (examples include but not limited to a history of acute diverticulitis, intra-abdominal abscess, abdominal carcinomatosis).</p> <ul style="list-style-type: none"> • Patients who have received a live vaccine within 30 days prior to the first dose of trial treatment. • Previous malignant disease within the last 5 years with the exception of basal or squamous cell carcinoma of the skin or cervical carcinoma in situ • Patients on anticoagulation medication. • Patients who have symptoms, which when assessed using CTCAE v.4.0, are of grade 2 severity or above. 	
Planned Sample Size	n=12 patients, single investigational site.	
Treatment duration	To be determined by treating doctor. Treatment duration (i.e. Avelumab administration) may extend to 6 months (12 cycles). It is estimated that the study will take 12 months to accrue 12 patients.	
Follow up duration	It is anticipated that the survival follow-up period may extend for a maximum of 24 months. Thus, the maximum anticipated date of study closure would be 3 years and 6 months from the start of the trial. The end of the study is defined as completion of the final survival follow up assessments in the last patient recruited.	
Planned Trial Period	3 years and 6 months (maximum duration)	
	Objectives	End-points / Outcome Measures
Primary	<ul style="list-style-type: none"> • Determine the safety and tolerability of avelumab at a fixed dose of 10mg/kg in combination with RT in patients with metastatic soft-tissue sarcoma. 	<ul style="list-style-type: none"> • Establish that a fixed dose of avelumab (10mg/kg) can be safely combined with hypofractionated radiotherapy to thorax/trunk or limb in the absence of dose limiting toxicity (DLT).
Secondary	<ul style="list-style-type: none"> • Evaluate local control (LC). • To determine the progression free survival 	<ul style="list-style-type: none"> • To measure the LC at 3 months. • To measure the PFS and

	<p>(PFS) and overall survival (OS).</p> <ul style="list-style-type: none"> • To determine acute toxicity. • To determine late toxicity. • To evaluate PFS and OS in a PD-L1 positive population. 	<p>OS at 6 months and 1 year.</p> <ul style="list-style-type: none"> • Measure acute \geq grade 2 toxicity from initiation of radiotherapy and avelumab up to 11 weeks following initiation of combined radiotherapy and avelumab • Measure late \geq grade 2 toxicity from 11 weeks plus one day after initiation of combined radiotherapy and avelumab up to confirmed disease progression or initiation of new anti-cancer treatment therapy. • To measure PFS and OS in PD-L1 positive population at 6 months and 1 year.
Exploratory	<ul style="list-style-type: none"> • To assess for evidence of abscopal response • To evaluate whether RT combined with Avelumab results in a measureable change in anti-tumour immunity. 	<ul style="list-style-type: none"> • To evaluate the abscopal effect when avelumab and RT are combined. • Identification of biomarkers that correlate with immunological response to therapy.
Investigational Medicinal Product(s)	Avelumab	
Formulation, Dose, Route of Administration	Intravenous avelumab and External Beam Radiotherapy	
Treatment/Main study Procedures	<p>All patients will receive avelumab (at a fixed dose of 10mg/kg) administered one day before radiotherapy (week 1), and then continued every 2 weeks until progression, unacceptable toxicities or discontinuation for other reasons or withdrawal from the study. The maximum duration of the study is anticipated to be 3 years and 6 months Figure 1 summarises the recruitment schedule. Figure 2</p>	

summarises the treatment schedule. Each patient will receive 36 Gy in 12 daily fractions of hypofractionated radiotherapy as per standard protocol.

Patients will undergo clinical assessment within 72 hours prior to each administration of avelumab. After the end of treatment (i.e. discontinuation of avelumab) each patient will attend safety follow-up visits at 30 days and 90 days (extended safety follow-up) or before initiation of a new cancer treatment, whichever comes first. Patients who discontinue for reasons other than disease progression will be followed up every 12 weeks for disease status until progression, initiating new cancer treatment, withdrawing consent or loss to follow-up. This will be done by reviewing the medical notes, contacting the patient's GP directly. Patients will remain on follow-up until death, withdrawal of consent, or the end of the study which is anticipated to be no more than 3 years and 6 months from the first administration of the first dose of avelumab in the first patient.

Patients will undergo tumour assessment by RECIST 1.1 every 12 weeks from the first dose of avelumab (irrespective of treatment delays) whilst they remain on therapy to establish disease response. They will also have a CT scan performed at 4 weeks following completion of RT (week 7) and 13 weeks. Additional imaging will be performed earlier if clinically indicated.

Funding

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Merck KGaA	Funding for phase 1

LIST OF ABBREVIATIONS

ADCC	Antibody-Dependent Cellular Cytotoxicity
ADL	Activities of daily living
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AR	Adverse Reaction
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CA	Competent Authority
CI	Chief Investigator
CL	Clearance
C _{max}	Maximum Plasma Concentration
C _{min}	Minimum Plasma Concentration
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Computerized Tomography
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumour DNA
CTIMP	Clinical Trial of Investigational Medicinal Product
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CTV	Clinical Target Volume
DAI	Dosage and Administration Instructions
DC	Dendritic Cells
DILI	Drug induced liver injury
DLT	Dose-Limiting Toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DSUR	Development Safety Update Report
DW-MRI	Diffusion weighted magnetic resonance imaging
EC	Ethics Committee
ECG	Electrocardiogram

ECI	Evidence of Clinical Interest
ECOG	Easter Cooperative Oncology Group
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EOT	End of Treatment
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
FDA	Food and Drug Administration
FFPE	Formalin Fixed, Paraffin Embedded
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GMP	Good Manufacturing Practice
GTV	Gross Target Volume
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HMGB1	High-mobility group box 1
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
ICR	Institute of Cancer Research
ICRU	International Commission on Radiation Units and Measurements
IEC	Independent Ethics Committee
IFN	Interferon
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
INR	International Normalized Ratio
irAE	Immune-related AE
IRB	Institutional Review Board
irECI	Immune-related Events of Clinical interest
iRECIST	Guidelines for response criteria for use in trials testing immunotherapeutic
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention to treat
IV	Intravenous

LC	Local Control
LFT	Liver Function Test
LLN	Lower limit normal
MA	Marketing Authorisation
mAb	Monoclonal Antibody
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
MS	Member State
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
NK	Natural Killer
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
OAR	Organs at risk
ORR	Objective Response Rate
OS	Overall Survival
OTC	Over-the-counter
PBMC	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PD-1	Programmed Death-1
PD-L1	Programmed Death-Ligand 1
PFS	Progression-Free Survival
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PK	Pharmacokinetics
PP	Per protocol
PR	Partial Response
PS	Performance Status
PT	Prothrombin Time
PTV	Planning Target Volume
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria in Solid Tumours

RM	G-SOPs
RNA	Ribonucleic Acid
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SAR	Serious Adverse Reaction
SD	Stable Disease
SDV	Source Data Verification
SMC	Safety Monitoring Committee
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SPC	Summary of Product characteristics
SRC	Safety Review Committee
SSI	Site Specific Information
StD	Standard Deviation
STS	Soft tissue sarcoma
SUSAR	Suspected Unexpected Serious Adverse Reaction
T4	free thyroxine
TEAE	Treatment Emergent Adverse Event
TIL	Tumour Infiltrating Lymphocytes
TMF	Trial Master File
TMG	Trial Management Group
TO	Target occupancy
Treg	Regulatory T cells
TSC	Trial Steering Committee
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
USM	Urgent safety measures
WBC	White Blood Cell

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1 Background

1.1 Pharmaceutical and Therapeutic Background

Avelumab (also referred to as MSB0010718C) is a fully human IgG1 antibody directed against PD-L1. Avelumab binds PD-L1 and blocks the interaction between PD-L1 and its receptors PD-1 and B7.1. This removes the suppressive effects of PD-L1 on anti-tumour CD8⁺ T cells, resulting in the restoration of cytotoxic T ligands, PD-L1 and PD-L2, PD-1 delivers a series of strong inhibitory signals through its cytoplasmic tail to inhibit T cell functions (Chemnitz et al 2004, Keir et al 2008, Riley 2009).

PD-L1 (also called B7-H1 and CD274) can be detected on resting and activated T cells, B cells, macrophages, dendritic cells, and mast cells; PD-L1 expression is greatly up-regulated after activation or interferon treatment (Keir et al 2008). Numerous results from in vitro cellular assays have demonstrated that blockade of the PD-1/PD-L1 interaction enhances T cell responses, such as increases in proliferation and cytokine production (Bennett et al 2003, Blank et al 2004, Blank et al 2006, Brown et al 2003, Dong et al 1999, Freeman et al 2000, Waeckerle-Men et al 2007). In PD-1^{-/-} mice both T and/or B cells responses are unregulated resulting in an array of autoimmune pathologies (Okazaki and Honjo 2006, Okazaki and Honjo 2007). Breaking tolerance through blocking PD-1 interaction with its ligands, and thus PD-1 signaling, can be applied to enhance T cell activity towards chronic pathologies such as cancer (Blank et al 2005).

External (Okazaki and Honjo 2007) and internal immunohistochemistry studies have demonstrated that PD-L1 is also expressed by a variety of human tumours, both by the tumour cells, as well as by the immune cells that are present in the tumour microenvironment. In contrast to very strong expression on syncytiotrophoblasts in the placenta and in cancer cells, low levels of PD-L1 expression were detected in some normal tissues including fetal cardiac tissue (Brown et al 2003). High levels of PD-L1 expression have been found to be associated with disease progression, increased metastasis, poor response to treatment, and decreased survival in a number of human cancers (Okazaki and Honjo 2007). Importantly anti-PD-L1 blockade has demonstrated therapeutic efficacy in a variety of murine tumour models as monotherapy and has shown synergistic effect in combination therapy setting (Blank et al 2004, Hirano et al 2005, Iwai et al 2002, Iwai et al 2004, Nomi et al 2007, Strome et al 2003, Zhang et al 2009).

The antitumour activity of avelumab has been investigated in various murine tumour models. Inhibition of the PD-1/PD-L1 interaction is proposed to exert a therapeutic effect by restoring anti-tumour CD8⁺ T cell responses.

To circumvent the need for a surrogate antibody, the lead candidate antibody was specifically selected for cross-reactivity to murine PD-L1, and, as consequence all of the nonclinical studies were conducted in syngeneic murine tumour models in which the immune system of the host is fully intact. It

was demonstrated that the inhibition of the PD-1/PD-L1 interaction restores anti-tumour CD8+ T cell responses, which results in an anti-tumour activity.

Avelumab has demonstrated significant nonclinical activity as a monotherapy and in various combination therapy settings. In general, the anti-tumour immunotherapy via blockade of the PD-1/PD-L1 axis seems not to be limited to any specific tumour types, but there is recent evidence that PD-L1 tumour expression is a pre-requisite to achieve an objective response upon blockade of the PD-1/PD-L1 axis (Topalian et al 2012b). The clinical relevance of PD-1/PD-L1 blockade has been demonstrated in Phase I trials performed with antibodies targeting either PD-L1 or PD-1 (Topalian et al 2012b, Brahmer et al 2012).

Given the important role of PD-L1 in the suppression of T-cell responses, and the mode of action of avelumab which blocks the interaction between PD-L1 and its receptors, avelumab is being developed as a potential therapy for subjects with various tumours.

2 Rationale

2.1 Rationale for combining anti-PD-L1 with radiation

There has been a recent shift in thinking that radiotherapy is a localised treatment and it is now accepted that it may mediate some of the anti-tumour response through systemic effects. Although radiotherapy has been used as an immunosuppressive agent in total body irradiation as conditioning prior to bone marrow transplant, it is also able to act as an immune stimulant in solid tumours (Sologuren et al 2014). Radiation damage results in necrotic and apoptotic cell death releasing large amounts of tumour antigens. These tumour associated antigens are available for uptake and processing by antigen presenting cells including dendritic cells and can lead to a specific anti-tumour immune response (Burnette et al 2013).

Radiotherapy creates an inflammatory tumour microenvironment by inducing proinflammatory cytokines that can cause tumour growth inhibition and cell death. In addition, there is upregulation of MHC class I, costimulatory molecules, adhesion molecules and death receptors on tumour cells and surrounding stroma potentiating the CD8+ T cell cytotoxic cell responses. Radiation induced cell damage leads to increased expression of markers of immunogenic cell death including translocation of calreticulin to the tumour cell surface and release of high-mobility group box 1 (HMGB1) which can activate dendritic cells.

Although radiotherapy has traditionally been delivered using low dose per fraction (between 1.8 and 2.0 Gy), there is evidence that giving a higher dose per fraction (greater than 2.0 Gy or

hypofractionation) may mediate more favourable immunological effects, generating a CD8+ T cell anti-tumour response (Burnette et al 2015). Unfortunately, although radiotherapy has the potential to offer both local control and treat metastatic disease, this effect does not translate into a meaningful clinical response due to tumour evasion of the immune response by either immune tolerance or suppression. If the radiotherapy induced immune response could be improved, this may translate into improved clinical outcomes.

Cancer immune tolerance is driven by several mechanisms including loss of MHC expression, and upregulation of inhibitory molecules of immune response including PD-1. Although the critical role of the immune system in mediating the therapeutic response following radiotherapy has been known over the last 40 years, we have only recently combined radiation and immunotherapy in increasing numbers in the preclinical and clinical setting.

There have been many pre-clinical *in vivo* studies conducted combining immunotherapeutic agents including anti-CTLA-4, Flt3 ligand, viral therapies and anti-PD-1 agents with radiotherapy in multiple tumour types. Most studies demonstrate an enhanced tumour response that was CD8+ cell dependent with evidence of increased CD8+ T cell activation. The pre-clinical mouse models also suggest that hypofractionated radiotherapy is more beneficial although the optimum schedule has not been defined. Multiple fractionation schedules have been investigated in studies, including 5 x 3 Gy, 5 x 6 Gy, 3 x 8 Gy, 1x 15 Gy, and 1 x 20 Gy, either in isolation or with monoclonal antibodies against CTLA-4, and more recently PD-1. A few studies demonstrated control of both the primary tumour and a distant secondary tumour. Most studies demonstrated either an increase in the CD8+ response or reduction in the Treg population. It remains unclear as to the optimum radiotherapy dose, and fractionation schedule. This clinical trial will provide more information on the T cell response in the clinical setting and provide information to design future radiotherapy and anti-PD-L1 therapy combination studies.

Many cancers including soft tissue sarcoma have demonstrated increased expression of PDL1 (Kim et al 2013, Kim et al 2016). Retrospective analysis of paired soft tissue sarcoma tumour samples pre- and post-radiotherapy have demonstrated changes in immune-related signatures suggesting scope for combining radiotherapy with immunotherapy (Sharma et al 2013). A mouse soft tissue sarcoma model demonstrated combining radiotherapy with intra-tumoural DC therapy resulted in an enhanced anti-tumour effect with an accompanying tumour-specific immune response (Teitz-Tennenbaum et al 2013). Clinical studies are now combining immunotherapy with radiation in patients with soft-tissue sarcoma. One study combined pre-operative radiotherapy with intratumoural injections of DC, resulting in a peripheral blood immune response with no increase in toxicity (Finkelstein et al 2012).

2.2 Preclinical and Clinical Trial Data on Avelumab

Refer to the current version of the Investigator's Brochure for Preclinical and Clinical data.

2.3 Rationale for the Trial and Selected Subject Population

Soft-tissue sarcomas (STS) are a rare heterogeneous group of neoplasms arising from mesenchymal tissue. The median survival for patients with metastatic STS is between 12 and 18 months (Harris et al, 2015). Extremity soft-tissue sarcomas (eSTS) most frequently metastasise to the lung. Metastatic STS patients are usually incurable and treated with systemic therapies, focusing on palliating symptoms, preventing disease progression and potentially prolonging survival (Linch et al, 2014).

Radiotherapy (RT) provides good local palliation in patients with metastatic STS. The standard of care in this cohort of patients is a short course of hypofractionated RT (fraction dose above 2 Gy) to control symptoms and offer local disease control concurrent or sequential to chemotherapy. Although the majority of patients respond to RT, they frequently develop progressive disease at other sites. When managing patients with several metastases, it can sometimes be difficult to irradiate multiple sites concurrently without causing an unacceptable level of radiation-induced toxicity.

The recent success of immune checkpoint inhibitors in melanoma and other solid tumours has brought immunotherapy to the forefront of cancer therapy. One cell surface protein, programmed death receptor 1 (PD-1) has been recently targeted with the checkpoint inhibitor, Pembrolizumab, in advanced melanoma with durable responses translating into a significant survival benefit (Ribas et al, 2015). Several monoclonal antibodies to PD-1 or programmed death ligand 1 (PD-L1) are currently being developed. Avelumab is a fully human IgG1 antibody that inhibits PD-L1, and is being tested across several tumour types in early phase clinical trials (Kelley et al 2015). Unlike other monoclonal antibodies to PD-1/PD-L1, Avelumab has been designed with the unique ability to mediate antibody-dependent cell-mediated cytotoxicity (ADCC), by inducing natural killer (NK) mediated tumour cell lysis.

There is a strong rationale for using immunotherapy in STS based on the underlying disease biology (genetic aberrations and complex chromosomal translocations). Chromosomal translocations resulting in fusion proteins (seen in some STS subtypes) represent attractive targets for immunotherapy. High expression of cancer testis antigen may also represent potential targets (NY-ESO-1 is expressed in synovial sarcoma and myxoid liposarcoma). Other STS subtypes express mutations that are also potential targets for immunotherapy (myxofibrosarcoma). The role of the PD-1 axis in STS is currently being investigated, and PD-1 staining in tumour infiltrating lymphocytes and PD-L1 overexpression in

tumour samples may correlate with a poorer prognosis (Kim JR et al, 2013). The initial checkpoint inhibitor trials in soft tissue sarcoma suggested targeting PD-1 alone in all STS subtypes did not result in tumour shrinkage (Paoluzzi et al, 2016; Tawbi et al 2016). Although tumour responses were seen in patients with undifferentiated pleomorphic sarcoma, it was suggested that another treatment may be needed to make these tumours more immunogenic.

Radiotherapy can cause immunogenic cancer cell death, resulting in cross-priming of tumour-specific T-cells, and increased NK cell cytotoxicity, acting as an in situ tumour vaccine. However, RT alone rarely induces a prolonged or effective anti-tumour immunity. There is a strong rationale to combine immunotherapy with RT in an attempt to introduce more robust anti-tumour immunity (Formenti SC et al 2013).

In this study we will irradiate an involved solitary thoracic, trunk or limb tumour deposit, radiation target volume between the neck and the diaphragm) in patients with metastatic STS, in combination with PD-L1 inhibition (Avelumab). The inclusion of a limited number of patients with extremity disease should not adversely affect conclusions about treatment tolerability.

We aim to generate a cytotoxic CD8 T-cell response resulting in an abscopal effect. We also wish to exploit the ability of Avelumab to activate the innate immune system through ADCC and enhance radiation-induced NK cytotoxicity. Using a higher dose per fraction RT schedule may induce more immunogenic cell death and cause immune priming. Combining this with PD-L1 blockade (and ADCC) should enhance the RT-induced immune response. From our experience, tumour deposits, located in the extremities, thorax, and trunk are amenable to treatment with a biologically effective dose of hypofractionated radiotherapy.

2.4 Rationale for Dose Selection/Regimen/Modification

In this clinical trial, the Avelumab dose will be fixed at 10 mg/kg, administered intravenously (iv) once every 2 weeks. This dose was selected for the expansion cohorts of Phase I trials, the Phase II pivotal trial (EMR 100070-003), and the ongoing Phase III trials based on the preliminary pharmacokinetic (PK), target occupancy, and preliminary clinical safety data collected in the clinical trials (see section below).

2.4.1 Pharmacokinetics and Target Occupancy

Avelumab plasma levels leading to full programmed death ligand 1 (PD-L1) receptor target occupancy (TO) on peripheral blood mononuclear cells (PBMC) resulted in tumour growth inhibition in a murine disease model. Therefore, full TO on PBMCs can be considered a PD marker for the ability of avelumab to act on its target and to show clinical activity. Preliminary PK data from EMR 100070-001 show that the concentration at the end of dose interval (C_{min}) increased more than proportionally to dose between 1 to 10 mg/kg, but proportionally for doses above 10 mg/kg. Consistently the $t_{1/2}$ also increased with the dose. However, the average value was 102 and 120 hours for 10 mg/kg and 20 mg/kg, respectively, with no significant difference between these two dose groups. This PK characteristic suggests that target mediated drug disposition is involved in the clearance of avelumab and a high PD-L1 TO is likely achieved at the trough concentration for doses of 10 mg/kg and 20 mg/kg. The in vitro target occupancy data further support that a high TO is likely achieved at 10 mg/kg and above.

- Target occupancy was measured ex vivo by flow cytometry on peripheral blood CD3+ T cells from patients (n=9) treated with avelumab. After the first dose of the initial dose-escalation portion of Trial EMR 100070-001, the observed mean target occupancy reached a plateau of about 90% on Day 15 pre-dose for dose levels of 3 mg/kg and above.
- In addition, in vitro target occupancy was measured using flow cytometry on peripheral blood CD3+ T cells from 8 healthy volunteers after spiking avelumab over a concentration range of 0.003 to 10 µg/mL. A 50% target occupancy was observed at a drug concentration (standard deviation [StD]) of 0.122 (0.042) µg/mL, and a concentration of 1 µg/mL avelumab was required for > 95% target occupancy. Based on these data and the trough serum levels observed in EMR 100070-001, target occupancy was projected to reach or exceed > 95% throughout the entire dosing interval for 10/13 subjects at 3 mg/kg, and for all (15/15) subjects at 10 mg/kg group from dose escalation group in EMR 1000700-001.

Based on the ex vivo peripheral blood CD3+ T cell and in vitro target occupancy results, the dose of 10 mg/kg every 2 weeks is expected to achieve target saturation during the entire dosing interval in the majority of patients.

2.4.2 Clinical Safety Data Related to Dose

As of the safety cut-off date of 05 November 2015, 1353 subjects have received at least 1 dose of avelumab at doses ranging from 1.0 to 20 mg/kg in the Phase I Trial EMR 100070-001, of which 1315 have received the proposed dose of 10 mg/kg (15 in the dose escalation part of the study and 1300 subjects in the pooled expansion cohort). In the dose escalation portion of the Phase I study, there was no evidence of differences in the safety profile across all administered dose levels from 1 mg/kg to 20 mg/kg. The MTD was not reached. Ongoing review of the safety data by the Safety Monitoring

Committee (SMC) suggests an acceptable safety profile of avelumab administered at the 10 mg/kg every 2 weeks dose and schedule. Treatment-related treatment-emergent adverse events (TEAEs) were observed in 813 (62.5%) subjects in the pooled expansion cohort. The most frequently observed treatment related TEAEs (incidence > 5%) were fatigue (212 subjects, 16.3%), infusion-related reaction (209 subjects, 16.1%), nausea (108 subjects, 8.3%), chills (102 subjects, 7.8%), diarrhoea (79 subjects, 6.1%), and pyrexia (72 subjects, 5.5%). Grade ≥ 3 treatment-related TEAEs were observed in 124 subjects (9.5%) in the pooled expansion cohort. The most frequently reported Grade ≥ 3 treatment related TEAEs were gamma-glutamyl transferase increased (GGT) and infusion-related reaction (each occurred in 9 subjects; 0.7%). Infusion-related reactions including drug hypersensitivity reactions and immune-mediated adverse reactions have been identified as expected adverse drug reactions of avelumab. The safety profile of avelumab is consistent with findings reported for other anti-PD-1 or anti-PD-L1 antibodies with data demonstrating immune-mediated colitis rate of 7.5% (Hassan et al, 2016) and immune-mediated pneumonitis rate of 2.9% (Investigator's Brochure). In conclusion, preliminary data from EMR 100070-001 showed that avelumab at doses up to 20mg/kg IV every 2 weeks was well tolerated, and the dose of 10 mg/kg iv every 2 weeks was considered to have an acceptable safety profile for further investigation in clinical studies.

2.4.3 Conclusion

Based on the PK results and the receptor occupancy data, sufficient trough concentrations appear to be achieved for full TO in the blood in the majority of subjects receiving the 10 mg/kg dose. Within the dose range of 1 mg/kg to 20 mg/kg, avelumab was well tolerated and is deemed to have an acceptable safety profile. Based on the above analyses, a dose of 10 mg/kg iv once every 2 weeks is considered to have a favourable risk benefit profile and thus represents an appropriate dose for further investigation in registration studies of avelumab.

2.5 Rationale for Endpoints

2.5.1 Safety, Tolerability, Progression free survival and Overall survival Endpoints

The primary objective of this study is to determine the safety and tolerability of combining avelumab with hypofractionated radiotherapy. This particular radiotherapy regimen is well tolerated, with a less than 5% risk of pneumonitis and less than 5% risk of colitis. Recently reported data demonstrate an avelumab colitis rate of 7.5% (Hassan et al, 2016). This study will combine these two treatments and will focus on \geq grade 2 pneumonitis (during radiotherapy not resolving to grade 2 within 72 hours of medical management) as the principle DLT. In the first three patients recruited, if ≥ 2 develop a DLT

the Safety Review Committee (SRC) will review the data and recommend either study termination or dose reduction to 3mg/kg. If 1 of the initial three patients recruited develops oesophagitis of \geq grade 4, or 2 patients develop myelitis of \geq grade 2, these events would lead to premature study termination. However, if these adverse events occurred in patients 4, 5 or 6, they would lead to dose de-escalation to 3mg/kg and the cohort would be expanded to 12 patients. An overview of study recruitment is depicted in Figure 1.

Tolerability will be assessed by documenting all AEs and serious adverse events (SAEs). Currently, the median PFS is 5 months and median OS is 12 months. The secondary endpoint of this study will include Progression free survival (PFS) and overall survival (OS). We expect combining avelumab with radiotherapy and continuing into a maintenance phase will improve the PFS and OS.

2.5.2 Efficacy Endpoints (Toxicity, PFS and OS, Abscopal effect, and Biomarker research)

Acute and late toxicity as assessed by CTCAEv4 will be used to judge the tolerability of combining avelumab with radiotherapy. Local control will be assessed by CT or MRI (extremity disease only, unless contraindication then CT). Distant control at 3 months will be assessed by CT imaging. Patients receiving maintenance therapy will have imaging (CT) repeated every 3 months until progression, discontinuation of avelumab due to toxicity or removal from the study. Patients will also have a CT scan performed 4 weeks following completion of RT (week 7). Additional imaging may be performed earlier dependent on clinical symptoms.

The abscopal effect is a rare phenomenon observed in the treatment of metastatic cancer where localised radiation of a specific tumour site results in tumour regression in a distant site outside of the irradiated volume. Although the exact mechanisms are unknown, the process is thought to be mediated by the immune system (Demaria et al 2004). It is possible that combining radiotherapy with immune checkpoint inhibition may result in a robust abscopal effect, leading to clinically meaningful anti-tumour responses and disease control. In this single arm study, we will conduct an exploratory analysis of this phenomenon by determining individual lesion response outside the irradiated area (using RECIST v1.1).

Newly collected tumour samples from the irradiated STS deposit will be obtained pre- and 7 weeks post- treatment for PD-L1 expression and biomarker research. These will be paired with optional tumour biopsies outside the irradiated field at identical time points. The tumour biopsies are done if patient consents and if this is deemed safely accessible for PD-L1 expression and biomarker research. Correlative blood samples will be taken at baseline, during and 4 weeks post radiotherapy for characterization of T cell functionality. Circulating tumour DNA analysis will also be performed. Preclinical translational research will be performed at the Institute of Cancer Research, London, and

The Leeds Institute for Cancer and Pathology (see below). Samples will be banked for future analysis.

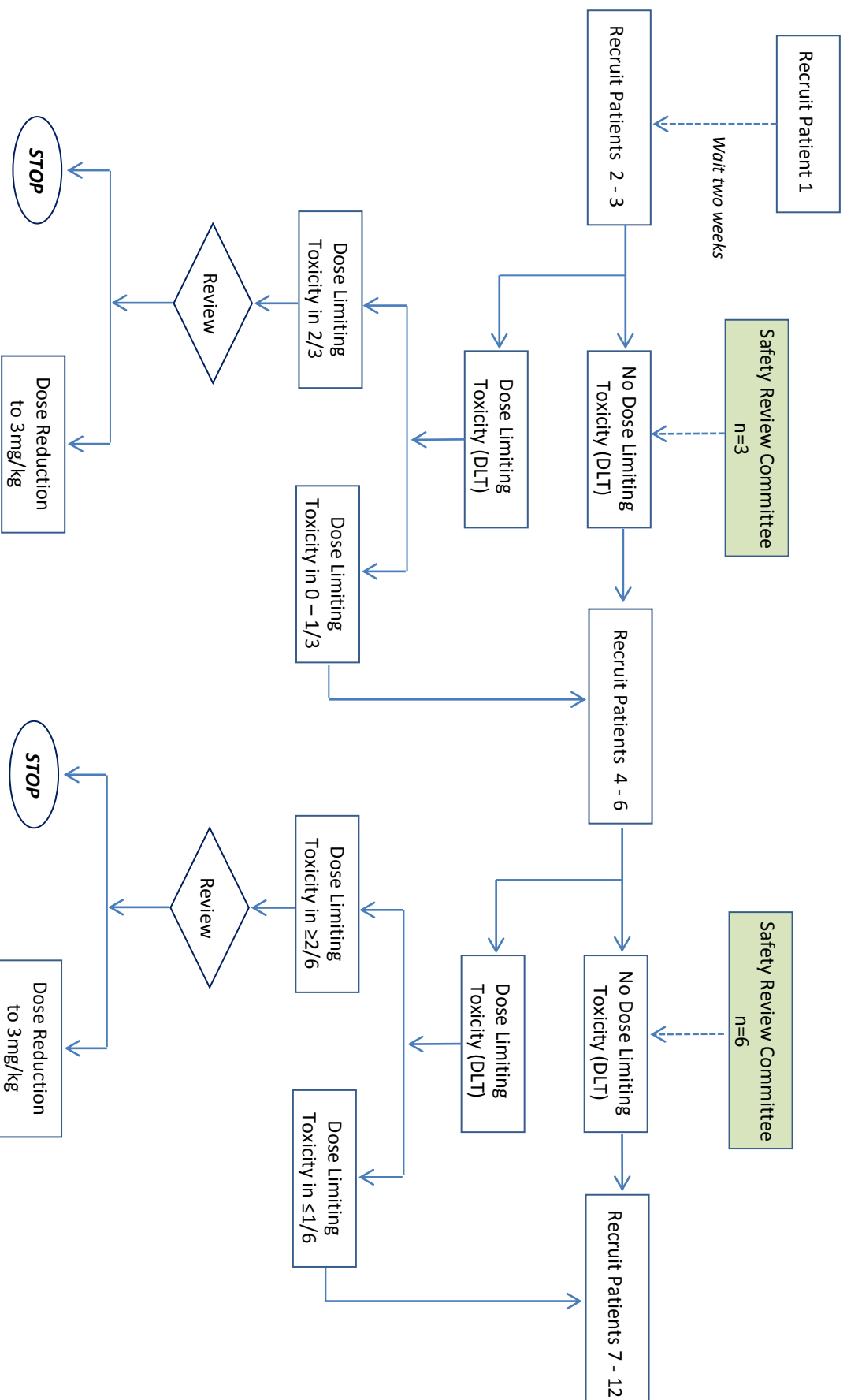


Figure 1 APPLE Recruitment Flow Chart

3 Objectives and Endpoints

3.1 Objectives

3.1.1 Primary Objective

Objective: To assess the safety and tolerability of combining hypofractionated radiotherapy (36 Gy in 12 fractions delivered daily over 2.5 weeks), with avelumab, an anti-PD-L1 antibody, treating advanced STS.

Hypothesis: Avelumab combined with hypofractionated radiotherapy in advanced STS is safe and well tolerated in the acute setting (i.e. from first combined administration of patient's radiotherapy and avelumab to a point 11 weeks from the start of the patient's radiotherapy), coincident with administration of cycle 6 of avelumab.

3.1.2 Secondary Objectives

Objective: To evaluate local control rates at 3 months achieved by combining avelumab with hypofractionated radiotherapy (based on CT/diffusion-weighted MRI).

Hypothesis: Avelumab combined with hypofractionated radiotherapy will improve the local control rate.

Objective: To evaluate progression free (PFS) and overall survival (OS).

Hypothesis: Combining avelumab with RT and with maintenance treatment leads to prolonged responses following palliative RT.

Objective: To evaluate acute toxicity, defined as toxicity occurring up to 11 weeks following initiation of combined radiotherapy and avelumab.

Hypothesis: Avelumab combined with hypofractionated radiotherapy in advanced STS does not result in unacceptable acute toxicity (defined as up to 11 following initiation of combined radiotherapy and avelumab).

Objective: To evaluate late toxicity, defined as toxicity occurring during the period commencing 11 weeks and one day after the initiation of radiotherapy and avelumab until confirmed disease progression or initiation of new anti-cancer treatment therapy.

Hypothesis: Avelumab combined with hypofractionated radiotherapy in advanced STS does not result in unacceptable late toxicity (defined as commencing at 11 weeks and one day from the initiation of combined radiotherapy and avelumab until confirmed disease progression or initiation of new anti-cancer treatment therapy).

Objective: To assess the frequency of PD-1/PD-L1 expression in advanced STS and evaluate PFS against PD-L1 expression.

Hypothesis: Prolonged responses following palliative RT are expected in patients with PD-L1 expression.

3.1.3 Exploratory Objectives

Objective: To determine individual tumour response rate in non-irradiated STS metastases measured by RECIST 1.1 and iRECIST at 3 months and 6 months after treatment with avelumab and radiotherapy. This will be used to determine local control and assess abscopal effect.

Hypothesis: Combining avelumab with RT leads to abscopal responses.

Objective: To evaluate whether hypofractionated radiotherapy combined with avelumab treating advanced STS results in a measurable change in anti-tumour immunity.

Objective: Identification of tissue and serum biomarkers that correlate with immunological response to therapy.

3.2 Endpoints

3.2.1 Primary Endpoint

1. To establish that Avelumab at a fixed dose of 10mg/kg can be safely combined with hypofractionated radiotherapy to the thorax, trunk or limb in the absence of dose limiting toxicity (DLT).

3.2.2 Secondary Endpoints

1. To assess the proportion of patients treated with a combination of avelumab and radiotherapy with local control of soft-tissue sarcoma at 3 months.
2. To assess the PFS and OS achieved with a combination of avelumab and radiotherapy followed by maintenance avelumab in patients with metastatic soft-tissue sarcoma at 6 months and 1 year.
3. To measure the rate of acute \geq grade 2 toxicity for 11 weeks following initiation of radiotherapy and avelumab.
4. To assess the rate of late \geq grade 2 toxicity assessed from 11 weeks and one day following the initiation of avelumab and radiotherapy until confirmed disease progression or initiation of new anti-cancer treatment therapy.
5. To measure PFS and OS in PD-L1 positive population at 6 months and 1 year.

3.2.3 Exploratory Endpoints

1. To assess the RECIST and iRECIST criteria response rates to treatment in (non-irradiated) soft-tissue sarcoma metastases at 3 and 6 months.
2. Analysis of research blood samples for ctDNA.
3. Characterisation of Tumour infiltrating lymphocytes (TILs) and tumour antigens in serum and tissue samples (as outlined in the immunotherapy trial manual).
4. Analysis of expression of immune-related gene panel by tumour and infiltrating immune cells, in pre- and post-radiotherapy tumour samples using Nanostring technology.

4 Trial Design

4.1 Overall Study Design

This is a single centre open label, non-randomized, non-placebo phase 1 clinical trial to establish the safety and tolerability of avelumab in combination with radiotherapy in patients with advanced soft tissue sarcomas (STS). Metastatic STS patients receiving radiotherapy to a tumour deposit above the diaphragm in the thorax, trunk or extremity, will receive hypofractionated radiotherapy (36 Gy in 12 fractions, delivered daily). This study will recruit 12 patients and run as a fixed dose study with starting dose of 10mg/kg. Patients will continue on the treatment regimen described in the study flow chart

(Figure 2, 4.2.2) unless they progress, suffer unacceptable toxicities, or withdraw from the trial. Recruitment is estimated to take 12 months and it is anticipated that a median 12 cycles of avelumab will be delivered over an elapsed time of 6 months. The maximum survival follow-up is estimated to be 24 months. Therefore the end of the study (i.e. follow-up completed in last patient recruited) is anticipated to be no more than 3 years and 6 months from the administration of the first dose of avelumab to the first patient.

4.2 Treatment Regimen

Each patient will receive a dose of 36 Gy in 12 daily fractions of hypofractionated radiotherapy as per standard protocol. All patients will receive a dose of avelumab at a dose of 10mg/kg, within 24 hours prior to radiotherapy (week 1), and then every 2 weeks until progression, unacceptable toxicities, discontinuation for other reasons or withdrawal from the study. The timing of radiotherapy relative to PD-L1 blockade is an important consideration and the optimal schedule remains unclear. Pre-clinical in vivo studies combining radiation with PD-1 blockade demonstrated the best local tumour control when administering antibody during radiotherapy (Dovedi et al, 2014).

Three patients will be recruited initially. If the incidence of DLTs in these patients is acceptable, a further 3 patients will be recruited (see figure 1) up to a maximum of 12 patients in total. A minimum gap of 2 weeks will be left between treatment of the first and second patient (with the combination of RT) to mitigate against multiple patients suffering acute toxicity. Acute radiotherapy toxicity monitoring will be undertaken from the start of the patient's radiotherapy and first dose of avelumab treatment for a period of 11 weeks.

4.2.1 Dose Levels

For this study, a Dose Limiting Toxicity (DLT) is defined as:

- \geq grade 2 pneumonitis
- \geq grade 4 Oesophagitis
- \geq grade 2 myelitis in 2 patients Any other grade 4 toxicity
- Any grade 3 non-haematological toxicity, likely to be related to study drug.
- Radiotherapy interruption >5 days

DLTs will be assessed from the start of the patient's radiotherapy and first dose of avelumab up to administration of Cycle 7 of avelumab (i.e. week 13 as depicted in Table 1, Section 7.1, Study Schedule) DLTs will be assessed using the Common Terminology Criteria for Adverse Events

(CTCAE) v4.0 and must be reviewed by the SRC (Safety Review Committee) once recruitment has reached 3 and 6 patients (see Figure 1). Recruitment will proceed to patients 7 to 12 provided DLTs are deemed acceptable by the SRC.

Presence of toxicity constituting DLT's will be assessed in each patient of the at start of radiotherapy, weekly during radiotherapy and at each clinic visit prior to the administration of avelumab until the administration of Cycle 7 at week 13. The recruitment of patients 7 – 12 will proceed as an expansion phase. Whilst toxicity will be monitored in these patients, the DLT window will have closed and thus adverse events occurring in these patients will not be defined as DLTs. Further, there will not be requirement for the SRC to meet unless triggered by the Chief Investigator.

Recruitment will proceed as shown in Figure 1 and as described below:

- If 0-1/3 patients experiences a DLT a further 3 patients will be recruited. .
- If $\leq 1/6$ patients experience a DLT then recruitment will continue to a total of 12 patients. .
- If $\geq 2/6$ patients experience a DLT, discussions will be undertaken with Merck KGaA as to whether to terminate recruitment or undertake a dose reduction to 3mg/kg. .
- If 2/3 patients experience a DLT, discussions will be undertaken with Merck KGaA as to whether to terminate recruitment or undertake a dose reduction to 3mg/kg.

A minimum of 3 patients will be recruited initially at the fixed dose of 10mg/kg, with a maximum of 12 patients to be recruited within the trial. Patients will initially receive avelumab at 10mg/kg. If 1 in 3 patients experience a dose limiting toxicity (DLT) then the cohort will be expanded to 6 patients and if ≤ 1 in 6 patients experience a DLT the cohort will be expanded to a maximum of 12 patients all receiving the same fixed dose (10mg/kg). , If ≥ 2 in 6 patients experience a DLT, discussions will be undertaken with Merck KGaA as to whether to terminate recruitment or undertake a dose reduction to 3mg/kg. If 2 out of 3 patients experience a DLT at dose level 1 then discussions will be undertaken with Merck KGaA as to whether to terminate recruitment or undertake a dose reduction to 3mg/kg.

4.2.2 Study Flow Chart

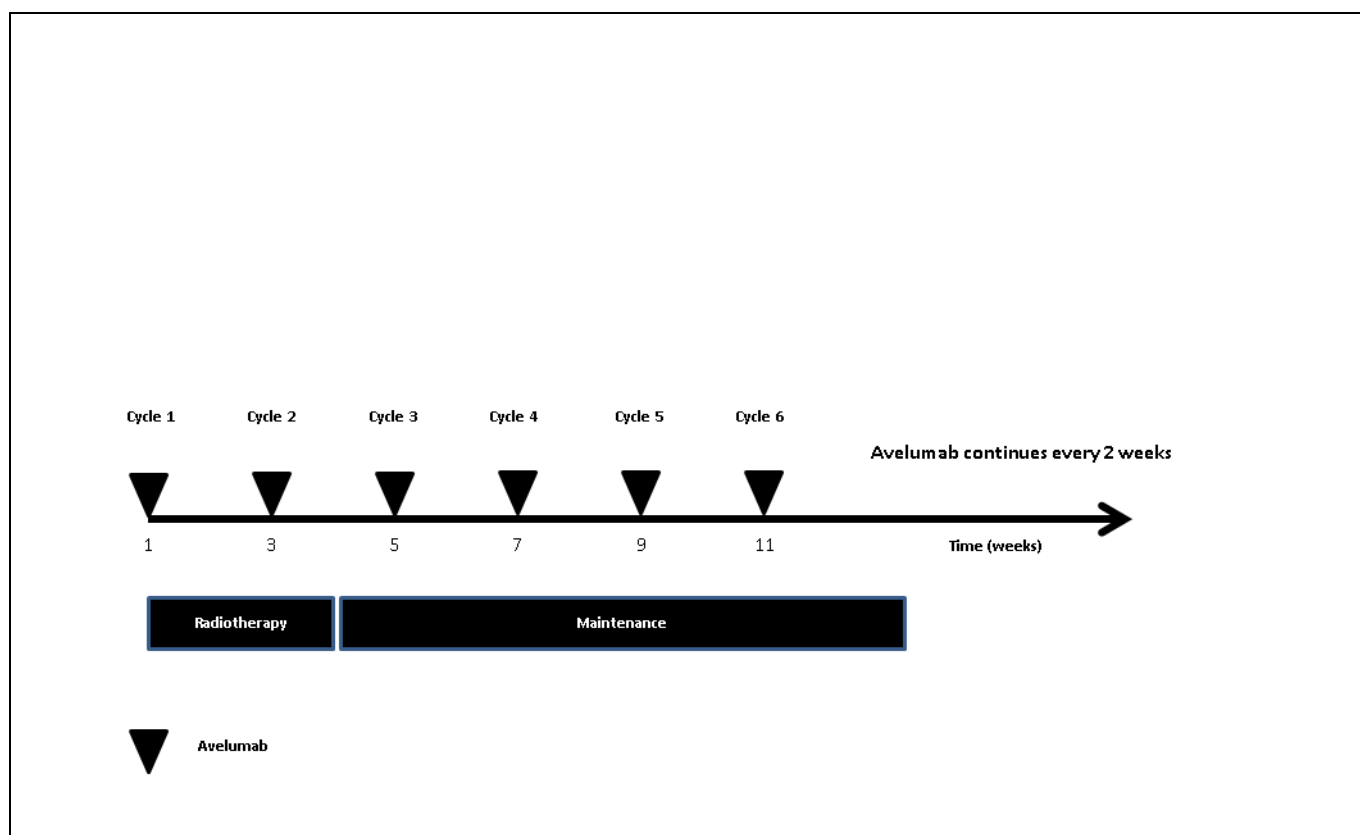


Figure 2: Study Flow chart

4.3 Follow-Up

4.3.1 30 day Safety Follow-up

All patients will be required to attend a safety follow-up visit at 30 days after the last dose of avelumab or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs and SAEs that occur prior to the safety follow-up visit should be reported as described in section 9. After the safety follow-up any unresolved AEs at the patient's last visit should be followed up for as long as medically indicated, but without further recording in the CRF.

4.3.2 Extended Safety Follow-up

Given the potential risk for delayed immune-related toxicities, safety follow-up must be performed up to 90 days after the last dose of Avelumab administration. The extended safety follow-up at 90 days after last study drug administration may be performed either via a clinic appointment or a telephone call with subsequent appointments requested in case any concerns are noted during the telephone call.

4.3.3 Follow-up

Patients who discontinue trial treatment for any reason other than disease progression will move into a follow-up phase and should be assessed every 12 weeks by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, withdrawal or end of the study. Information regarding post-study anticancer treatment will be collected if new treatment is initiated.

4.3.4 Survival Follow-up

Once a patient experiences confirmed progressive disease or starts a new anti-cancer therapy, the patient moves into the survival follow-up phase and will be followed up every 12 weeks to determine their disease status until the end of the trial which is anticipated to be no more than 3 years and 6 months from the date of enrolment of the first patient. The follow-up disease status review will be done by reviewing the patient's medical notes and/or contacting the patient and/or General Practitioner directly. Patients will remain on this follow-up until death, withdrawal of consent, or the end of the study, whichever occurs first.

4.4 Study Termination

The end of the study is defined as completion of the final survival follow-up assessment of the last subject recruited which is anticipated to be ≤ 24 months from end of avelumab treatment.

4.4.1 Clinical Criteria for Early Termination

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

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to patients.
4. The occurrence of 1 patient with oesophagitis \geq grade 4, at any dose level.
5. The occurrence of 2 patients with myelitis \geq grade 2, at any dose level
6. Plans to modify or discontinue the development of the study drug In accordance with the conditions of supply agreement with Merck KGaA, ample notification will be provided to the sponsor and site should alterations to the drug supply change. This is to allow time for appropriate adjustments to be made in regards to the patient's treatment.

4.5 Treatment after Study Termination

Following participation in the study patient care will be decided by the local doctor according to local standard practice.

5 STUDY SETTING

This is a single centre single site study that will be performed at The Royal Marsden NHS Foundation Trust Hospital. The identification of potentially eligible patients will be performed by clinicians at multidisciplinary Sarcoma cancer meetings and/or from patients attending routine outpatient clinics. Pre-screening of multidisciplinary meetings and outpatient clinics attended by clinicians will be performed by members of the clinical care team supported by members of the research team. No participants will be recruited by publicity using posters, leaflets, adverts or websites, although the trial will be registered in the public domain. The listed inclusion and exclusion criteria will be used to judge eligibility, but other factors will influence suitability and appropriateness of seeking written informed consent. Responsibility for seeking informed consent lies with the oncologist managing the patient, but other clinical staff, including Sarcoma Trial Nurse(s), will assist in this process as delegated.

6 Eligibility Criteria

The following eligibility criteria were designed to select patients for whom the protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into

consideration when deciding whether this protocol is suitable for a particular patient. Eligibility criteria may not be waived by the investigator.

Patients with metastatic soft-tissue sarcoma will be offered recruitment into the trial providing they meet the below criteria.

6.1 Inclusion criteria

- i. Patients must have a diagnosis of advanced soft tissue sarcoma with at least 2 metastases not suitable for cure using conventional treatments. At least one lesion must be suitable to receive palliative radiotherapy. The radiation tumour target tumour volume must be between the neck and the diaphragm in the thorax, trunk or an extremity.
- ii. Histologically confirmed diagnosis of metastatic soft-tissue sarcoma of including but not limited to one of the following subtypes: soft tissue sarcomas (leiomyosarcoma, myxoid liposarcoma, liposarcoma, undifferentiated pleomorphic sarcoma, fibrosarcoma, epithelioid, clear cell, and synovial sarcoma).
- iii. Age ≥ 18 years.
- iv. Life expectancy of >12 weeks.
- v. At least one site of accessible disease for pre- and post-treatment core biopsies.
- vi. At least two sites of measurable disease on CT/MRI scans as defined by RECIST 1.1.
- vii. ECOG Performance Status of ≤ 1 .
- viii. Adequate bone marrow function, defined as:
 - a. Absolute Neutrophil Count (ANC) $\geq 1.5 \times 10^9/L$ ($\geq 1,500/\mu l$);
 - b. Platelets $\geq 100 \times 10^9/L$ ($\geq 100,000/\mu l$);
 - c. Hemoglobin ≥ 9 g/dL (>5.6 mmol/L).
 - d. Prothrombin Time (PT) $\leq 1.5 \times$ ULN
 - e. Activated Partial Thromboplastin Time (aPTT) $\leq 1.5 \times$ ULN
 - f. Patients must be transfusion independent (ie, no blood product transfusions for a period of at least 14 days prior to study entry – to be assessed as part of the patient's medical history).
- ix. Adequate renal function defined by an estimated creatinine clearance ≥ 30 mL/min according to the Cockcroft-Gault formula.
- x. Adequate liver function, including:
 - a. Total serum bilirubin $\leq 1.5 \times$ upper limit of normal (ULN);

- b. Aspartate and Alanine aminotransferase (AST & ALT) $\leq 2.5 \times \text{ULN}$ or $\leq 5 \times \text{ULN}$ for patients with liver metastases.
- xi. Written, voluntary informed consent.
- xii. Patients that have had no previous chemotherapy treatment or have received ≥ 1 or more lines chemotherapy.
- xiii. Male patients and women of childbearing potential (WOCBP) and their male partners must agree to use 1 highly effective methods of contraception and a condom from giving informed consent for a period of 35 days prior to administration of first dose of avelumab, throughout treatment with avelumab and for at least 60 days after avelumab treatment. Women of childbearing potential include pre-menopausal women and women within the first 2 years of the onset of menopause. Women of childbearing potential must have a negative pregnancy test ≤ 72 hours prior to Day 1 of study as defined in section 7.3.7.
- xiv. Women of childbearing potential include pre-menopausal women and women within the first 2 years of the onset of menopause. Women of childbearing potential must have a negative pregnancy test ≤ 72 hours prior to Day 1 of study as defined in section 7.3.7. Further they will be asked to receive monthly pregnancy tests whilst on avelumab treatment and at the end of treatment. See [CTFG Contraception Guidance 15.09.2015](#). Subjects requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses ≤ 10 mg or 10 mg equivalent prednisone per day
- xv. Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) are acceptable.
- xvi. Patients with a contraindication to MRI (standard of care imaging for extremity disease only) can be entered into the study and will have CT based RECIST 1.1 assessments.
- xvii. In patients who have symptoms, when assessed using CTCAE v.4.0, these are of grade 0 or 1 severity only.
- xviii. **Patients who are on anti-coagulants can be considered at the investigator's discretion (includes patients in whom the anti-coagulant can be safely discontinued for the purpose of conducting a biopsy)**

6.2 Exclusion criteria

- i. Systemic chemotherapy within 35 days prior to study entry.

- ii. Prior systemic therapy target11/ng PD-1: PD-L1 axis.
- iii. Patients who are curable by conventional multidisciplinary management.
- iv. Patients with known central nervous system metastatic disease are ineligible for enrolment.
- v. Patients with severe and/or uncontrolled concurrent medical disease that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol.
- vi. Patients who have received radiotherapy ≤ 4 weeks prior to Day 1 of study or who have not recovered adequately from side effects.
- vii. Previous radiotherapy within the treatment area.
- viii. Patients who have active infections requiring therapy.
- ix. Patients with a history of Human Immunodeficiency Virus (HIV), Hepatitis B or Hepatitis C. Positive test for HBV surface antigen and / or confirmatory HCV RNA (if anti-HCV antibody tested positive).
- x. Patients that have a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the trial.
- xi. Patients who received systemic anti-cancer treatment prior to the first dose of study drug within the following time frames:
- xii. Patients who have received biologic therapy (e.g., antibodies) within 4 weeks.
- xiii. Patients who have undergone major surgery ≤ 2 weeks prior to starting study drug
- xiv. Patients with active autoimmune disease or a documented history of autoimmune disease or syndrome that requires systemic steroids or immunosuppressive agents. Patients with vitiligo or resolved childhood asthma/atopy would be exception to this rule. Patients that require inhaled steroids or local steroid injections would not be excluded from the study. Patients with hypothyroidism not from autoimmune disease that is stable on hormone replacement will not be excluded from the study.
- xv. Current use of immunosuppressive medication, EXCEPT for the following: a. intranasal, inhaled, topical steroids, or local steroid injection (eg, intra-articular injection); b. Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent; c. Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).
- xvi. Active autoimmune disease that might deteriorate when receiving an immuno-stimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible.
- xvii. Prior organ transplantation including allogenic stem-cell transplantation.
- xviii. Current severe acute or chronic colitis, inflammatory bowel disease, pneumonitis, pulmonary fibrosis.

- xix. Women who are pregnant or nursing/breastfeeding.
- xx. Known hypersensitivity to avelumab or another mAb.
- xxi. Patients with a history of non-infectious pneumonitis that has required a course of oral or intravenous steroids to assist with recovery, or interstitial lung disease.
- xxii. Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (\geq New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.
- xxiii. Patients requiring steroid replacement doses above physiological requirements will be considered ineligible for this study: allowed up to 20 mg hydrocortisone (or 5 mg of prednisolone) in the morning and 10 mg hydrocortisone (or 2.5 mg prednisolone) in the evening.
- xxiv. Patients with the risk factors for bowel obstruction or bowel perforation (examples include but not limited to a history of acute diverticulitis, intra-abdominal abscess, abdominal carcinomatosis).
- xxv. Patients who have received a live vaccine within 30 days prior to the first dose of trial treatment.
- xxvi. Previous malignant disease within the last 5 years with the exception of basal or squamous cell carcinoma of the skin or cervical carcinoma in situ.
- xxvii. Persisting toxicity related to prior therapy (NCI CTCAE v. 4.03 Grade > 1); however, alopecia, sensory neuropathy Grade \leq 2, or other Grade \leq 2 not constituting a safety risk based on investigator's judgment are acceptable.
- xxviii. Patients who have symptoms, which when assessed using CTCAE v.4.0, are of grade 2 severity or above.

7.1 Study Schedule Trial Period	Screening phase	Avelumab administration during Radiotherapy										End of treatment (if applicable) ⁶	Post-treatment			Survival Follow up to a maximum of 24 months		
		(can be repeated beyond 10 cycles to progression)											Safety Follow-up (30 days)	Extended Safety Follow-up (90 days)	Follow up Visits			
		C1	C2	C3	C4	C5	C6	C7	C8	C9	C10							
Treatment Cycle/ Title:		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 9	Wk 11	Wk 12	Wk 13	Wk 15	Wk 17	Wk 19	Every 12 wks from SFL		
Scheduling (Day)	-35 to -1	RT# 1-5	RT# 6-10	RT# 11-12														
Informed Consent	X																	
Inclusion/Exclusion	X																	
Demographics, Medical & Treatment History	X																	
Survival Status																		
New Anti-cancer therapy review																X		
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Con. Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Radiation Toxicity (RTOG)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Full Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Directed Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Vital Signs & Weight ¹	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Height	X																	
ECOG Performance	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Pregnancy Test ²	X								X wk8				X wk16		X wk20			
PT and aPTT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Haematology & Biochemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Urinalysis ³	X																	
T3, FT4 and TSH ⁴	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Admin.of Avelumab		X							X				X					
Admin of Radiotherapy		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Tumour Imaging-CT+/- MRI	X ⁵																	
Archival/New Tissue Sample	X															X ⁸		
Research biopsy (within irradiated site)	X ⁹																	
Optional research biopsy (outside irradiated site)	X ⁹																	
PD-L1 Sample collection	X																	
Research Blood Sample	X				X													

Table 1: Study Schedule

1. Weight can be performed within 72 hrs in advance of dosing.	7. Or before the initiation of a new anti-cancer therapy.
2. Pregnancy test will be performed within 72 hours prior to day 1 and monthly during treatment	8. Scans to follow standard of care, i.e. every 3 months
3. Urinalysis will be performed at least every 2 weeks during administration of IMP.	9. The tumour biopsies are done if patient consents and if this is deemed safely accessible for PD-L1 expression and biomarker research.
4. Thyroid Function Tests to be conducted every cycle (i.e. every fortnight) for the first 3 months and then monthly thereafter	
5. Imaging should every 12 weeks (regardless of treatment delays) after CT scans have been performed at weeks 7 and 13 (+/- 2 weeks). Images can be up to 7 days before visit to ensure results at the visit except for images acquired at 13 weeks which may be +/- 2 weeks. Extremely tumours to be imaged using MRI with staging CT. MRI intolerant patients will be imaged using CT only.	
6. This visit is only applicable if the patient comes off study for reason other than disease progression and no measurement had been taken within the last 4 weeks.	

7.2 Administrative Procedures/Assessments

7.2.1 Informed Consent

It is the responsibility of the Investigator / designee to give each patient, prior to inclusion in the trial, full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. Sufficient time should be allowed for the patient to decide on trial entry. Patients must be informed about their right to withdraw from the trial at any time. Written patient information must be given to each patient before enrolment. The written patient information is an approved patient information sheet (PIS) according to national guidelines.

The Investigator must obtain documented written informed consent from each potential patient prior to participating in a clinical trial. Consent must be documented by the patient dated signature on a consent form along with the dated signature of the person conducting the consent discussion. If the patient is illiterate, an impartial witness should be present during the entire informed consent reading and discussion. Afterwards, the patient should sign and date the informed consent, if capable. The impartial witness should also sign and date the informed consent along with the individual who read and discussed the informed consent. Only the Principal Investigator (PI) and those Sub-Investigator(s) delegated responsibility by the PI, having signed the delegation of responsibilities log, are permitted to gain informed consent from patients and sign the consent form. All signatures must be obtained before the occurrence of any medical intervention required by the protocol.

A copy of the signed and dated consent form should be given to the patient before participation in the trial. The original consent form should be stored in the site file and their participation in this trial recorded in their medical notes. Results from tests conducted as part of patients' standard care may be used as part of screening to determine eligibility as long as the tests were conducted within the acceptable time window.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the patient must receive the REC approval/favourable opinion in advance of use. The patient should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the patient's dated signature. The informed consent will adhere to REC requirements, applicable laws and regulations.

7.2.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria (see section 6) will be reviewed by the investigator or qualified designee to ensure that the patient qualifies for the trial.

7.2.3 Demographic Data, Medical History and Treatment History

Demographic data collected will include date of birth and race/ethnicity. A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. In addition any abnormal and clinically significant results seen during the screening period should be recorded in the medical history form. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history. In addition to the medical history the investigator or qualified designee will obtain details the patient's current disease status and treatment history including:

- Prior and current details regarding disease status
- Review all prior cancer treatments including systemic treatments, radiation and operations.

We will not routinely screen all patients with central nervous system imaging prior to entering this study. CNS metastases in soft tissue sarcoma are extremely rare (<5%). If a patient is suspected to have central nervous system metastatic disease then a CT/MRI scan will be performed to exclude disease involvement prior to consideration for entering the study.

7.2.4 Anti-Cancer Therapy Review

Patients that discontinue from avelumab for any other reason than progression will have a follow-up visit every 12 weeks in which the investigator should review all new anti-cancer therapy initiated after the last dose of trial treatment. If a patient initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-Up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the patient will move into the survival follow-up period which is not anticipated to extend beyond 24 months

7.2.5 Survival Status

The investigator or qualified designee will assess the patient for survival status at specified visits as defined in the schedule of study assessment (Table 1, Section 7.1) The assessment will include the patient status and if applicable details of patient death or details if patient has been lost to follow up. It is not anticipated that the survival phase will extend beyond 24 months for any given patient. Thus the end of the trial is anticipated to be no more than 3 years and 6 months from the date of enrolment of the first patient.

7.2.6 Prior and Concomitant Medications Review

7.2.6.1 Prior Medications

The investigator / designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the patient within 35 days before starting the trial. Treatment for the disease for which the patient has enrolled in this study will be recorded separately and not listed as a prior medication.

7.2.6.2 Concomitant Medications

In addition the investigator / designee will record all medication, if any, taken by the patient during the trial. All medications related to reportable SAEs and overdose and liver toxicity ECIs should be recorded as defined in Section 7.

7.3 Clinical Procedures/Assessments

7.3.1 Adverse Event (AE) Monitoring

The investigator / designee will assess each patient for potential new or worsening AEs as specified in the schedule of study assessment (Table 1, Section 7.1) and more frequently if clinically indicated. Adverse events will be graded and recorded from the first dose of avelumab until the patients' 30 day safety follow-up visit (following the last administration) according to NCI CTCAE Version 4.0 (see Appendix 1). Toxicities will be characterised in terms regarding seriousness, causality, toxicity grading,

and action taken with regard to trial treatment. An extended 90 day safety follow-up will be carried out during which toxicities will be similarly captured and characterised.

All AEs of unknown aetiology associated with avelumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) or a potentially immunologic aetiology (irAE). See Section 9 and Appendix 5 regarding the identification, evaluation and management of AEs of a potential immunological aetiology. Please refer to section 9 for detailed information regarding the assessment and recording of AEs.

7.3.2 Radiation Toxicity Assessment

Radiotherapy toxicity will be assessed using the RTOG radiation toxicity grading system (Appendix 2). Assessments will take place weekly during administration of Avelumab and during the maintenance phase.

7.3.3 Full Physical Exam

The investigator / designee will perform a complete physical exam at screening period. Clinically significant abnormal findings should be recorded as adverse events during the trial.

7.3.4 Directed Physical Examination

For cycles that do not require a full physical exam as described in the schedule of assessment (Table 1, Section 7.1), the investigator / designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.3.5 Vital Signs

The investigator / designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the schedule of study assessment (Table 1, Section 7.1) Vital signs should include pulse, weight and blood pressure. The weight can be measured 72 hours in advance of dosing. Where an accurate dose has been prescribed with a variation in the weight from baseline, a maximum of +/- 10% variance in dosage calculation is permitted.

7.3.6 Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator / designee will assess ECOG status (Table 2) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the study schedule of assessments (Table 1, Section 7.1).

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light Housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry Out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
*As published in Am. J. Clin. Oncol.:Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J ClinOncol 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

Table 2: ECOG Performance Status

7.3.7 Pregnancy Tests

Female patients (women) of childbearing potential (WOCBC) should have a negative urine or serum pregnancy test within 72 hours prior to administration of first dose of avelumab for confirmation of study eligibility. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Female patients will also be required to undergo additional pregnancy tests monthly from administration of first avelumab treatment, throughout treatment and at the end of avelumab treatment.

7.3.8 Haematology, Clinical Biochemistry and Urinalysis (β -hCG, PT, aPTT, T3,T4 and TSH)

Laboratory tests (including those carried out as part of routine care before consent and within 35 days of Day 1) will be performed during the screening phase and at the 30 days and 90 days post-treatment safety follow-ups. After this all pre-dose laboratory procedures should be conducted no more than 72 hours prior to dosing. Urinalysis will be performed at least every 2 weeks. Results must be reviewed by the investigator / designee and found to be acceptable prior to each dose of trial treatment. Samples will be analysed by the local study site laboratory using standard methods for routine tests.

The following variables (Table 3) will be measured:

Haematology	Chemistry	Urinalysis	Other
Haemoglobin	ALT	Blood	Thyroid Function Tests: TSH, free T4
Platelets	AST	Glucose	
WBC	Alk Phos	Protein	
Absolute Neutrophils	Sodium	Leucocytes	
Absolute Lymphocytes	Potassium	MC+S if urine dipstick positive	
Absolute Monocytes	Magnesium		
Absolute Eosinophils	Chloride		
Absolute Basophils	Total Calcium		
Prothrombin Time	Total Bilirubin		
Activated Partial Thromboplastin Time	BUN or Urea		
	Creatinine		
	Uric Acid		
	Glucose (non-fasted)		
	Albumin		
	Phosphorous or Phosphate		
	Total protein		
	Gamma glutamyl transferase		

Table 3: Required Laboratory Assessments

Adrenal insufficiency will be monitored with a clinical assessment (history and examination) and serum cortisol, electrolyte and glucose levels. Due to the low prevalence (0.6%) we have not mandated routine testing for adrenal insufficiency. Monitoring of adrenal function is included under the biochemistry testing (prior to administration of each cycle of avelumab, See Table 1).

7.3.9 Tumour Imaging and Assessment of Disease

7.3.9.1 Baseline Tumour Imaging

Imaging should be undertaken to confirm that the patient has disease that is measurable disease based on RECIST v1.1 where palliative radiotherapy is considered appropriate. The scan will also be assessed for a second lesion that will be outside the proposed irradiation field to assess for abscopal response. All baseline CT scans should be performed within 4 weeks of confirmation of eligibility of the trial entry. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within the correct time window. If these scans are done at baseline they can be used to assess local control at 7 weeks (4 weeks post radiotherapy). In addition, patients with limb tumours would normally have imaging using an MRI scan. A CT scan can be performed if the patient is unable to tolerate an MRI scan.

7.3.9.2 Follow-Up Tumour imaging

Follow-up CT scans (thorax abdomen and pelvis) should be performed every 12 weeks after starting avelumab. Patients will also have a CT scan performed at week 7 (4 weeks after completion of radiotherapy) and at week 13 (10 weeks after completion of radiotherapy). Additional scans will be taken every 12 weeks (regardless of treatment delays) until documented disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. Images can be taken up to 7 days prior to a scheduled visit to allow availability of results.

7.3.10 Tumour Tissue Collection and Correlative Studies Blood Sampling

7.3.10.1 Archival Tumour Tissue Samples

Archival tissue samples will be requested from the referring hospital for central pathological review (standard of care) to confirm histological diagnosis and will not routinely undergo further analysis. Archival tumour blocks will be returned to source at the end of the study or, upon request, earlier if required for the patient's clinical management. Cut sections will be retained by the study team. These are archived samples and as such participating patients will not need to attend extra visits or undergo extra procedures. All collected archival samples will be classed as pre-treatment samples and may be used as such in the immunological evaluation as described below.

7.3.10.2 Tumour Biopsies and Research Blood Samples

Research blood samples will be obtained in EDTA and/or Streck tubes (for ctDNA) at baseline and at 2 other time points during ongoing treatment. Circulating tumour DNA analysis will be analysed in the ICR according to standard operating procedures. Samples will undergo next generation sequencing to identify predictive biomarkers. Tumour and blood samples from this study will be sought for potential

future correlative work. Analysis of these samples will not yield genetic information of immediate concern to patients and thus results will not be shared with patients.

Tumour biopsies will be obtained during the screening period and if the patient consents optional research blood samples will be obtained at week 1, week 3 and week 7. Tumour and blood samples from this study may undergo proteomic, genomic and transcriptional analyses. Assays may include, but are not limited to:

- Characterisation of TILs and tumour antigens Immunohistochemistry (IHC) will be used to assess the number and composition of immune infiltrates in order to define the immune cell subsets present within formalin-fixed, paraffin embedded (FFPE) tumour tissue before and after exposure to therapy. These IHC analyses will include, but not necessarily be limited to, the following markers: CD4, CD8, FOXP3, PD-1, PD-L1, and PD-L2 (see Immunotherapy Trials Manual).

- ctDNA

7.4 Subject replacement Strategy

All patients who have received at least one cycle of avelumab and one fraction of radiotherapy will be included in the intention to treat population. However, for any patients unable to complete four fractions of radiotherapy, at least 2 doses of avelumab and the 11 weeks post initiation of radiotherapy and avelumab assessment (i.e. for acute toxicity), additional patients may be recruited. If a patient withdraws from the study before the 11 week post radiotherapy time point for reasons other than experiencing a DLT, then they cannot be included in making dose-escalation decisions. Up to a maximum of 16 patients can be recruited (due to funding restrictions), providing the reason for non-completion of therapy was not toxicity. A patient that discontinues the trial for progressive disease after the 11 week post radiotherapy acute toxicity assessment or a drug-related AE will not be replaced and will be counted in the evaluable population of patients for the respective cohort.

8.0 Treatments

8.1 Trial Treatments

Patients will be given avelumab in addition to palliative RT.

8.2 Standard Treatment-Radiotherapy

Radiotherapy will be delivered as outlined below. Patients will be treated with external beam RT. Planning will be done by conformal radiotherapy. The use of IV contrast is permitted if felt necessary. The gross target volume (GTV) will be defined as visible tumour on a planning CT scan. When administered without concurrent systemic therapy, 36 Gy in 12 fractions is within the normal radiotherapy tissue tolerance for all the organs at risk (OAR). Avelumab will be combined with radiotherapy, hence 3D dose-volume information for the tumour and the normal tissues will be obtained for subsequent analysis.

The CTV/PTV margin will be defined using standard Royal Marsden Hospital criteria for each anatomical site. Dose will be prescribed at 100% as per ICRU guidelines. Treatment verification with on-board imaging will be carried out as per departmental protocol.

8.2.1 Selection of sites suitable for radiotherapy

Patients must have at least two sites of measurable metastatic disease on CT/MRI scans defined by RECIST 1.1. Lesions must be at least 1 cm in size as measured by the widest dimension on CT/MRI scan. No upper limit of size is defined and this is left to the discretion of the clinical oncologist, taking into account the organs at risk (OAR) normal tissue tolerance constraints associated with irradiating each lesion. The radiation target volume must be between the neck and diaphragm, may include limbs, and be amenable to an image guided biopsy pre- and post- radiotherapy for the translational study.

8.2.2 Patient Preparation and Positioning

See Royal Marsden Hospital radiotherapy guidelines

8.2.3 Scan Limits and Slice Thickness

Recommended scanning levels are at least 4cm above and below the target volume to include the entire bowel or lungs. Target volumes will be defined on CT scan reconstructions and the CT slice thickness should be 3mm or less.

8.2.4 Localisation of the target volume and organs at risk (OAR), Volume Definition.

(See Royal Marsden Hospital Sarcoma radiotherapy guidelines)

The clinical target volume (CTV) is the contour encompassing the visible tumour, with a margin (1-2 cm) dependent upon the at risk area. The CTV will be expanded as to create the PTV. Organs at risk (OAR) will be outlined as solid structures by defining their outer wall. Normal structures to be outlined for post treatment analysis are dependent upon the anatomical site being irradiated:

Chest; heart, lungs and spinal cord

Limb; no OAR required unless tumour extends into the chest (then as above)

Volumes will be defined according to the International Commission on Radiation Units and Measurements (ICRU) report 50, supplement report ICRU 62: Prescribing, Recording and Reporting Photon Beam Therapy and ICRU 83: Prescribing, Recording and Reporting Photon-Beam Intensity Modulated radiotherapy (IMRT). Outlining should be carried out with the aid of all diagnostic MRI and CT scans.

8.2.5 Radiotherapy Treatment Administration

Lesion(s) will be irradiated to a dose 36Gy in 12 daily fractions over 2.5 weeks.

8.3 Trial Treatment-Avelumab

8.3.1 Investigational Product

Avelumab is a fully human antibody of the IgG1 isotype that specifically targets and blocks the ligand (PD-L1) for PD-1. Merck KGaA will package and distribute the IMP to the site via their distribution vendor - Fisher Clinical Services. The IMP will be shipped in transport cool containers (20°C to 80°C) that are monitored with temperature control devices.

8.3.2 Product Preparation

The investigational product avelumab is a sterile, clear, colourless and non-pyrogenic solution for intravenous infusion. It is presented in Type I glass vials filled with 10 mL of liquid (200 mg/vial), closed with a rubber septum and sealed with an aluminum flip off seal. Each single-use vial contains 200 mg of avelumab, formulated as a 20 mg/mL preservative-free acetate buffered solution at pH 5.2 in presence of Polysorbate 20 and Mannitol. This product requires further dilution prior to IV infusion. The IMP will be labelled with a medication number however supplies will be manually assigned by the pharmacy site personnel to study participants (no use of interactive voice/web response system).

8.3.3 Storage and Handling

8.3.3.1 Storage

Avelumab drug product must be stored at 2°C to 8°C until use. The storage condition is based on data from ongoing long term stability studies with avelumab. Avelumab drug product stored at room (23°C to 27°C) or higher temperatures for extended periods of time might be subject to degradation. Avelumab drug product must not be frozen. Rough shaking of the solution must be avoided.

For administration in clinical trials, avelumab drug product must be diluted with 0.9% saline solution (sodium chloride injection) supplied in an infusion bag; alternatively a 0.45% saline solution can be used if needed. The chemical and physical in-use stability for the infusion solution of avelumab in 0.45% or 0.9% saline solution has been demonstrated for a total of 24 hours at room temperature. However, from a microbiological point of view, the diluted solution should be used immediately and is not intended to be stored unless dilution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions prior to administration are the responsibility of the user.

No other drugs should be added to the solution for infusion containing Avelumab.

8.3.3.2 Handling

For administration in clinical trials, avelumab drug product must be diluted with 0.9% saline solution (sodium chloride injection) supplied in an infusion bag; alternatively a 0.45% saline solution can be used if needed. Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the manual of preparation (ISS avelumab Pharmacy Manual Template). Dose rounding to the nearest 0.1 mL is permitted.

To prepare the dilutions, subsequent preparation steps must be accomplished by adequate trained personnel under a laminar flow box using aseptic techniques:

Prior to the preparation of the dilution for final infusion, allow each vial to equilibrate to room temperature. Use a disposable syringe equipped with a needle of suitable size to remove a volume of sodium chloride solution to be replaced by avelumab from the infusion bag and discard the removed solution. Use a new disposable syringe equipped with a needle of suitable size to inject a volume of avelumab drug product identical to the discarded volume of sodium chloride solution into the infusion bag. Gently invert the mixture 10 times. Infusion bags must not be shaken, in order to avoid foaming

or excessive shearing of the protein solution. The preparation must be carefully inspected as it should result in a homogeneous looking clear solution, free of visible particles.

For detailed information on the assigned dose levels and the concrete volumes to be replaced to prepare the target doses, please refer to the Investigator's Brochure.

8.3.4 Supply, Packaging and Labelling information

Avelumab will be supplied by Merck KGaA as a sterile solution for dilution. Avelumab will be packaged, labelled and delivered to the participating site by Merck KGaA. The IMP will be supplied specifically for the trial and should not be used for any other purpose than that stated in this protocol. The drug will be labelled in accordance to Good Manufacturing Practice. As a minimum the labels will include the following information:

- a. name of the Sponsor (The Royal Marsden Hospital)
- b. each single vial contains 10 mL liquid (Avelumab), formulated as a 20 mg/mL solution
- c. batch number to identify the contents and packaging operation;
- d. blank space for recording the patient trial ID;
- e. directions for use;
- f. PI name
- g. Trial EudraCT number, Merck Serono protocol number, Royal Marsden protocol (CCR) number
- h. storage conditions;
- i. expiry date;
- j. "for clinical trial use only";
- k. "keep out of reach of children".

8.3.5 Returns and Reconciliation

The Investigator/designee is responsible for keeping accurate accountability records for avelumab including the amount dispensed to and returned for each patient and the amount remaining on site at the conclusion of the trial.

Upon completion or termination of the study, it is the Investigators/designee responsibility to ensure all unused drug is returned to Merck KGaA and partially used trial medication will be destroyed at the site per local guidelines and provide appropriate records of disposal to the sponsor with a copy being stored in the pharmacy site file.

8.3.6 Dose Selection

The rationale for selection the fixed dose to be used in this trial is provided in Section 2.4 –Rationale for Dose Selection/Regimen/Modification.

8.3.7 Administration of Avelumab

All patients will receive Avelumab administered as per standard procedures following manufacturer's instructions. Avelumab dose interval is 14days +/- 7 days. Tolerability of combining avelumab with radiotherapy will be examined at the fixed dose of 10mg/kg. In the event that incidence of DLTs indicate trial termination or dose reduction, dose may be reduced to 3mg/kg. In order to mitigate infusion-related reactions, a premedication with an antihistamine and with paracetamol (acetaminophen) 30 to 60 minutes prior to each dose of avelumab is mandatory (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol IV or oral). This may be modified based on local treatment standards and guidelines, as appropriate (see IB section 6.2.3).

Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access. Following avelumab infusions, patients must be observed for 30 mins post-infusion for potential infusion-related reactions.

Drug	Dose level	Dose/Potency	Dose Frequency	Route of administration	Regimen/Treatment Period
Avelumab	1	10 mg/kg	Week 1/ Week 3	IV infusion	During RT phase
			Every 2 weeks from week 5	IV infusion	Maintenance phase Until progression
Avelumab	0	3 mg/kg	Week 1/ Week 3	IV infusion	During RT phase
			Every 2 weeks from week 5	IV infusion	Maintenance phase Until progression
The Avelumab dosing interval may be increased due to toxicity as described in Section 8.3.8					

Table 4: Avelumab treatment regimens for each dosing level.

Trial treatment should begin within 2 weeks of confirmation of eligibility and as close as possible to the date on which treatment is allocated/assigned. Details on the preparation and administration of avelumab are provided in the IMP handling guidelines. These guidelines contain specific instructions for avelumab reconstitution, preparation of the infusion fluid, and administration.

8.3.8 Dose Modification

Avelumab will be withheld for drug-related grade 4 haematological adverse events and non-haematological adverse events of toxicity \geq Grade 3 including laboratory abnormalities (except for toxicities seen commonly with radiotherapy alone, namely grade 3 cystitis, urinary frequency and urinary incontinence). Drug will be withheld for grade 4 urinary toxicity and severe or life-threatening AEs as per Table 5 below.

Toxicity	NCI CTCAE Severity Grade	Treatment Discontinuation	Timing for Restarting Treatment
Haematological abnormalities	1	no	N/A
Haematological abnormalities	2	no	<ul style="list-style-type: none"> If toxicity resolves to Grade ≤ 1 by the next administration, treatment may continue. If toxicity does not resolve to Grade ≤ 1 by the next administration despite optimal treatment, next cycle infusion should be omitted. If, at the end of the following cycle, the event has not resolved to Grade ≤ 1, the patient should permanently discontinue treatment. Upon the second occurrence of the same Grade 2 toxicity that does not resolve to Grade ≤ 1 by the next administration, treatment must be permanently discontinued.
Haematological abnormalities	3	yes	Permanent discontinuation. <ul style="list-style-type: none"> Exceptions are: Single laboratory values that do not have any clinical correlate, and resolve to Grade ≤ 1 within 7 days with adequate medical management.
Haematological	4	yes	Permanent discontinuation.

abnormalities			<ul style="list-style-type: none"> Exceptions are: Single laboratory values that do not have any clinical correlate, and resolve within 7 days with adequate medical management.
Infusion-related Reaction	1-4		See section 16.5.1 and Table 11
Hypersensitivity reactions	3-4		See section 16.5.1
Tumour lysis syndrome	1-4		See section 16.5.1 and Figure 2
Immune-related AE (irAE)	1-4		See section 16.5.1 and Table 12
Other Non-hematologic Toxicities and Laboratory Abnormalities	1	no	Continue as per schedule
Other Non-hematologic Toxicities and Laboratory Abnormalities	2	no	<ul style="list-style-type: none"> If toxicity resolves to Grade ≤ 1 by the next administration, treatment may continue. If toxicity does not resolve to Grade ≤ 1 by the next administration despite optimal treatment, next infusion should be omitted. If after an additional 4 weeks the event has not resolved to Grade ≤ 1, the patient should permanently discontinue treatment (except for hormone deficiencies that can be managed by replacement therapy and for which up to 2 additional subsequent doses may be omitted). Upon the second occurrence of the same Grade 2 toxicity (except for hormone deficiencies that can be managed by replacement therapy), the treatment must be permanently discontinued.
Other Non-hematologic Toxicities and Laboratory Abnormalities	3	yes	<ul style="list-style-type: none"> Permanent discontinuation, Exceptions are: <ul style="list-style-type: none"> Transient (≤ 6 hours) flu-like symptoms or fever, which is controlled with medical management. Transient (≤ 24 hours) fatigue, local reactions, headache that resolves to Grade ≤ 1. Nausea and vomiting controlled by medical therapy Diarrhoea, skin toxicity, or liver function test (ALT, AST, or GGT) that resolves to \leq Grade 1 in less than 7 days after medical management (eg, immunosuppressant treatment) has been initiated. Amylase or lipase abnormality that is not associated with symptoms or clinical

			<p>manifestations of pancreatitis.</p> <ul style="list-style-type: none"> • Tumour flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumour. • Non hematologic laboratory abnormality that do not require medical intervention or hospitalization • Single non hematologic laboratory values that do not have any clinical correlate, and resolve to \leq Grade 1 within 7 days with adequate medical management.
Other Non-hematologic Toxicities and Laboratory Abnormalities	4	yes	<p>Permanent discontinuation.</p> <ul style="list-style-type: none"> • Exceptions are: <p>Non hematologic laboratory abnormality that does not require medical intervention or hospitalization</p> <p>Single non hematologic laboratory values that do not have any clinical correlate, and resolve within 7 days with adequate medical management.</p>

Table 5: Dose modification guidelines for drug-related AEs.

If the toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued at the discretion of the investigator. Patients with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. For information on the management of AEs, see section 9.

Patients who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of avelumab should be discontinued from trial treatment. RT-related AEs will be managed as per institution clinical guidelines.

Events of Clinical interest (ECI) can be potential immune related AEs and dose modifications for these toxicities should they occur can be found in Appendix 5.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 5 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

8.3.9 Timing of Dose Administration

Avelumab will be administered on an outpatient basis on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the schedule of study assessments (Table 1, Section 7.1). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. All trial treatments will be administered on an outpatient basis.

Avelumab will be administered as a 60 minute IV infusion (treatment cycle intervals or infusion length may be increased due to toxicity as described in Section 8.5.1.5). Due to the variability of infusion pumps from site to site, a window of -10 minutes and +20 minutes is permitted (i.e., infusion time is 60 minutes: -10 min/+20 min). In addition, infusion length may be increased due to toxicity as described in Section 8.5.1.5.

8.3.10 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor, investigator and patient will know the treatment being administered.

8.4 Concomitant Medications/Vaccinations (allowed and prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are also not allowed during the trial. If there is a clinical indication for one of these or other prohibited medications or vaccinations then discontinuation from trial therapy may be required. The Investigator should discuss any questions regarding this with the CI/designee/RM-CTU. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary physician. However, the decision to continue the patient on trial therapy schedule requires the mutual agreement of the Investigator, CI/designee, and the patient.

8.4.1 Acceptable Concomitant Medications

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

eCRF/CRF. All concomitant medications received within 35 days before the first dose and until the safety follow up visits at 30 and 90 days should be recorded.

8.4.2 Prohibited Concomitant Medications

Patients are prohibited from receiving the following therapies during the screening and treatment phase (including retreatment for post-complete response relapse) of this trial:

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Radiotherapy not specified in this protocol
- Investigational agents other than avelumab
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic aetiology. The use of physiologic doses of corticosteroids may be approved after consultation with the CI/designee.

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Patients may receive other medications that the investigator deems to be medically necessary. The Exclusion Criteria describes other medications which are prohibited in this trial. There are no prohibited therapies during the Post-Treatment Follow-up Phase.

8.5 Rescue Medications and Supportive Care

8.5.1 Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

8.5.1.1 Diarrhoea:

Patients should be carefully monitored for signs and symptoms of:

- Enterocolitis (diarrhoea, abdominal pain, blood or mucus in stool, with or without fever)
- Bowel perforation (peritoneal signs and ileus). In symptomatic patients, infectious aetiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.
- In patients with severe enterocolitis (Grade 3 with the exception of grade 3 diarrhoea during delivery of radiotherapy for <72 hours which responds to anti-diarrhoeal medication and becomes Grade 2 or less):
 - o Avelumab will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisolone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.
- In patients with moderate enterocolitis (Grade 2):
 - o Avelumab should be withheld and anti-diarrhoeal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisolone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Guidelines for continuing treatment with Avelumab can be found in Appendix 5.
 - o All patients who experience diarrhoea 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.

8.5.1.2 Nausea/vomiting:

Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.

8.5.1.3 Anti-infectives

Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

8.5.1.4 Immune-related adverse events:

Please see Section 8.5.2 below and the separate ECI guidance document regarding diagnosis and management of adverse experiences of a potential immunologic aetiology.

8.5.1.5 Management of Infusion Reactions:

Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumour pain (onset or exacerbation of tumour pain due to treatment); Urticaria (hives, welts, wheals); Vomiting.

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h.	Temporarily discontinue avelumab infusion. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop avelumab infusion immediately and disconnect infusion tubing from the subject. Subjects have to be withdrawn immediately from study avelumab and must not receive any further avelumab treatment.
<p>- If avelumab infusion rate has been decreased by 50% or interrupted due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed in the next scheduled infusion, the infusion rate may be returned to baseline at the subsequent infusions based on investigator's medical judgment.- If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice.</p>	

IV = intravenous; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs.

Table 6: Treatment guidelines for patients who experience an infusion reaction associated with administration of Avelumab.

8.5.2 Supportive Care Guidelines for Immune-related Adverse Event (irAE) and Immune-related Events of Clinical interest (irECI)

Immune-Related Adverse Events

Since inhibition of PD-L1 stimulates the immune system, immune-related AEs (irAEs) may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade):

Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring

Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4)

Grade 3 to 4: treat with high dose corticosteroids

Treatment of irAEs should follow guidelines set forth in the table below Table 7.

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v4)	Initial Management	Follow-up Management
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (e.g. loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2, 3 or 4.
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Withhold avelumab therapy Symptomatic treatment	If improves to Grade \leq 1: Resume avelumab therapy If persists > 5-7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4 Diarrhea (Grade 3): \geq 7 stools per day over Baseline; incontinence; IV fluids \geq 24 h; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated,	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone IV or equivalent Add prophylactic antibiotics for	If improves: Continue steroids until Grade \leq 1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3). If worsens, persists > 3 to 5 days, or recurs after improvement:

peritoneal signs Grade 4: life-threatening, perforation	opportunistic infections Consider lower endoscopy	Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.
Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4)	Initial Management	Follow-up Management
Grade 1 to 2 Covering ≤ 30% body surface area	Continue avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids)	If Grade 2 persists > 1 to 2 weeks or recurs: Withhold avelumab therapy Consider skin biopsy Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Covering > 30% body surface area; Grade 4: Life threatening consequences	Withhold avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	If improves to Grade ≤ 1: Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	Initial Management	Follow-up Management
Grade 1 Radiographic changes only	Consider withholding avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-assess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4.

Grade 2 Mild to moderate new symptoms	Withhold avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily; consider hospitalization 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤ 1 , taper steroids over at least 1 month, and then resume avelumab therapy following steroids taper If not improving after 2 weeks or worsening or for recurrent Grade 2: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening	Permanently discontinue avelumab therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤ 1 : Taper steroids over at least 1 month If not improving after 72 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4)	Initial Management	Follow-up Management
Grade 1 Grade 1 AST or ALT $> \text{ULN}$ to $3.0 \times \text{ULN}$ and/or Total bilirubin $> \text{ULN}$ to $1.5 \times \text{ULN}$	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4.
Grade 2 AST or ALT > 3.0 to $\leq 5 \times \text{ULN}$ and/or total bilirubin > 1.5 to $\leq 3 \times \text{ULN}$	Withhold avelumab therapy Increase frequency of monitoring to every 3 days.	If returns to Grade ≤ 1 : Resume routine monitoring; resume avelumab therapy. If elevation persists > 5 to 7 days or worsens: Treat as Grade 3 to 4.
Grade 3 to 4 AST or ALT $> 5 \times \text{ULN}$ and/or total bilirubin $> 3 \times \text{ULN}$	Permanently discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/	If returns to Grade ≤ 1 : Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local

	hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	guidelines.
Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4)	Initial Management	Follow-up Management
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue avelumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue avelumab therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	If returns to Grade ≤1: Taper steroids over at least 1 month.
Cardiac irAEs		
Myocarditis	Initial Management	Follow-up Management
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy. Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis.	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult,

	Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A).
<p>*Local guidelines, or eg. ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001</p>		
Endocrine irAEs		
Endocrine Disorder	Initial Management	Follow-up Management
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis	If secondary thyroid and/or adrenal	Resume avelumab once

(secondary endocrinopathies)	<p>insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH) :</p> <ul style="list-style-type: none"> Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) Hormone replacement/suppressive therapy as appropriate Perform pituitary MRI and visual field examination as indicated <p>If hypophysitis confirmed:</p> <ul style="list-style-type: none"> Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. Add prophylactic antibiotics for opportunistic infections. 	<p>symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement).</p> <p>In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented.</p> <p>Continue hormone replacement/suppression therapy as appropriate.</p>
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4)	Initial Management	Follow-up Management
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Speciality consult as appropriate	If improves to Grade ≤ 1 : Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy	If improves to Grade ≤ 1 : Taper steroids over at least 1

	1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Speciality consult as appropriate	month.
Grade 4	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Speciality consult as appropriate.	If improves to Grade \leq 1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency Persistent Grade 2 or 3 irAE lasting 12 weeks or longer	Permanently discontinue avelumab therapy Speciality consult	

Table 7: Management of Immune-Related Adverse Events

ADL = activities of daily living; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; irAE = immune-related adverse event; IV=intravenous; LFT = liver function test; LLN = lower limit of normal; MRI = magnetic resonance imaging; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; T4 = free thyroxine; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

8.5.3 Supportive Care Guidelines for Pneumonitis

Monitor patients for signs and symptoms of pneumonitis. If pneumonitis is suspected, evaluate with radiographic imaging. Exclude other causes of pneumonitis, and manage treatment in accordance with the guidelines above. Administer corticosteroids, withhold avelumab for moderate (Grade 2) pneumonitis, and permanently discontinue avelumab for severe (Grade 3) or life-threatening (Grade 4) pneumonitis.

8.6 Diet/Activity/Other considerations

8.6.1 Diet

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

8.6.2 Contraception

Avelumab may have adverse effects on a foetus in utero. Furthermore, it is not known if avelumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breastfeeding women may be enrolled if they are willing to use 1 highly effective methods of birth control and a condom or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥ 45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. Male patients and women of childbearing potential (WOCBP) and their male partners must agree to use 1 highly effective methods of contraception and a condom during the screening period (i.e. for a period of 35 days from giving informed consent prior to starting Avelumab), throughout treatment with avelumab and for at least 60 days after avelumab treatment. Women of childbearing potential include pre-menopausal women and women within the first 2 years of the onset of menopause. Women of childbearing potential must have a negative pregnancy test ≤ 72 hours prior to Day 1 of study as defined in section 7.3.7. They will also be asked to have pregnancy tests monthly whilst receiving avelumab treatment and at the end of treatment.

Birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Patient will be asked to adopt 1 of these methods and a condom. They include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
 - o oral
 - o intravaginal
 - o transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation
 - o oral
 - o injectable
 - o implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence

Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception. Patients should be informed that taking the study medication may involve unknown risks to the foetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the safety follow-up period. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study. See CTFG Contraception Guidance 15.09.2015.

8.6.3 Use in Pregnancy and Nursing Women

If a patient inadvertently becomes pregnant while on treatment with avelumab, the patient will immediately be removed from the study. The clinical team will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. If the outcome of the pregnancy is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn) this will be reported to RM-CTU without delay including the CI and sponsor within 24 hours. The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the foetus or newborn to the RM-CTU. If a male patient impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to RM-CTU and followed as described above and in Section 9.

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

8.7 Treatment of Overdose of IMP

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for avelumab by 5% over the prescribed dose. Please see section 9.7 for definitions and reporting procedures.

8.8 Permanent Discontinuation of Trial Medication and Withdrawal from Study

8.8.1 Permanent Discontinuation of Trial Medication

A patient may be permanently discontinued from the trial medication for any of the following reasons:

- The subject withdraws consent.
- Confirmed radiographic disease progression

Note: A patient may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved.

- Unacceptable adverse experiences as described in Section 8.5
- Intercurrent illness that prevents further administration of treatment
- The patient has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Administrative reasons

Trial patients will not be enrolled more than once. The primary reason for discontinuation should be recorded on the eCRF/CRF. Once the trial medication has been discontinued the patient should complete the end of treatment (if applicable) and safety follow-up visit procedures as listed in the schedule of study assessments (Table 1, Section 7.1). After the end of treatment, patients will continue to be assessed for AE and SAE monitoring until completion of the safety follow up visit. Patients who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone or in clinic for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

8.9 Withdrawal from the Study

Withdrawal from the study refers to discontinuation of both trial medication and future study visits / assessments; this can occur at any time according to the following reasons:

- Patient decision
- Lost to follow-up
- Death
- PI decision

Patients may withdraw consent at any time for any reason or have trial treatment stopped at the discretion of the investigator should any untoward effect occur. In addition, a patient may be withdrawn by the investigator if enrolment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. When a patient discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of

discontinuation. Any adverse events which are present at that time should be followed in accordance with the safety requirements outlined in Section 9.

9 Pharmacovigilance

Pharmacovigilance has been delegated by the Sponsor (Royal Marsden) to the Chief Investigator.

9.1 Definition of an Adverse Event (AE)

An AE is defined as any untoward medical occurrence (including deterioration of a pre-existing medical condition) in a patient or clinical trial patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol specified procedure.

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

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, onset of menses or menopause occurring at a physiologically appropriate time.

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

9.1.1 Disease Progression

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

9.1.2 New Cancers

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

9.1.3 Abnormal Laboratory Test Results

All clinically important abnormal laboratory test results occurring during the study will be recorded as AEs. Clinically important test results are those that require a medical intervention or change to IMP dosage. Any lab abnormalities considered to be related to the IMP will also be classed as AEs. The clinically important abnormal laboratory tests will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator, or until a diagnosis that explains them is made.

9.1.4 Pregnancy and Lactation

Pregnancy and lactation are not considered adverse events, however these events should be reported to the RM-CTU following guidance in section 9.2.2.

9.1.5 Radiotherapy toxicities

Radiotherapy toxicities are detailed in Table 10, Appendix 2. Except for 'myelitis', where all occurrences of any grade of severity must be regarded as unexpected, all radiotherapy toxicities of severity Grade 3 or above must be regarded as unexpected. No localised toxicities below the diaphragm are expected to occur as the radiotherapy treatment fields are not expected to extend below this point.

9.2 Assessing and Recording Adverse Events

All adverse events will be recorded from the time the consent form is signed until completion of the Safety Follow-up (30 days) and the Extended Safety Follow-up (90 days) in the eCRF/CRF. AEs will be followed up until resolution, stability or it is clinically feasible to do so. The final outcome must not only be documented in the eCRF/CRF but also recorded in the participant's medical records. Serious Adverse Events (SAEs) will also be recorded throughout the study until the two Safety follow-up visits outlined above (i.e. 30 and 90 days). The reporting timeframe for adverse events meeting any serious criteria is described in section 9.5.

Any unresolved AEs at the patient's last visit should be followed up for as long as medically indicated, but without further recording in the eCRF/CRF.

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

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

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

In addition, any adverse events occurring during the screening period that are a result of a protocol-specified intervention should also be recorded according to guidelines for standard AE reporting.

9.2.1 Evaluating Adverse Events

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

9.2.1.1 Determining AE Severity and Grade

AE severity and grade will be evaluated according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 and LENT SOMA radiation toxicity grading system. Any adverse event which changes CTCAE grade over the course of a given episode should be closed at the date the severity changed and a new AE recorded on the AE e-case report forms from that date at the new severity.

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation or hospitalisation indicated; disabling; limiting self-care ADL.

Grade 4 Life threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE

9.2.1.2 Determining AE Causality

The Investigator must endeavour to obtain sufficient information to determine the causality of the AE (i.e. IMP, other illness, progressive malignancy etc.) and must provide his/her opinion of the causal relationship between each AE and IMP. This may require instituting supplementary investigations of significant AEs based on their clinical judgment of the likely causative factors and/or include seeking a further opinion from a specialist in the field of the AE.

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

Table 8: Causality is the relationship of an AE to the IMP and will be determined as follows.

9.2.2 Reporting of Pregnancy and Lactation

It is the responsibility of investigators or their designees to report any pregnancy or lactation in a patient (spontaneously reported to them), including the pregnancy of a male patient's female partner that occurs during the trial or within 60 days of completing the trial, or 60 days following cessation of treatment if the patient initiates new anticancer therapy, whichever is earlier. All patients and female partners of male patients who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, foetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported. Such events must be reported within 24 hours to RM-CTU by Fax 0208 915 6762 who will inform CI, Sponsor and Merck KGaA.

9.3 Definitions of Serious Adverse Events (SAE)

An SAE is an AE occurring during any part of the study that meets one or more of the following criteria:

- Results in death;
- Is life threatening; or places the patient, in the view of the investigator, at immediate risk of death from the event as it occurred¹
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalisation²;
- Is a congenital anomaly/birth defect (in offspring of patient taking the product regardless of time to diagnosis);
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event.
- Is an important medical event that may not result in death, not be life threatening, or not require hospitalisation but may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the patient and require medical or surgical intervention to prevent such an outcome.

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

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

9.4 Definitions of Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events can also be classified as Events of Clinical Interest (ECI) and must be reported as described in section 9.6. Events of clinical interest for this trial include:

1. An overdose of avelumab, as defined in Section 9.7 that is not associated with clinical symptoms or abnormal laboratory results.

2. A Drug induced liver injury (DILI) defined as elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal AND / OR An elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal AND / OR An alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

3. Any AEs identified in the below table can be classified as immune-related events of clinical interest. A detailed narrative of the event should be reported as an ECI as described in section 9.6:

Pneumonitis - (reported as ECI if ≥Grade 2)		
Pneumothorax (reported as ECI if ≥ Grade 3)		
Acute interstitial Pneumonitis	Interstitial Lung Disease	Pneumonitis
Colitis - (reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotising colitis	Diarrhoea	
Endocrine - (reported as ECI if ≥Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis	Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA)	
Endocrine (reported as ECI)		
Type 1 diabetes mellitus (if new onset)		
Hematologic - (reported as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Autoimmune haemolytic anaemia	Aplastic anaemia	Thrombotic thrombocytopenic purpura

Idiopathic thrombocytopenia purpura	Disseminated intravascular coagulation	Haemolytic uraemic syndrome
Any grade 4 anaemia regardless of underlying mechanism		
Hepatic - (reported as ECI if ≥Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Hepatitis	Autoimmune hepatitis	Transaminase elevations (ALTand/or AST)
Infusion reactions - (reported as ECI for any grade)		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular - (reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Uveitis	Iritis	
Renal - (reported as ECI for ≥Grade 2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations - (report as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin - (reported as ECI for any grade)		
Dermatitis exfoliate	Erythema multiforme	Stevens-Johnson Syndrome
Toxic epidermal necrolysis		
Skin - (reported as ECI for ≥ Grade 3)		
Pruritus	Rash	Rash generalised
Rash maculo-papular	Any rash clinical significant in the physicians judgement.	
Other - (reported as ECI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other grade 3 event which is considered immune-related by the physician.		

Table 9: Immune related AEs considered ECIs.

A separate guidance document has been provided entitled “Event of Clinical Interest Guidance Document.” This document provides guidance regarding identification, evaluation and management of ECIs and irAEs. Any additional ECIs identified in this guidance document should also be reported as described in section 9.6. Patients should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and patients should be asked for signs and symptoms suggestive of an immune-related event. Patients who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune related.

9.5 Reporting of SAEs

Any SAE whether or not related to avelumab, occurring from informed consent up to the Safety Follow-up (30 days) and the Extended Safety Follow-up (90 days) following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, must be reported on an SAE report form within 24 hours of the PI or designee becoming aware of the event to the RM-CTU by Fax 0208 915 6762 who will inform the Chief Investigator and Merck KGaA.

All SAEs regardless of causality, pregnancy (as per section 9.2.2) or overdose (as per section 9.7) should be documented and each episode of an SAE must be recorded on a separate SAE report form. The NCI CTCAE Version 4 must be used to grade each SAE, and the worst grade recorded.

If new or amended information on a previously reported SAE becomes available, the Investigator should report this to the RM-CTU on a new SAE report form. If the SAE has not been reported within the specified timeframes, a reason for lateness must be included when sending the SAE report form. Please refer to the SAE completion guidelines for further information.

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

9.5.1 Events exempt from being reported as SAEs

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

1. Elective admissions to hospital for procedures which were planned and documented in the medical records at the time of consent are not SAEs, and do not require SAE reporting.
2. Hospitalisation for administration of the IMP, or to facilitate study procedures according to the trial protocol, is also exempt from being reported as an SAE.
3. Hospitalisation for the treatment of symptoms resulting from disease progression.

9.5.2 Determining SAE Expectedness

Assessment of expectedness for all SAEs will be made by the PI/designee and Chief Investigator or delegate against the current version of the Investigator Brochure. Section 6.2.6 of the IB, Table 52 'Expected Adverse Reactions in Patients treated with avelumab in Clinical Studies' defined expectedness of adverse reactions. It is important to note that, with reference to this table, the identification of any adverse reactions of Grade 3 and above where the number of Adverse Reactions (ARs) reported is '1' or '0' must be regarded as unexpected. In addition, the identification of any serious adverse reactions (SARs) where the number of SARs reported is '1' or '0' must be regarded as unexpected. If updated versions of the investigator brochure are released during the course of the trial then assessment of expectedness will be made against the current regulatory approved version.

9.6 Reporting of ECIs

Any ECIs irrespective of aetiology or whether or not related to the avelumab, occurring from the first dose until 30 days following the last treatment dose, or the initiation of a new anticancer therapy, whichever is earlier, must be recorded on the AE e-case report forms. These events should be reported using the SAE/ECI report form within 24 hours of the PI/designee becoming aware of the event to the RM-CTU who will inform the Chief Investigator, the Sponsor and Merck KGaA.

9.7 Definition of an Overdose for this Protocol and Reporting of Overdose

At present no specific information is available on the treatment of overdose of avelumab. For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for avelumab by 5% over the prescribed dose. In the event of overdose, avelumab should be discontinued and the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of avelumab, the adverse event(s) should be recorded on the AE eCRF/CRF and documented in the patients' medical records. The AE should also be reported as a serious adverse event, even if no other seriousness criteria are met. If an overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is again recorded as an AE on the eCRF/CRF and reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect." All reports of overdose either SAE or ECI must be reported within 1 working day of the PI or designee becoming aware of the event to the RM-CTU by Fax 0208 915 6762 who will inform the Chief Investigator and Merck KGaA.

9.8 Definition of Serious Adverse Reaction (SAR)

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

9.9 Definition of Suspected, Unexpected, Serious, Adverse Reactions (SUSARS)

A SUSAR is a SAR that is classified as 'unexpected' i.e. a SAR, the reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the Investigator Brochure (IB) for that product.

9.10 Reporting of SUSARS

The Investigator and local study team will rapidly report all SUSARs to the RM-CTU within 24 hours of becoming aware of the event.

The RM-CTU will ensure that SUSARs are notified to the appropriate regulatory authority, the relevant Independent Ethics Committee (IEC) / Institutional review board (IRB), the Chief Investigator, Merck KGaA, the Sponsor and the participating Principal Investigators in accordance with regulatory requirements and within the timelines as defined below:

- For fatal and life-threatening SUSARs the sponsor should report at least the minimum information as soon as possible and in any case no later than seven days after being made aware of the case.
- SUSARs which are not fatal and not life-threatening are to be reported within 15 days

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

9.11 Annual Reporting of Serious Adverse Events

Annual reports will be submitted to regulatory authorities and Independent Ethics Committees (IEC) by the Sponsor in accordance with all applicable global laws and regulations. Copies will be forwarded to the RM-CTU Trial Manager and Investigators.

9.12 Urgent Safety Measures

The Sponsor or Investigator may take appropriate urgent safety measures (USMs) in order to protect the patient of a clinical trial against any immediate hazard to their health or safety. This includes

procedures taken to protect patients from pandemics or infections that pose serious risk to human health. USMs may be taken without prior authorisation from the competent authority. The Medicines and Healthcare products Regulations Agency (MHRA) and the Research Ethics Committee (REC) must be notified within three days of such measures being taken.

Should the site initiate a USM, the Investigator must inform RM-CTU APPLE Trial Manager either by:

email: Apple.trial@rmh.nhs.uk

Telephone: 020 8915 6767

Fax: 020 8915 6762

The notification must include:

- the date of the USM;
- who took the decision; and
- why action was taken.

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

9.13 Safety reporting to Merck KGaA

The following reportable event's sponsor team must be submitted to Merck within 2 business days or 3 calendar days (whichever comes first) using the applicable safety report form for the study. APPLE Trial Manager in RM-CTU will assume responsibility for submitting the reportable event(s) to Merck as well as ensuring that any local reporting requirements are completed in parallel.

- Serious Adverse Events
- Exposure during Pregnancy or Breastfeeding (even if not associated with an adverse event)
- Occupational exposure (even if not associated with an adverse event)
- Events of Clinical Interest (ECI)
- Potential drug-induced liver injury (Hy's Law cases): These events are considered important medical events and should be reported as SAEs.

10 Statistics and Data Analysis

10.1 Sample size calculation

The sample size for this phase 1 study is not based on a formal sample size calculation as no statistical hypothesis is being tested. The total number of patients has been based on a desire to

obtain adequate tolerability, safety data while exposing as few patients as possible to the IMP and radiotherapy. From clinical experience, 36 Gy in 12 fractions delivered daily to the thorax, trunk, or extremities, is well tolerated with minimal toxicity.

Following entering the first 3 patients, recruitment will be deferred until they have been assessed for acute toxicity (i.e. 11 weeks from the initiation of combined radiotherapy and avelumab) by the SRC before recruitment of patients 4 to 6 can proceed – see Figure 1. The SRC will review toxicity following recruitment following recruitment of patient 6. If the incidence of DLTs is within acceptable limits (see Figure 1) and in the absence of grade 3/4 toxicity (RTOG ACUTE radiation Morbidity), the cohort will be expanded up to 12 patients. We will also monitor for grade 3/4 avelumab related toxicity as per the IMP brochure. We expect minimal overlapping toxicity between avelumab and radiotherapy.

10.2 Planned recruitment rate

The planned recruitment rate is one patient per month.

10.3 Subject Analysis Population

- The intention-to-treat (ITT) population

The ITT population will consist of all patients who receive 1 dose of avelumab and 1 fraction of radiotherapy.

- Acute toxicity population

The acute toxicity population will consist of all patients who received at least 1 dose of avelumab and at least 1 fraction of radiotherapy and are assessed up to 11 weeks from the start of radiotherapy and avelumab treatment unless they exhibit a DLT during this period).

- Late toxicity/efficacy population

The late toxicity population will include all patients who received at least one dose of avelumab and at least one fraction of radiotherapy and will be reported from 11 weeks+1 day from the start of radiotherapy and avelumab treatment until confirmed disease progression or initiation of new anti-cancer treatment therapy.

- Other secondary and exploratory objectives/endpoints population

This population will include all patients who received at least one dose of avelumab and at least one fraction of radiotherapy.

10.4 Statistical analysis plan summary

This is a phase 1 study designed to exclude a significant rate of G3-4 toxicity after an initial abbreviated dose escalation phase.

10.4.1 Primary and secondary outcomes and exploratory analysis methods

This study will recruit patients (radiation tumour target volume above diaphragm). Acute toxicity will be reported by week using CTCAEv4 grades, using the acute toxicity population. Worst grade will be reported as counts and percentages, by type of toxicity and over all types. Numbers of patients with missing and non-missing toxicity assessments will be reported for each week. Worst grades by type of toxicity and overall types will also be reported at all time points up to and including week 11 from the start of radiotherapy. The number and reasons for withdrawal before treatment completion will be stated. Acute toxicity will be reported for all patients grouped together regardless of dose level or disease stage.

Late toxicity will be reported by time point. The number and percentage of worst grade at that time point by type of toxicity, and overall types will be reported. Number of patients with missing and non-missing toxicity assessment will also be reported for each week. The late toxicity endpoint of the study will be reported as the number and percentage of patients experiencing any grade 2+ and grade 3+ late toxicity from week 11+1 day from the start of radiotherapy treatment. This will be reported at month 6 and month 12 from completion of radiotherapy. The late toxicity population will be used for all endpoints. An additional time to event analysis will be performed using Kaplan-Meier methods to show time to any grade 3+ toxicity from 11 weeks+1 day from the start of radiotherapy and avelumab treatment. Late toxicity will be reported for all patients grouped together regardless of dose level or disease stage.

Duration of local control will be measured from end of radiotherapy to date of first recorded local progression, using Kaplan-Meier methods. Patients without local progression will be censored at date of last follow-up or death from any cause. The percentage and 95% confidence intervals for rate of local control at 3 months after end of radiotherapy will be given. The late toxicity population will be used for this endpoint.

Local control will be reported for all patients comprising the cohort. Progression free survival and overall survival will be reported using Kaplan Meier methods, and will be measured from the start of avelumab treatment in the acute toxicity population. Survival rates and 95% confidence intervals will be given at 1 and 2 years.

All exploratory endpoints will be described using summary statistics (counts and percentages). A full

Statistical Analysis Plan (SAP) will be written and agreed by the Statistician and Chief Investigator before any analysis is performed. The total numbers of patients in the ITT population will be stated together with reasons for early withdrawal.

10.5 Timing and responsibility for analyses

The primary endpoint may be analysed and reported no earlier than 11 weeks following the start of radiotherapy and avelumab treatment for the last trial patient. All other secondary and exploratory endpoints may be analysed and reported no earlier than 6 months following the completion of radiotherapy treatment for the last trial patient. All endpoints will be reported only once, with the exception of late toxicity, progression free and overall survival, which may be reported for a second and final time once all patients have recorded any one of withdrawal, disease progression, death, or three years follow-up post radiotherapy.

11 Data Handling

11.1 Source Data

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

11.2 Language

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

11.3 Data Collection

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

11.4 Recording of Data

Patients' data will be recorded on a trial specific CRF designed by RM-CTU. Upon signing the informed consent form, the patient is assigned to the next sequential patient trial identification number available. To ensure recruitment is not delayed in any way a paper CRF will be available for use in the event that the electronic CRF is not ready for use.

The Investigator is responsible for ensuring the accuracy, completeness, clarity and timeliness of the data reported in the CRFs. Only the Investigator, and those personnel who have completed the Study Team Responsibilities Signature Log/Delegation Log as authorised by the PI, should enter or change data in the CRFs. All protocol required investigations must be reported in the CRF. The Investigators must retain all original reports, traces and images from these investigations for future reference. The data will be entered in a clinical trials database (Macro V4). If a patient withdraws from the study, the reason must be noted on the CRF.

Authorised site personnel must not enter study-specific data directly into CRFs and must ensure all results are appropriately documented in the patients' medical records. The CRF will be signed by the Investigator or by an authorised staff member. Study specific information will be entered into a CRF visit by visit. Data that are derived should be consistent with the source documents or the discrepancies should be explained. All CRF data should be anonymous, i.e. identified by study patient number only.

Once the patient is 'off study' and the CRF has been fully completed, the Investigator must provide a signature to authorise the complete patient data.

11.5 Data Management

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

12 Trial Oversight, Monitoring, Inspection and Audit

12.1 Study Management Structure

12.1.1 Delegations of Responsibilities

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

RM-CTU

RM-CTU has overall responsibility for facilitating and coordinating the conduct of the trial and is also responsible for collating data obtained, and undertaking and reporting all analyses.

The responsibilities of RM-CTU for the day-to-day management of the trial will include the following.

- Ensuring an appropriate ethics opinion has been sought, and any amendments have been approved.
- Giving notice of amendments to protocol, make representations about amendments to the Main REC and MHRA as applicable.
- Notifying site and Sponsor that the trial has ended.
- Raising and resolving queries with local investigators.
- Keeping records of all SAEs, overdose incidents, pregnancies and overdose and liver toxicity ECIs reported by investigators.
- Notifying the Main REC, MHRA and Investigators of related SAEs.

Merck KGaA

- Provision of avelumab

Participating Site

- Putting and keeping in place arrangements to adhere to the principles of GCP.

- Keeping a copy of all 'essential documents' (as defined under the principles of GCP) and ensuring appropriate archiving of documentation once the trial has ended.
- Taking appropriate urgent safety measures.
- Centres wishing to recruit to this study will be asked to provide evidence that they can deliver protocol treatment.
- Responsibilities are defined in an agreement between an individual participating centre and RM-CTU, which must be signed and in place before recruitment can commence.

12.2 Protocol compliance and amendments

The participating site will be required to sign an agreement with RM-CTU that includes requirement to sign and adhere to the trial protocol. Any protocol amendment should be agreed with the trial management group (TMG) and be approved by the sponsor prior to submission and review by the relevant Ethics Committee and the MHRA where required. Once favourable opinion from REC and if applicable the MHRA has been obtained the amendment can be distributed to the site and implemented. It is the responsibility of the Principal Investigator to submit amendment to their R&D department for R&D approval.

12.3 Trial Management

The RM-CTU will be responsible for trial management. This includes all duties relating to safety reporting. Once all relevant trial approvals are in place an initiation visit will be conducted. In addition, training and ongoing advice will be provided by the trial management team.

12.3.1 Trial Management Group (TMG) & Safety Review Committee (SRC)

A Trial Management Group (TMG) will be set up and membership will include Chief Investigator, Co-Investigators, Trial Statistician and Trial Manager. Principal Investigators and other key study personnel will be invited to join the TMG as appropriate. The role of the TMG will be defined in a TMG charter. Responsibilities will include, but not be limited to: operational responsibility for the conduct of the trial, monitoring of recruitment, safety and governance of the trial as well as collaborating with subsequent translational sub-studies. A Safety Review Committee will also be set-up and will have an independent Chair. The TMG will work in close co-operation with the SRC and as appropriate, will review any safety concerns as identified by the SRC. The membership of the SRC will be defined in an SRC Charter which will define the role of the Group and the frequency of meetings to ensure that all safety related events and side effects of all patients in the APPLE study are reviewed on a timely

basis. The statistician may not be required at every meeting but should be called upon if necessary. The format of this meeting will be concordant with that used for Phase I studies at RMH.

12.4 Monitoring

During the study, data quality will be monitored in accordance with relevant standard operating procedures (SOPs). Incoming data will be monitored for protocol compliance and if any inconsistent or missing data is identified queries will be sent to the site for resolution. Any systematic inconsistencies may trigger an onsite monitoring visit. The study will be monitored according to a risk-based monitoring plan. Remote monitoring and remote source data verification due to COVID-19 are to be amended on the risk-based monitoring plan.

The trial statistician will periodically examine the data for anomalies and outliers. Queries will be raised by the trial coordinators in such situations and communication with the clinical teams will take place. In addition statistical monitoring of unusual dates and inconsistent data will take place (for example clinic visits on Sundays). Again these will raise queries via the trial coordinators.

12.5 Quality Control and Quality Assurance

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

12.6 Clinical Study Report

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

12.7 Record Retention

Essential documents are documents that individually and collectively permit evaluation of the conduct of the trial and substantiate the quality of the data collected. During the clinical trial and after trial closure the Investigator must maintain adequate and accurate records to enable both the conduct of a

clinical trial and the quality of the data produced to be evaluated and verified in accordance with current legislation.

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

13 Ethical and Regulatory Considerations

13.1 Good Clinical Practice

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

13.2 Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

Before starting the trial, the protocol, patient information sheet, consent form, any other written information that will be provided to the patients and any advertisements that will be used and details of any patient compensation must be approved by the RM/ICR joint Committee for Clinical Research. Once approved, the study will then be submitted to the relevant Ethics Committee for their review and approval.

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

13.2.1 Initial Approval

Before starting the trial, the protocol, patient information sheet, consent form, any other written information that will be provided to the patients and any advertisements that will be used and details of any patient compensation must be approved by the RM/ICR joint Committee for Clinical Research and Merck. Once approved, the study will then be submitted to the relevant Ethics Committee and the

Health Research Authority (HRA) for their review and approval. Prior to the shipment of IMP and the enrolling of any patients the Investigator at the site is responsible for any site specific assessments and obtaining local R&D approval for the study.

13.2.2 Approval of Amendments

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

13.2.3 Annual Safety Reports and End of Trial Notification

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

13.3 Regulatory Authority Approval

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

13.4 Notifications of Serious Breaches to GCP and / or the Protocol

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

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

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

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

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

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

13.5 Insurance and Liability

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

13.6 Contact with General Practitioner (GP)

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

13.7 Patient Confidentiality

13.7.1 Patient Confidentiality and Data Sharing

The Chief investigator must ensure that the patient’s confidentiality is maintained in compliance with the UK Data Protection Act of 1998. On the CRFs or other documents submitted to the RM-CTU, patients should be identified by their initials and a patient study number only.

In compliance with GCP guidelines, it is required that the investigator and institution permit authorized representatives of the sponsor and of the regulatory agency(s) direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analysing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

13.7.2 Pharmacogenetics Confidentiality

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

13.8 Data collection and documentation

It is the Investigator's responsibility to ensure that all relevant data is clearly recorded in the medical records. The Investigator must allow the RM-CTU direct access to relevant source documentation for verification of data entered into the CRF, taking into account data protection regulations. The clinical data should be recorded in the CRF and the following must be verifiable by the source data: patient consent, medical history, patient's eligibility for participation in the trial, study treatment administration (avelumab and RT), routine haematology and biochemistry and response to treatment.

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

The Chief Investigator should confirm agreement with his/her local NHS Trust to ensure that

- sufficient data is recorded for all participating patients to enable accurate linkage between hospital records and CRFs
- source data and all trial related documentation are accurate, complete, maintained and accessible for monitoring and audit visits

- original consent forms are dated and signed by both patient and investigator and are kept together in a central log together with a copy of the specific patient information sheet(s) given at the time of consent
- all essential documents must be retained after the trial ends to comply with current legislation

No study document will be destroyed without prior written agreement between the Sponsor and the PI. Should the PI wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

13.9 End of Trial

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

13.10 Post trial access

If the study closes early, patients who continue to benefit from treatment will continue to receive avelumab and Merck will continue to supply the drug free of charge for these patients.

14 Dissemination policy and Authorship eligibility guidelines

The Study sponsor is The Royal Marsden Hospital and the trial will be registered on a publically accessible clinical trial registry (e.g. clinicaltrials.gov). The trial results will be submitted for publication in a relevant medical journal with authorship according to the criteria defined by the ICMJE (<http://www.icmje.org>). These state that: Authorship credit should be based 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3. A lay summary of the results will also be made available on the Royal Marsden's website.

Draft publications (manuscripts, abstracts, slides and posters) should be submitted to the RM-CTU for circulation to the relevant parties to allow sufficient time for review prior to submission. There will be a fifteen (15) day period to review abstracts or posters and a thirty (30) day period to review slides and manuscripts and respond to the author with any revisions.

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16. Appendices

16.1 Appendix 1: Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. Expected *versus* unexpected events are detailed for each organ system. For Myelitis (see end of Table) all occurrences of any grade of severity must be regarded as unexpected. <http://ctep.cancer.gov/reporting/ctc.html>

16.2 Appendix 2: RTOG Toxicity

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Skin	Follicular, faint or dull erythema / epilation / dry desquamation / decreased sweating	Tender or bright erythema, patchy moist desquamation / moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis	Death directly related to radiation effects
	<i>Expected</i>		NOT EXPECTED		
Pharynx & esophagus	Mild dysphagia or odynophagia / may require topical anesthetic or non-narcotic analgesics / may require soft diet	Moderate dysphagia or odynophagia / may require narcotic analgesics / may require puree or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss > 15% from pretreatment baseline requiring NG feeding tube, IV fluids, or hyperalimentation	Complete obstruction, ulceration, perforation, fistula	Death directly related to radiation effects
	<i>Expected</i>		NOT EXPECTED		

Upper GI	Anorexia with \leq 5% weight loss from pretreatment baseline / nausea not requiring antiemetics / abdominal discomfort not requiring parasympatholytic drugs or analgesics	Anorexia with \leq 15% weight loss from pretreatment baseline / nausea and/or vomiting requiring antiemetics / abdominal pain requiring analgesics	Anorexia with $>$ 15% weight loss from pretreatment baseline or requiring NG tube or parenteral support. Nausea and/or vomiting requiring tube or parenteral support / abdominal pain, severe despite medication / hematemesis or melena / abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Ileus, subacute or acute obstruction, perforation, GI bleeding requiring transfusion / abdominal pain requiring tube decompression or bowel diversion	Death directly related to radiation effects
	<i>Expected</i>		NOT EXPECTED		
Lung	Mild symptoms of dry cough or dyspnea on exertion	Persistent cough requiring narcotic, antitussive agents / dyspnea with minimal effort but not at rest	Severe cough unresponsive to narcotic antitussive agent or dyspnea at rest / clinical or radiological	Severe respiratory insufficiency / continuous oxygen or assisted ventilation	Death directly related to radiation effects

			evidence of acute pneumonitis / intermittent oxygen or steroids may be required		
	<i>Expected</i>		NOT EXPECTED		
Liver Bilirubin		<1.5 X N	1.5 - 3.0 X N	>3.0 X N	Death directly related to radiation effects
	<i>Expected</i>		NOT EXPECTED		
Liver Transaminase (SGOT, SGPT)	<=2.5 X N	2.6 - 5.0 X N	5.1 - 20.0 X N	>20.0 X N	Death directly related to radiation effects
	<i>Expected</i>		NOT EXPECTED		
Liver Alkaline Phosphatase or S'nucleotidase	<=2.5 X N	2.6 - 5.0 X N	5.1 - 20.0 X N	>20.0 X N	Death directly related to radiation effects
	<i>Expected</i>		NOT EXPECTED		
Liver/Clinical			Precoma	Hepatic coma	Death directly related to radiation effects
	<i>Expected</i>		NOT EXPECTED		

Nervous System Disorders Myelitis	Asymptomatic mild signs (e.g. Babinski's reflex or Lhermitte's sign)	Moderate weakness or sensory loss; limiting instrumental ADL	Severe weakness or sensory loss; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
NOT EXPECTED					

Table 10: RTOG toxicity

16.3 Appendix 3: Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumours

RECIST version 1.1* will be used in this study for assessment of tumour response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

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

16.4 Appendix 4: Immune-Related Response Criteria

The immune-RECIST (iRECIST)* will also be used in this study for assessment of tumour response.

*As published in HHS Public Access. Author manuscript *Lancet Oncol*. Author manuscript; available in PMC 2017 October 19. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. L.Seymour, J.Bogaerts, A.Perrone, R.Ford, L.H. Schwartz, S. Mandrekar, N.U. Lin, S. Litière. **16.5 Appendix 5: Management of Avelumab-Specific Adverse Events or Adverse Drug Reactions**

Once the avelumab infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for all subsequent infusions. If the subject has a second infusion-related reaction Grade ≥ 2 on the slower infusion rate, the infusion should be stopped and the subject should be removed from study treatment. If a subject experiences a Grade 3 or 4 infusion-related reaction at any time, the subject must discontinue study drug.

Severe Hypersensitivity Reactions and Flu-Like Symptoms

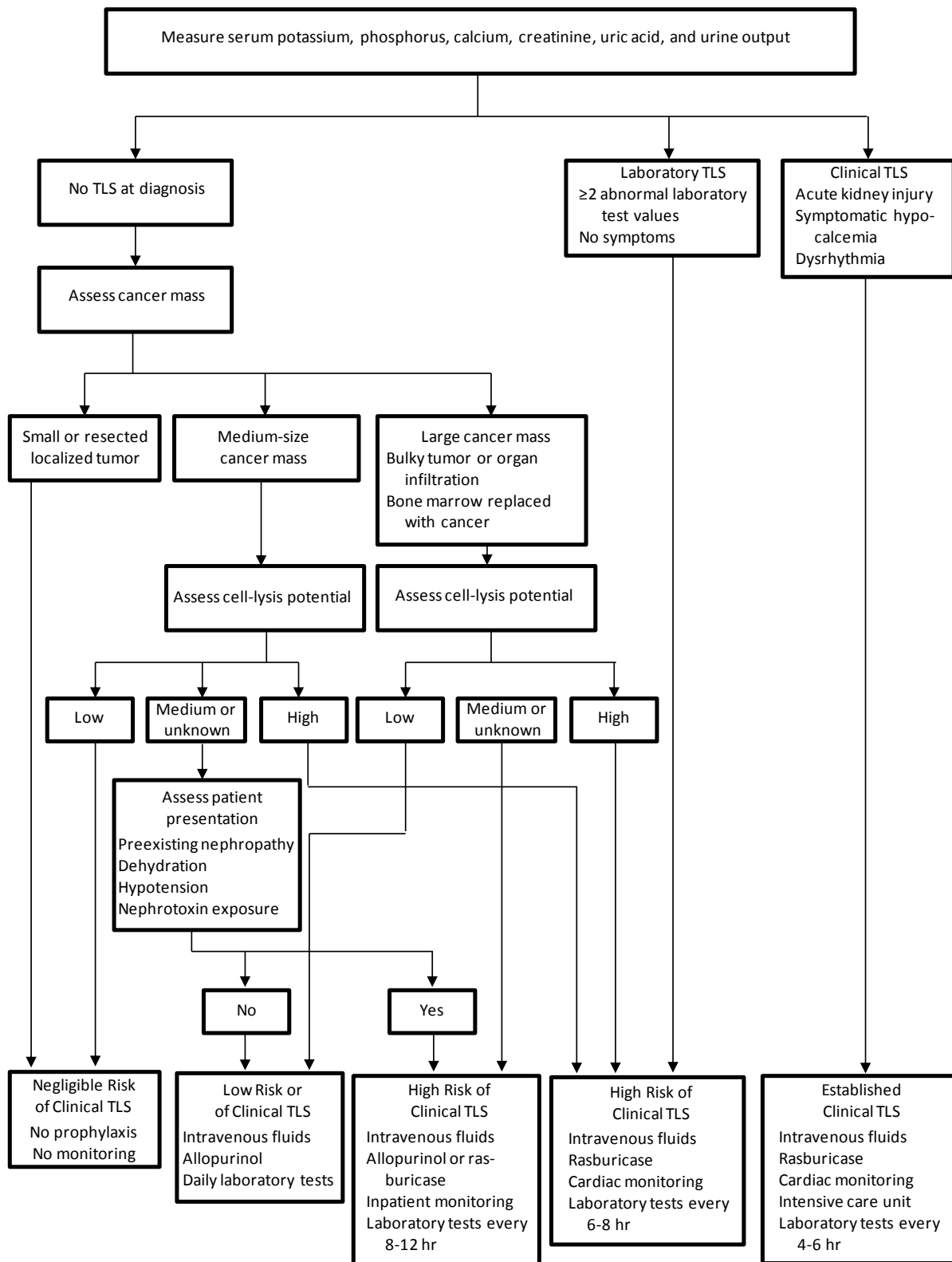
If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. Subjects should be instructed to report any delayed reactions to the Investigator immediately.

For prophylaxis of flu-like symptoms, 25 mg of indomethacin or comparable nonsteroidal anti-inflammatory drug (NSAID) dose (for example, ibuprofen 600 mg, naproxen sodium 500 mg) may be administered 2 hours before and 8 hours after the start of each dose of avelumab IV infusion. Alternative treatments for fever (for example, paracetamol) may be given to subjects at the discretion of the Investigator.

Tumour Lysis Syndrome

In addition, since avelumab can induce antibody-dependent cell-mediated cytotoxicity, there is a potential risk of tumour lysis syndrome. Should this occur, subjects should be treated per the local guidelines and the management algorithm below ([Howard et al, 2011](#)).

Assessment and Initial Management of Tumour Lysis Syndrome



TLS = tumour lysis syndrome - Figure 2

Immune-Related Adverse Events

Since inhibition of PD-L1 stimulates the immune system, immune-related AEs (irAEs) may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade):

Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring

Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4)

Grade 3 to 4: treat with high dose corticosteroids

Treatment of irAEs should follow guidelines set forth in the Table 7.

16.6 Appendix 6: Management of Spontaneous Pneumothorax

Management of spontaneous pneumothorax should be carried out as described in the BTS Guideline document (MacDuff et al 2010).

16.7 Appendix 7: Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
First Approved Final Version for external submission and appended to Contract	1.0	2 Jan 2018	CI / Trial Manager	First approved protocol with incorporation of CCR and PV comments.
Updated version in response to MHRA Grounds for Non-Acceptance	1.1	6 Mar 2018	Trial Manager	Incorporation of MHRA comments to address grounds for non-acceptance.
Updated version in response to REC comments (received: 06/03/2018) and Sponsor comments (received: 13/04/2018)	2.0	19 April 2018	Trial Manager / Chief Investigator	Incorporation of REC comments and including Sponsor comments following review of REC-included comments.

Change (v 3.0) 15 th Jan 2020	Rationale	Relevant protocol sections
Inclusion of ClinicalTrials.gov registration number. Update Protocol version & Date	NCT Number obtained since previous version.	Title page / Summary Table
Updates to signature page	Sign-off of new version	Signature page
Updates to Key Trial Contacts	Change of personnel	Key Trial Contacts and protocol Contributors
Clarification of inclusion criteria regarding: 1) number of lines of previous chemotherapy allowed 2) Patients on anti-coagulants	Statement clarified to avoid possible misinterpretation and to make it clear that CT naïve patients are eligible Patients on anti-coagulants need not be excluded if the Investigator agrees that their anti-coagulant can be safely discontinued for the purposes of conducting a biopsy	Summarised Eligibility Criteria, bullet point 6 Section 6.1, Inclusion Criteria, number xii Section 6.1, Inclusion Criteria, number xviii and Exclusion Criteria, number xxviii
Clarification regarding the conducting of optional biopsies.	New wording added at request of CI to ensure appropriate patient protection and that patients that may be at risk of potential SAE during the procedure are not invited to receive an optional biopsy	Section 2.5.2, paragraph 3
Clarification of definition of DLT	The term 'colitis / diarrhoea' is felt to be more appropriate than diarrhoea alone. Further, colitis which is relevant was not previously stated.	Section 4.2.1, bullet points 2 & 3
Updates to the Trial Procedures table	Inclusion of fortnightly thyroid function tests as recommended by ESMO guidelines Clarification that it is PD-L1 sample collection as opposed to collection and analysis – which may be performed at a later stage.	Section 7.1 'Trial Procedures' table

	Clarification of the key to the table.	
Allowance of flexibility in delivery interval of 14 days between administrations of IMP.	A window for administration is required to accommodate ad-hoc and unavoidable changes in IMP administration.	Section 8.3.7
Clarification of the time-period and tool used to assess radiotherapy-induced toxicity (RTOG). Removal of CTCAE grading in this respect. Update time-period for toxicity review during the maintenance phase (i.e. post-radiotherapy) to allow flexibility in the time-frames for capturing this information.	Consistency with other studies in which RTOG is used for the assessment of radiotherapy-induced toxicity. Increased flexibility in toxicity assessments post-radiotherapy.	Section 7.3.2
Replacement of all references to irRECIST with iRECIST	iRECIST is now the recommended tool to assess tumour response in studies employing immunotherapy agents (e.g. PD-L1).	References throughout the protocol.
PIS – ICF	Include GDPR Statement Include changes to the Investigator Broucher v10	PIS – ICF version 4.0 15 Jan 2020 Immune side effects observed in less than 1% of patients. A disease that results when the immune system blocks the normal nerve activity in the muscles causing muscle weakness (myasthenia gravis/myasthenic syndrome); may include weakness in the arms, hands, fingers, legs, and neck weakness of the eye muscle; double vision; drooping eyelid; difficulty swallowing; impaired speech;

		and shortness of breath.
PIS – Biopsy – ICF	Patient to sign consent the day of the biopsy	PIS – Biopsy PIS + ICF Clean v1.0 Jan 2020