Imperial College London

A Phase Ib Study of Pembrolizumab following Trans-Arterial Chemoembolization in Primary Liver Carcinoma

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Imperial College London

CONTACT LIST

Chief Investigator

Dr. David James Pinato, MD MRes MRCP (UK) PhD

Imperial College London
Level 2 IRD Building
Hammersmith Hospital
Du Cane Road
London
Email: David.Pinato@imperial.ac.uk
Tel: +44 (0) 207 594 2804
Fax: +44 (0) 203 311 0203

Sponsor

Ruth Nicholson, Head of Research Governance and Integrity Team Imperial College London
Room 221
Medical School Building
St Mary's Campus
Norfolk Place
London, W2 1PG
Email: r.nicholson@imperial.ac.uk
Tel: +44 (0) 20 75941872
Fax: +44 (0)20 33110203

Funder

Merck Sharp & Dohme Limited
West Hill Cottage,
Hertford Rd, Hoddesdon,
Hertfordshire EN11 9BU,
United Kingdom
Tel: +44 1992 467272

Laboratories

Frank Lynch, Vice President / COO

QualTek Molecular Laboratories
300 Pheasant Run
Newtown, PA 18940
USA
Tel: (215) 504-7402

Investigational Medicinal Product (IMP)/Device Manufacturing Facilities

MSD Ireland (Carlow)
Dublin Road
Carlow
Ireland
Tel: +353 (0) 59917 2600

ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	Aspartate aminotransferase
BCLC	Barcelona Clinic Liver Cancer
BP	Blood pressure
BW	Body Weight
CI	Confidence Interval
CI	Chief Investigator
CrCl	Creatinine Clearance
CTC	Circulating Tumour Cells
CNS	Central Nervous System
CR	Complete Response
CRP	C reactive Protein
CT	Computed Tomography
DBL	Database Lock
DEB	Drug-eluting beads
dL	Deciliter
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DRAE	Drug Related Adverse Events
EASL	European Association for the Study of the Liver
EC50	Half maximal effective concentration
eCRF	electronic Case Report Form
ECI	event of clinical interest
ECG	Electrocardiogram
ECI	Evidence of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Collection
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End Of Treatment
EOT	End Of Trial
EPO	Erythropoietin
FBC	Full Blood Count
FDA	Food and Drug Administration
FIH	First In Human
FU	Follow Up
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GMP	Good Manufacturing Practice
GPC3	Glypican-3
HCC	Hepatocellular Cancer
HCV	Hepatitis C Virus
HCV- RNA	Hepatitis C Virus - Ribonucleic Acid
Hif-1a	Hypoxia-inducible factor 1-alpha
HIV	Human Immunodeficiency Virus
HRA	Health Research Authority
IB	Investigator Brochure
ICF	Informed Consent Form

ICH	International Conference on Harmonisation
ICH GCP	International Conference on Harmonisation for Good Clinical Practice
ITT	Intention to Treat
IDSMC	Independent Data & Safety Monitoring Committee
Ig	Immunoglobulin
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
irAE	Immune-related adverse events
irECI	Immune-Related Evidence of Clinical Interest
ITIM	Immunoreceptor Tyrosine-based Inhibition Motif
iTMF	Investigator Trial Master File
ITSM	Immunoreceptor Tyrosine-based Switch Motif
ISF	Investigator Site File
IV	Intravenous
L	Litre
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
m	Metre
m2	Metre2
mAb	Monoclonal Antibody
mcL	Microlitre
MedDRA	Medical Dictionary for Regulatory Activities
MEL	Melanoma
mg	Milligramme
MHRA	Medicines and Healthcare Products Regulatory Agency
µM	microMolar
min	Minute
mL	Millilitre
mM	Millimolar
mmol/L	Millimoles per litre
mRECIST	modified Response Evaluation Criteria In Solid Tumours
MSD	Merck Sharp & Dohme Limited
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
NCI-CTCAE	National Cancer Institute –Common Terminology Criteria for Adverse Events
NIMP	Non Investigational Medicinal Product
NICE	National Institute for Health and Clinical Excellence
nmol	Nanomoles
nmol/L	Nanomoles per litre
NSCL	Non-Small Cell Lung
NSCLC	Non-Small Cell Lung Cancer
OL	Open Label
ORR	Overall Response Rate
OR	Odds Ratio
OS	Overall Survival
OTC	Over-the-counter
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive Disease
PD	Pharmacodynamic
PFS	Progression-Free Survival
PFSR	Progression-Free Survival Rate
PI	Principal Investigator

PIS	Participant Information Sheet
PK	Pharmacokinetic
PR	Partial Response
PS	Performance Status
PT	Prothrombin Time
PT	Preferred term
QOL	Quality Of Life
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q8W	Every 8 weeks
QA	Quality Assurance
QC	Quality Control
RBC	Red Blood Cell
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Stable Disease
SFU	Safety Follow Up
SJS	Stevens-Johnson Syndrome
SOC	Standard of Care
SOC	System Organ Class
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAA	Tumour Associated Antigens
TACE	Trans-Arterial Chemoembolization
TB	Tuberculosis
TEN	Toxic Epidermal Necrolysis
T3	Triiodothyronine
T4	Thyroxine
TILs	Tumour-infiltrating lymphocytes
TK	Toxicokinetic
TMG	Trial Management Group
TSH	Thyroid-Stimulating Hormone
UK	United Kingdom
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell
WHO DD	World Health Organisation Drug Dictionary

Contents

TRIAL SUMMARY

Title	A Phase Ib Study of Pembrolizumab following Trans-Arterial Chemoembolization in Primary Liver Carcinoma (PETAL).
Trial Phase	Ib
Clinical Indication	Primary Liver Cancer
Trial Type	Open label (OL), Single arm
Route of administration	Intravenous (IV)
Trial Blinding	None
Treatment Groups	1
Number of Trial Participants/ Sites	26-32 evaluable participants / 1-4 UK sites
Estimated duration of trial	3 Years 3 Months
Duration of Participation	Until disease progression or intolerance, withdrawal or completion of 1 year of treatment.
Study Objectives	*Primary Objective* • To determine the safety and tolerability of Pembrolizumab following Trans-Arterial Chemoembolization (TACE). *Secondary Objective* • To evaluate the efficacy of Pembrolizumab following TACE by improving progression-free survival rates (PFSR) as measured by modified Response Evaluation Criteria In Solid Tumours (mRECIST) criteria at pre-defined 12-weekly timepoints. *Exploratory Objective* • To evaluate predictive correlates of response to Pembrolizumab in hepatocellular cancer (HCC).
Study Endpoints	*Primary Endpoint* • To assess the safety and tolerability of Pembrolizumab using National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (NCI CTCAE v4). *Secondary Endpoints* • To evaluate the efficacy of Pembrolizumab following TACE using PFSR at 12 weeks (every 4 cycles) based on mRECIST criteria. *Exploratory Endpoints* • To evaluate the efficacy of Pembrolizumab following TACE by improving PFSR as measured by standard Response Evaluation Criteria In Solid Tumours (RECIST) criteria v 1.1 at pre-defined 12-weekly timepoints. • To identify biomarkers of immune response to Pembrolizumab using high-throughput technologies.

Summary of Main Inclusion Criteria	In order to be eligible for participation in this trial, the participant must: 1. Be willing and able to provide written informed consent/assent for the trial. 2. Be ≥ 18 years of age on day of signing informed consent. 3. Have a diagnosis of Hepatocellular Cancer (HCC) based on AASLD criteria (Appendix 1). 4. Have at least one uni-dimensional lesion measurable by Computed Tomography (CT)-scan or Magnetic Resonance Imaging (MRI) based on mRECIST criteria. 5. Patients who received prior TACE treatment (conventional or DEB-TACE) are eligible, provided they have at least one previously untreated lesion that is measurable based on mRECIST criteria. 6. Be ineligible for surgical resection or liver transplantation. 7. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale 8. Demonstrate adequate organ function 9. Have an overall Child-Pugh score ≤7 10. Female subject of childbearing potential should have a negative urine or serum pregnancy. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. 11. Women of childbearing potential must be willing to use a highly effective method of contraception as outlined in Section 6.9.2 for the course of the study through 120 days after the last dose of Investigational Medicinal Product (IMP). *Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.* 12. Sexually active males must agree to use an adequate method of contraception as outlined in Section 6.9.2 starting with the first dose of IMP through 120 days after the last dose of study therapy. *Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.*
Summary of Main Exclusion Criteria	The participant must be excluded from participating in the trial if the participant: 1. Has extrahepatic metastasis. 2. Systemic anticancer treatment for HCC. 3. Has any contraindication for TACE including portosystemic shunt, hepatofugal blood flow, known severe atheromatosis. 4. Has history of bleeding within the 4 weeks preceding study enrolment. 5. Has hepatic encephalopathy. 6. Has ascites that is refractory to diuretic therapy. 7. Has documented occlusion of the hepatic artery or the main portal vein (segmental portal vein thrombosis does not represent exclusion criterion provided this does not contraindicate TACE).

	8. Is currently participating and receiving therapy or has participated or is participating in a study of an IMP or used an investigational device within 4 weeks of the first dose of IMP. 9. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy. 10. Has a known history of active Bacillus Tuberculosis (TB) 11. Hypersensitivity to Pembrolizumab or any of its excipients. 12. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or *in situ* cervical cancer. 13. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. 14. Has known history of, or any evidence of active, non-infectious pneumonitis. 15. Has an active infection requiring systemic therapy. Exceptions relating to Hepatitis B and C virus infection are documented in Section 5.3.1, Table 5. 16. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating Principal Investigator (PI). 17. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial. 18. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through to 120 days after the last dose of IMP. 19. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent. 20. Has a known history of Human Immunodeficiency Virus (HIV; HIV 1/2 antibodies). 21. Has received a live vaccine within 30 days of first dose of IMP administration. *Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.*
Treatment / Main Study Procedures	**TACE.** Trans-arterial chemoembolization will be performed as a background treatment and as such is classed as a Non Investigational Medicinal Product (NIMP) for the purpose of this study. Treatment will consist of the infusion of cytotoxic chemotherapy after arterial hepatic angiogram, followed by

	either selective or super-selective embolization of the arterial vascular bed perfusing the tumour with gelatin/sponge particles. TACE procedure will be standardised across sites and will consist of conventional or drug-eluting beads (DEB) transcatheter superselective arterial chemoembolization utilising doxorubicin at either a fixed dose of 60 mg (for conventional TACE) or a dose ranging from 75-150mg depending on the size of the tumour (for DEB-TACE) followed by tumour vasculature embolization with gelatin sponge particles. TACE is normally administered as a short elective inpatient treatment to allow for monitoring of immediate post-procedural complications. Radiologic follow up after TACE with contrast-enhanced CT or MRI scan will be performed approximately 30 days after TACE as part of SOC prior to IMP administration. Participants who fail to achieve complete tumour devascularisation after the first session of TACE as assessed by follow-up contrast-enhanced scan may be allowed up to 1 further TACE session as per European Association for the Study of the Liver (EASL)/European Organisation for Research and Treatment of Cancer (EORTC) clinical guidelines unless clinical or technical factors preclude repeat treatment. In patients requiring re-treatment, re-screening is not required and time intervals for commencement of IMP and subsequent Dose Limiting Toxicity (DLT) window will remain unchanged. **Pembrolizumab.** IMP administration will begin no earlier than 30 + 3 days following TACE administration. IMP should be administered on an outpatient basis on Day 1 ± 3 days of each cycle after all procedures/assessments have been completed. Pembrolizumab will be administered at the pre-planned dose as a 30 (-5/+10) minute (min) IV infusion every 3 weeks (Q3W).

1.0 INTRODUCTION

1.1 Background

1.1.1 Hepatocellular Carcinoma and trans-arterial chemoembolization.

Hepatocellular carcinoma is the sixth commonest and third most lethal solid malignancy on a global scale[1]. Approximately 60% of patients who are newly diagnosed with HCC do not qualify for curative treatments including liver resection or transplantation[2]. Patients presenting with liver-confined HCC, preserved liver function and performance status cluster into "intermediate stage" or Barcelona Clinic Liver Cancer (BCLC) B stage. In this patient subgroup, where overall survival (OS) often extends beyond 2 years, guidelines recommend TACE with the intent of prolonging OS by achieving local disease control and prevent systemic spread of the disease [3].

The use of TACE in unresectable HCC as a palliative measure to improve survival whilst maintaining quality of life (QOL) is supported by level I evidence stemming from 2 primary randomized controlled trials and subsequent meta-analyses. The efficacy of TACE relies on the dual ischaemic and cytotoxic effect stemming from the sequential intra-arterial delivery of cytotoxic chemotherapy (doxorubicin, epirubicin or cisplatin) followed by direct occlusion of the arterial neo-vascular supply to the tumour. Clinically, this translates into radiologically measured responses in 35% of patients (range, 16%-61%), which correlate with a 14% improvement of patients' survival at 2-years (odds ratio [OR], 0.53; 95% confidence interval [CI], 0.32-0.89; P =.017)[3].

1.1.2 Pharmaceutical and Therapeutic Background

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumours to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Immunoglobulin (Ig) superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double

negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumours. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumour-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumour immune evasion and should be considered as an attractive target for therapeutic intervention[4].

Anti-tumour immunotherapy with monoclonal antibodies blocking the PD-1/PD-L1 “immune synapse” is gaining momentum in the treatment of a growing number of malignancies, where immune checkpoint inhibitors directed against PD-1 including nivolumab (Opdivo™, BMS) or Pembrolizumab (Keytruda™, MSD) have, amongst others, received accelerated regulatory approval for the treatment of solid tumours[5-7].

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

In the specific setting of HCC, immunotherapy represents an appealing treatment strategy in view of inherent property of HCC to evoke spontaneous, although exhausted immune responses. The process of oncogenic transformation that leads to the onset of HCC is in fact characterised by a continuum between inflammation-fibrosis and carcinoma, where the innate and adaptive immune response exert a synergistic pathogenic role[8, 9].

In this context, chronically inflamed hepatocytes up-regulate the expression of a repertoire of tumour associated antigens (TAAs) including alpha-fetoprotein, glypican-3 (GPC3) and many other proteins pertaining, amongst others, to the cancer/testis antigen family[10, 11]. A number of studies have demonstrated that T cell responses against immune-dominant epitopes from these proteins exist in a suppressed state in HCC patients, suggesting they might be amenable to therapeutic modulation to overcome immune-evasion of cancer [12, 13].

In addition, the high mutational burden of HCC, which amounts to 2 mutations per Mb, with a median of 45 non-synonymous events, makes this disease particularly neoantigen-rich, therefore expanding the overall antigenicity of HCC[14, 15]. Unsurprisingly, in keeping with this view, evidence of dense lymphocytic infiltration is in fact commonly found in histological specimens of human HCC and is often mirrored by discernible CD8+, tumour-antigen specific T-cell responses in peripheral blood[16]. Taken together, these data suggest that anti-cancer immune response exists in HCC patients and is crucially down-regulated by different mechanisms during the clonal evolution of HCC[17].

Cancer immunogenicity is not a static determinant, but rather a dynamic process that can be positively influenced by treatment. Clinical studies have shown that TACE can modulate both the innate and specific immune response in HCC and that the differential activation of the adaptive immunity may underlie the heterogeneity observed in patients' survival following TACE[18, 19].

In aggregate, the evidence presented so far and the accumulating data from ongoing phase I trials of immunotherapy agents in HCC sustain the combination between TACE, a potential loco-regional inducer of immunogenic cell death with the restoration of a functional and antigenically broader antitumour immune response achieved by sequential PD-1 directed checkpoint inhibition.

1.2 Preclinical and Clinical Trial Data

1.2.1 Preclinical Safety and Efficacy Summary.

Pre-clinical toxicology studies on Pembrolizumab were conducted in accordance to the International Conference on Harmonisation (ICH) S6 Guidance for Biopharmaceuticals.

The 1- and 6-month toxicity and toxicokinetic (TK) studies in Cynomolgus monkeys showed no Pembrolizumab–related effects on any parameter evaluated [electrocardiograms (ECG), general veterinary and physical examinations with body temperature and blood pressure (BP), clinical observations, and histopathology of tissues from the cardiovascular, respiratory, renal, and nervous systems].

Pre-clinical efficacy studies have shown that Pembrolizumab enhances T-cell responses in human donor blood cell cultures, with a half-maximal effective concentration (EC50) of approximately 0.1 to 0.3 nanoMoles (nM). Pembrolizumab strongly enhances T lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and Cynomolgus monkeys. The antibody potentiates existing immune responses only in the presence of antigen-receptor stimulation and does not specifically activate all T-cells.

PD-1 blockade using the anti–mouse PD-1 surrogate antibody J43, is demonstrated to significantly inhibit tumour growth in a variety of syngeneic murine tumour models.

Importantly, Pembrolizumab does not bind to superfamily members CD28, CTLA-4, and ICOS. Although Pembrolizumab acts as an immunomodulatory agent, it is distinct from agents such as those targeting CD3 or CD28 because it does not inadvertently activate immune responses. Pembrolizumab was evaluated in an assay described by Stebbings et al, 2007, used to assess the risk of acute cytokine release in participants following treatment with immune-modulatory agents. Unlike an agonist anti-CD28 mAb, incubation of human peripheral blood mononuclear cell (PBMC) with Pembrolizumab in the absence of additional stimulation did not induce production of IL-2, to further prove its specificity.

1.2.2 Clinical Safety and Efficacy Summary.

To date, approximately 11,000 patients in clinical trials and 27,000 patients in the post-marketing setting have been treated with KEYTRUDA®.

The clinical safety profile of Pembrolizumab as monotherapy has emerged from a number of clinical studies including P001/P002, P012, P013, and P028, plus the P011 monotherapy arm.

In the Pembrolizumab monotherapy trials, in general, the most commonly reported Adverse Events (AEs) included fatigue, diarrhoea, decreased appetite, nausea, dyspnoea, and anaemia. The incidence of drug-related AEs (DRAEs) ranged from 39.8% (35 of 88 subjects in P013) to 80.0% (8 of 10 subjects in P011). The incidence of Grade 3-5 DRAEs across studies ranged from 6.8% (6 of 88 in P013) to 12.0% (187 of 1562 subjects) in P001/P002.

The most commonly reported Grade 3-5 DRAEs were anaemia, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, and colitis.

The majority of subjects who experienced an AE continued in the study, with the incidence of AEs leading to discontinuation ranging from 4.2% (18 of 430 subjects in P028) to 12.3% (192 of 1562 subjects in P001/P002). The majority of AEs leading to discontinuation were not considered drug related. Discontinuations due to a DRAE were infrequent and ranged from 0% (no subjects in P011) to 4.5% (4 of 88 subjects in P013). The most commonly reported DRAE leading to discontinuation was pneumonitis.

Hepatotoxicity, a clinically important safety concern in this study, is overall infrequent as a Pembrolizumab-related AE. Out of a total of 1562 subjects with advanced malignancies treated with Pembrolizumab monotherapy across a wide range of clinical trials, hepatic, drug-related autoimmune toxicity was identified in 8 subjects (0.5%), with 2 subjects qualifying for grade 3 toxicity (0.1%). Data from the use of Pembrolizumab in other indications, in absence of background hepatic impairment, suggest that liver toxicity did not appear to be a dose-dependent, but rather a stochastic immune-related AE. Management with oral corticosteroids for a median duration of 7 days has proven beneficial to antagonise this AE.

Efficacy data are available for a total of 655 P001 melanoma subjects treated with Pembrolizumab and 540 P002 melanoma subjects treated with either Pembrolizumab or chemotherapy. For both clinical studies, assessment of overall response rate (ORR) was based on RECIST 1.1 and performed by blinded central reviewers.

The P001 ORR demonstrated the antitumour activity of Pembrolizumab in subjects with melanoma (ipilimumab-naïve and previously treated with ipilimumab).

P002 demonstrated superior Progression Free Survival (PFS) for both Pembrolizumab treatment arms compared to the chemotherapy control arm. Treatment with Pembrolizumab lead to an ORR that was >4 fold higher than the response rate of the chemotherapy control arm. This difference was highly statistically significant, with a one sided p-value of <0.0001. The overall response rates for Pembrolizumab treatment in P001 and P002 compared favourably to historical response rates for available treatments for melanoma, particularly in subjects who had progressed after multiple prior therapies. For example, the largest randomised clinical trial in previously treated advanced melanoma subjects, in which carboplatin and paclitaxel were used in the control arm, and sorafenib plus carboplatin and paclitaxel in the experimental arm, produced a response rate of 11% and 12%, respectively.

One fatal case of Stevens-Johnson Syndrome (SJS) in a clinical trial and one fatal case of Toxic Epidermal Necrolysis (TEN) in the post-marketing setting have been reported in patients treated with KEYTRUDA®. Including these cases, there have been 8 cases of SJS (6 in clinical trials, and 2 post-marketing) and 2 cases of TEN (both post-marketing) all of which were serious.

- The risk of SJS and TEN is reported at approximately 0.4 - 7 cases per million patient years in the general adult population.

- Independent risk factors include certain medications such as anticonvulsants, sulfonamides, aminopenicillins, allopurinol, and NSAIDs. Non-medication triggers include infection, contrast media, and vaccinations.
- Malignancy is associated with an increased mortality rate in patients with SJS and TEN.

A total of 6 cases of myocarditis have been reported in patients treated with KEYTRUDA® in clinical trials or in an expanded access program. There were was 1 fatal case reported in a clinical trial.

- A search of the literature identified neither background incidence rates nor prevalence of myocarditis specifically among cancer patients.
- Immune-mediated myocarditis should be suspected if other causes of myocarditis, such as infection or prior radiation therapy, have been excluded.
- Risk factors include certain medications and treatment modalities such as radiation, anthracycline, alkylating agents and most recently checkpoint inhibitors.

A comprehensive summary of the pre-clinical and clinical development of Pembrolizumab is available in the IB.

1.3 Rationale for the study

1.3.1 Rationale for the Trial and Selected Subject Population

In the clinical context of HCC, TACE is indicated by current guidelines as first-line treatment in asymptomatic patients with compensated cirrhosis, a Child-Pugh score <8, ECOG of 0 and lack of portal vein thrombosis or extra-hepatic spread[3].

However, it is widely accepted that the survival benefit deriving from loco-regional therapies is not evenly distributed across all the patients receiving TACE. Despite meeting eligibility criteria for TACE, a subset of patients do not respond to therapy[20]. Furthermore, patients with initial radiological response to treatment may subsequently become ineligible to repeat TACE due to further disease progression either within or outside the liver[21]. The paucity of effective systemic treatments for HCC further limits therapeutic options, where the only approved orally active multi-kinase inhibitor sorafenib has produced a 2.8 months improvement in survival in advanced disease but has failed to show benefit in the adjuvant setting[22].

Immune checkpoint blockade targeted to PD-1 has emerged as promising anticancer therapy across a growing variety of malignancies. Preliminary results from the CA209-040 study, a Phase I/II dose-ranging trial evaluating the safety and tolerability of the anti-PD-1 antibody nivolumab (Opdivo, BMS), has confirmed an OS rate of 62% at 12 months in HCC, with established radiologic responses in 8 (19%) of 42 evaluable patients. Whilst treatment responders achieved duration of response ranging between 1.4 – 12.5 months, a total of 26 patients (62%) ultimately experienced progression of their disease, to suggest underlying biologic heterogeneity in the disease-modulating effects from treatment[23].

Increasing evidence has suggested a role for the activation of both the innate and specific branches of the immune system as a key prognostic determinant in patients undergoing TACE, with chronic modulation of the T-helper-2 lymphocyte response playing a role in influencing long-term survival [24-26]. Similarly, studies in HCC patients undergoing TACE have suggested a differential regulation of T-cell suppressive responses in relation to the efficacy of TACE, making restoration of an effective anti-tumour adaptive immunity an appealing therapeutic strategy in HCC [18, 27].

A key question now is to understand whether the ischaemic and cytotoxic damage imposed by TACE to the tumour may facilitate priming of the antigen-specific branch of the immune system to a broad range of previously inaccessible neo-epitopes, potentially enabling an enhanced activity of PD-1/PD-L1 inhibitors. Mechanistic evidence suggests PD-L1 expression to be under the transcriptional control of the Hif-1a[28], which further strengthens the rationale of combining TACE with PD-1/PD-L1 inhibitors in light of the documented role of TACE in activating a sustained hypoxic response and promote the release of circulating Vascular Endothelial Growth Factor (VEGF) levels and other pro-antiogenic cytokines[29].

Whilst optimal dosing of Pembrolizumab has been established in advanced solid tumours[30], the immune-mediated adverse event profile of the compound and the potential interaction with TACE warrants preliminary safety and tolerability evaluation in BCLC-B stage disease, a subgroup of HCC patients who have by definition optimal performance status and liver functional reserve, rendering them normally able to tolerate liver ischaemia following selective intra-arterial targeting of the tumour nodules up to Child-Pugh B7 criteria.

1.3.2 Rationale for Dose Selection/Regimen/Modification.

Pembrolizumab has been studied in doses ranging from 2 mg/kg Q3W to 10 mg/kg Q2W, with the maximum dose that has been studied being 10 mg/kg Q2W.

The rationale for dose selection originates from the results of an OL, Phase I trial (Protocol 001) conducted to evaluate the safety and clinical activity of single agent Pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered Q2W in participants with advanced solid tumours. All three dose levels were well tolerated and no DLTs were observed. This first in human (FIH) study of Pembrolizumab showed evidence of target engagement and objective evidence of tumour size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No Maximum Tolerated Dose has been identified to date. Recent data from other clinical studies within the Pembrolizumab program has shown that a lower dose of Pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

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

A population PK analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of Pembrolizumab were found to be dependent on body weight (BW). The relationship between clearance and BW, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both BW normalised dosing or a fixed dose across all BW. Pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W BW based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for Pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumour burden on exposure. In addition, exposure was similar between the Non-Small Cell Lung Carcinoma

(NSCLC) and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

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

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of Pembrolizumab showing that the fixed dose of 200 mg Q3W provides exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose Q3W, 2) will maintain individual exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual participants exposure in the exposure range established in melanoma that are well tolerated and safe. A fixed dose regimen simplifies the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme reduces complexity in the logistical chain at treatment facilities and reduces wastage.

There are currently no clinical data illustrating the safety and tolerability of Pembrolizumab following TACE. Whilst TACE is expected to produce low-grade hepatitis, occasionally amounting to post-embolisation syndrome with fevers and abdominal pain, these events are self-resolving and clinical studies have shown that the peak of cytokine as well as AST/ALT release happens approximately 7 days after TACE and subsequently spontaneously resolves [31].

There are limited data to define the safety of PD-1 directed therapies in the context of chronic viral infection. Preliminary data reporting on the use of the anti-PD-1 antibody nivolumab have reassuringly shown no evidence of hepatitis flares in virally infected HCC patients[23]. Interim results from the ongoing CA209-040 study have demonstrated Grade 3 and 4 AST and ALT increase in approximately 10-12% of participants with advanced HCC as potential DRAEs. However, drug discontinuation rates secondary to all-cause DRAEs was low at interim analysis amounting to only 5%[23].

Similar safety signals emerge from the appraisal of immunotherapy trials of anti-CTLA-4 checkpoint inhibitors, which – although different by mechanism of action – might have toxicity overlap with anti-PD1 antibodies due to the potential of evoking undesired immune-pathology.

Reassuringly, a clinical trial of tremelimumab in 20 participants with Hepatitis C-virus (HCV) related advanced HCC has similarly shown no evidence of hepatitis flares. Conversely, the majority of participants with active HCV viraemia at baseline demonstrated falling HCV- Ribonucleic Acid (RNA) levels following tremelimumab treatment to suggest dual anti-viral and anti-tumoural immune-reconstitution. The same trial has however confirmed an acute, transient transaminase (ALT, AST) release in up to 45% of the participants, which however did not warrant treatment discontinuation [32]. A similar pilot trial tremelimumab following TACE or radiofrequency ablation in hepatobiliary tumours has shown good tolerability of the combination both in terms of viral kinetics and risk of acute hepatotoxicity following treatment. A dual anti-viral and anti-tumour activity was again confirmed and importantly, no DLTs were reached in the combination study[33].

Critical appraisal of the safety data of pembolizumab across all indications seem to suggest the lack of a strict dose-dependent correlation between drug exposure and DRAEs. For these reasons, this study will evaluate the safety and tolerability of Pembrolizumab following TACE at 200 mg Q3W, which equates to the currently recommended therapeutic dose of Pembrolizumab in other indications. Pending evaluation of DRAEs in a first subset of 6 subjects within the pre-specified DLT evaluation period of 21 days, the treatment schedule of Pembrolizumab may be changed to extend the pembrolizumab to TACE interval from 30 (+3 days) to at least 45 days (+3 days) of TACE in an expansion cohort of maximum 26 patients.

At least 1 participant will be mandated to meet Child-Pugh B7 criteria in the safety run-in phase to ensure wide generalisability of the safety outcomes to the full spectrum of severity of background liver dysfunction.

1.4 Rationale for Endpoints

1.4.1 Safety Endpoints

Safety and tolerability of Pembrolizumab following TACE represent the primary endpoints of this study and will be recorded and presented descriptively. Adverse events will be graded according to NCI CTCAE v4 and other safety data (e.g. ECG, vital signs, laboratory results etc) will be collected.

1.4.2 Efficacy Endpoints

Efficacy outcome measures will represent a secondary study endpoint and will be recorded and presented with an exploratory intent. The efficacy of treatment will be evaluated radiologically in terms of PFSR defined as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) at 12 weeks post treatment according to mRECIST. Contrast-enhanced CT of the chest abdomen and pelvis will be mandated at study baseline and at subsequent study endpoints. Baseline CT/MRI scans do not need to be repeated if obtained within 35 days of first IMP administration. MRI of the liver is allowed to analyse intrahepatic tumour response following TACE at the discretion of the PI. However, if this method is elected for the baseline evaluation of the disease, the same modality must be used for all follow-up assessments and coupled with full CT restaging of extrahepatic disease. Radiologic evaluation of the disease will be performed centrally to ensure maximal reproducibility. The efficacy of treatment will also be evaluated by PFS rate at 12-weekly timepoints (as assessed by mRECIST), defined as the proportion of participants who did not fulfil the criteria of progressive disease. Tumour reassessments will be concurrently captured using standard RECIST criteria v. 1.1.

1.4.3 Biomarker Research.

A biomarker tumour sample will be mandated at screening. For all other biomarker samples, participants enrolled into this study will be invited to donate additional blood, urine and stool biomarker samples for the discovery of immune-response biomarkers. A separate biomarker consent form for these optional biomarker samples will be provided to participants. Refusal to consent to these optional biomarker sample collections will not exclude the participant's participation in the trial.

Biomarker samples will be collected at screening, throughout treatment (predose) and at end of treatment (EOT) as indicated in the Time & Events table. Stool and urine samples may be collected up to 3 days prior to the visit.

The overall aim of this project is to initiate an exhaustive, multi-technology, high-throughput analysis of prospectively collected tissue and bio-fluid samples to explore the molecular and immunological determinants underlying the anti-tumour response to Pembrolizumab in HCC and investigate the escape mechanisms that characterise resistance to treatment.

Participant samples will be stored for future correlative research which may be in collaboration with MSD.

1.5 Risk / Benefit Assessment.

Whilst PD-1/PD-L1 blockade has been extensively characterised for safety outcomes in hundreds of patients with advanced malignancies, intermediate-stage HCC represents a special population, for which the main safety questions are represented by the concomitant presence of chronic hepatitis and the underlying liver functional impairment stemming from liver cirrhosis. Furthermore, there are no clinical data to support combination of PD-1 directed checkpoint inhibitors with TACE. Whilst TACE is expected to produce low-grade hepatitis, occasionally amounting to post-embolisation syndrome with fevers and abdominal pain, these events are self-resolving and clinical studies have shown that the peak of cytokine as well as AST/ALT release happens approximately 7 days after TACE and subsequently spontaneously resolves.

Whilst the safety data available to date show Pembrolizumab to be a generally safe and well tolerated treatment, confirmatory studies to support the use of the compound in the context of HCC are required prior to efficacy testing.

In the present study the protocol has been designed to mitigate the risks potentially arising as a result of the combination of Pembrolizumab with TACE:

- A long interval of at least 30 + 3 days between TACE and systemic treatment has been adopted to guarantee full resolution from the ischaemic/cytotoxic damage to the healthy liver parenchyma following loco-regional treatment.
- Accounting for the great heterogeneity of participants presenting with intermediate-stage HCC, at least 1 participant will be selected to correspond to Child Pugh B7 class criteria. This guarantees that participants at the worse end of the liver functional reserve spectrum are adequately captured at each dose level.
- An initial safety run-in phase (Part 1) will allow for preliminary safety characterisation of the IMP before subsequent expansion. Pending evaluation of DRAEs in the first cohort of 6 subjects within the pre-specified DLT evaluation period, the Independent Data Safety Monitoring Committee (IDSMC) will review the DRAE profile and agree on a recommended interval between TACE and Pembrolizumab to be adopted in the subsequent expansion phase.
- Due to the peculiar immune-mediated toxicity related to Pembrolizumab and the kinetics of liver functional recovery following TACE a time window of 21 days is deemed biologically adequate to characterise acute liver-related toxicity emerging from Pembrolizumab treatment and will be considered as the DLT window of the study. In Part 1 and Cycle 1 only study participants will attend weekly for laboratory evaluations (Viral load if indicated, PT/INR and aPTT, haematology, biochemistry, T3, T4 & TSH, cortisol).

- In the case that DLTs are observed only in the Child Pugh B7 participants but not in the Child Pugh A participants, only Child Pugh A participants will be recruited to the expansion cohort as determined by the IDSMC.
- The overall safety profile of Pembrolizumab will be fully characterised during the whole study period, including a safety follow up (SFU) visit 30 ± 7 days post-discontinuation and a telephone follow-up visit 130 ± 7 days after the last IMP dose.
- A review will be conducted at the end of Part I by the IDSMC. A final analysis will be conducted at the end of the study. Analyses will include an intention to treat (ITT) analysis including all participants enrolled and a per protocol analysis using all participants who complete the study without major protocol violations.

2.0 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

To determine the safety and tolerability of Pembrolizumab following TACE in participants with intermediate-stage HCC.

2.2 Secondary Objective

To determine the efficacy of Pembrolizumab following TACE in participants with intermediate-stage HCC.

2.3 Tertiary Objective

To identify predictive correlates of immune response to Pembrolizumab in HCC.

2.4 Primary Endpoint

To assess the safety and tolerability of Pembrolizumab using NCI CTCAE v4.

2.5 Secondary Endpoints

To evaluate the efficacy of Pembrolizumab following TACE using PFS rates at 12 weeks (every 4 cycles) using mRECIST and standard RECIST v. 1.1 criteria.

2.6 Tertiary Endpoints

2.6.1 To identify biomarkers of immune response to Pembrolizumab using high-throughput technologies.

Biomarker blood, tissue urine and stool sample collection connected to this study will be established for biomarker research using high throughput proteomic and genomic analysis. Functional characterisation of circulating lymphocyte populations will be performed in parallel. The biomarker biopsy tissue sample taken at screening is optional. Participants will be invited to provide all other additional biomarker blood, urine and stool sample samples for research as well as provide consent for research to be performed on all leftover samples and tissue taken for diagnostic purposes.

2.6.2 To evaluate the efficacy of Pembrolizumab following TACE by improving PFS rates as measured by standard RECIST criteria v 1.1 at pre-defined 12-weekly timepoints.

3.0 STUDY DESIGN

3.1 Design

The study will be performed at 1-4 sites in the UK and will recruit up to a maximum of 32 evaluable participants. This study is an OL, single arm, sequential phase study evaluating safety, tolerability and preliminary efficacy of sequential TACE followed by Pembrolizumab and will be conducted in two parts.

3.1.1 Part One

Part 1 of the study will consist of a safety run-in of up to 6 participants treated with Pembrolizumab at the clinically recommended dose of 200 mg Q3W. Subjects will be observed for determination of DLTs over a 21 day time window with weekly laboratory assessments in Cycle 1 only (Viral load if indicated, PT/INR and aPTT, haematology, biochemistry, T3, T4 & TSH, cortisol). Particular attention will be given to liver function tests (LFT). Whilst no DLTs were observed nor Maximum Tolerated Dose (MTD) was defined in dose escalation studies of Pembrolizumab monotherapy, the safety run-in phase of this study will allow us to verify protocol procedures and assess the safety of the combination with TACE. The decision to undertake the main feasibility trial for the TACE followed by 200 mg dose with at least 30 days interval or to increase the window between TACE and Pembrolizumab to at least 45 days will be made by the IDSMC who will consider the general safety profile with a particular focus on acutely occurring liver-related toxicity.

If there are zero DLTs and no other safety concerns the feasibility trial with be undertaken using the standard 200 mg Q3W dose with at least 30 days window between TACE and Pembrolizumab. If there are one to two DLTs, the IDSMC will then advise to continue with either at least 30 days interval or to increase the window between TACE and Pembrolizumab to at least 45 days for the expansion cohort based on additional information and general safety profile. If three or more DLTs are observed in the six participants of the safety run-in the trial will be stopped.

In the safety run-in and at the start of the feasibility trial, as a safety measure, participants 2-6 will be dosed after an interval of one week following the first dose received by the first participant.

Accounting for the great heterogenecity of participants presenting with intermediate-stage HCC, at least 1 participant in Part 1 will be mandated to correspond to Child Pugh B7 class criteria which will ensure wide generalisability of the safety outcomes to the full spectrum of severity of background liver dysfunction.

If a participant withdraws or is withdrawn from the study prior to completion of the first 21 day treatment period, in the absence of a DLT, that subject must be replaced and the replacement dosed at the current dose level under evaluation. In addition, if a participant is withdrawn for any reason before receiving Pembrolizumab, replacement with an additional will be allowed. Participants in Part 1 will be screened after providing written informed consent a maximum of 28 days prior to receiving TACE. Once recruited to the study and after having completed a 30 + 3 days interval post TACE they will be given Pembrolizumab at 200mg Q3W until radiologically confirmed disease progression, unacceptable toxicity, participant withdrawal or a maximum of 1 year of treatment has been completed.

3.1.2 Part Two

Once the data for 6 patients are reviewed by the IDSMC in part 1 a further 26 evaluable participants will be recruited to the study with the same regimen - TACE followed by 200 mg Pembrolizumab after at least 30

days window or with TACE followed by 200 mg after at least 45 days. This will further characterise the safety and tolerability of Pembrolizumab in this population.

In this part of the study, if a participant withdraws or is withdrawn from the study prior to completion of the first 21 day treatment period, in the absence of a DLT, that participant must be replaced. If a participant is withdrawn for any reason before receiving Pembrolizumab, replacement with an additional participant will be allowed.

Participants entering part two of the study must be assessed up to 28 days prior to TACE to confirm eligibility and be recruited onto the trial. They will be scheduled for Pembrolizumab dosing as per agreed time window determined by IDSMC and will be given Pembrolizumab every Q3W ± 3 days until radiologically confirmed disease progression, unacceptable toxicity, withdrawal or a maximum of 1 year of treatment has been completed.

If the pembrolizumab dosing scheduled is set at 45 days after TACE, at least 1 participant will be mandated to meet Child-Pugh B7 criteria in the safety run-in phase to ensure wide generalisability of the safety outcomes to the full spectrum of severity of background liver dysfunction.

3.2 Treatment regimens

All participants entered into the study will receive Pembrolizumab 200 mg every Q3W ± 3 days until radiologically confirmed disease progression, unacceptable toxicity, withdrawal or a maximum of 1 year of treatment has been completed. The study will first assess safety and tolerability of the standard dose level of 200 mg Q3W at least 30 days post TACE. This window may be increased to at least 45 days in Part 2 pending assessment of the safety profile of Pembrolizumab in sequential combination with TACE.

Table 1: Study Dosing Schedule

	TACE	**Treatment Window**	**Dosage**	**Frequency**	**No of evaluable participants**
Part 1	As per SOC	At least 30 days	200 mg	Every 3 Weeks	6
Part 2	As per SOC	Either at least 30 days or 45 days as per IDSMC recommendation	200 mg	Every 3 Weeks	26
				Total number of evaluable participants	***32***

This study will be conducted following the proposed flow chart.

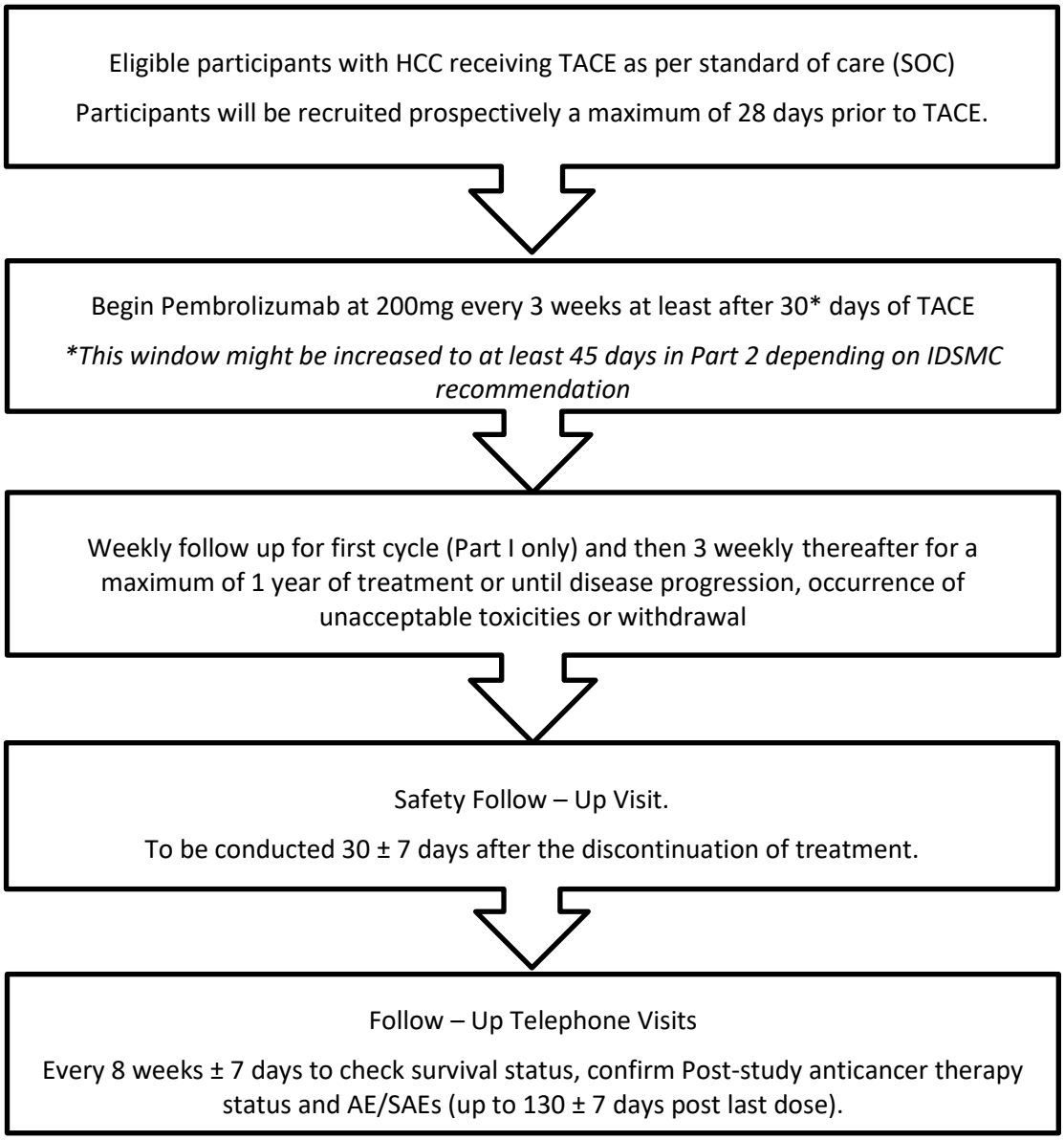

Figure 1: Study flow chart

4.0 PARTICIPANT ENTRY

4.1 Study population

This is a phase Ib, open label, single arm trial designed to evaluate safety and preliminary efficacy of sequential combination of TACE followed by Pembrolizumab in participants with intermediate-stage HCC.

4.1.1 Inclusion criteria

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

1. Be willing and able to provide written informed consent/assent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Have a diagnosis of Hepatocellular Cancer (HCC) based on AASLD criteria (Appendix 1).
4. Have at least one uni-dimensional lesion measurable by CT-scan or MRI based on mRECIST criteria.

5. Patients who received prior TACE treatment (conventional or DEB-TACE) are eligible, provided they have at least one previously untreated lesion that is measurable based on mRECIST criteria.
6. Be ineligible for surgical resection or liver transplantation.Have a performance status of 0 or 1 on the ECOG Performance Scale (Appendix 2).
7. Demonstrate adequate organ function as defined in the table below.

System	Laboratory Value
Haematological	
Absolute neutrophil count (ANC)	≥1,500 mcL
Platelets	≥60,000 mcL
Haemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or Erythropoietin (EPO) dependency
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (CrCl) calculated by Cockcroft Gault criteria [Glomerular Filtration Rate (GFR) can also be used in place of creatinine or CrCl]	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X ULN
Hepatic	
Serum total bilirubin	≤ 3 X ULN (level of normality <21 µmol/L)
AST and ALT	≤ 5 X ULN
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]CrCl should be calculated per institutional standard.	

Table 2 Adequate Organ Function Laboratory Values

8. Have an overall Child-Pugh score ≤7
9. Female subject of childbearing potential should have a negative urine or serum pregnancy. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
10. Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section 6.9.2 – Contraception for the course of the study through 120 days after the last dose of IMP.
    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
11. Sexually active males must agree to use an adequate method of contraception as outlined in Section 6.9.2- Contraception, starting with the first dose of IMP through 120 days after the last dose of IMP.
    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

4.1.2 Exclusion criteria

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

1. Has extrahepatic metastasis.
2. systemic anticancer treatment for HCC.
3. Has any contraindication for TACE including portosystemic shunt, hepatofugal blood flow, known severe atheromatosis.
4. Has history of bleeding within the 4 weeks preceding screening.
5. Has hepatic encephalopathy.
6. Has ascites that is refractory to diuretic therapy.
7. Has documented occlusion of the hepatic artery or the main portal vein (segmental portal vein thrombosis does not represent exclusion criterion provided this does not contraindicate TACE).
8. Is currently participating and receiving IMP or has participated in a study of an IMP and received IMP or used an investigational device within 4 weeks of the first dose of IMP.
9. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy.
10. Has a known history of active TB (Bacillus Tuberculosis)
11. Hypersensitivity to Pembrolizumab or any of its excipients.
12. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or *in situ* cervical cancer.
13. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
14. Has known history of, or any evidence of active, non-infectious pneumonitis.
15. Has an active infection requiring systemic therapy. Exceptions relating to Hepatitis B and C virus infection are documented in Section 5.3.1, Table 5.
16. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the participant to participate, in the opinion of the PI.
17. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
18. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting from screening through to 120 days after the last dose of IMP.
19. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
20. Has a known history of HIV (HIV 1/2 antibodies).
21. Has received a live vaccine within 30 days of first dose of IMP.

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

5.0 PROCEDURES AND MEASUREMENTS

5.1 Screening evaluations

Written informed consent will be obtained before the participant undergoes any study-specific procedures. Each participant will undergo screening during the 28 days prior to receiving TACE to confirm eligibility. Clinical data obtained as SOC prior to consent may be used for the study provided they comply with the protocol-defined criteria and protocol-specified timelines. Baseline CT/MRI scans do not need to be repeated if obtained within 35 days of first dose.

Each eligible participant enrolled into the trial will be assigned a unique participant number for use during the trial. A screening and enrolment log will be completed for all participants who enter screening for the study. A subject identification log will be completed for all participants who go on to be enrolled. This subject identification log will include the allocated participant number as well as the participant identifiable data including name, hospital number and date of birth. These logs will be maintained at each site.

5.2 Trial Procedures

The Time & Events Table (Table 3) summarises the trial assessments and procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically or logistically necessary by the PI or delegate.

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

Table 3: Time & Events

	Screening	**TACE**		**Treatment Cycles[1]**									**End of Treatment**	**Post-Treatment**	
									To be repeated beyond 9 cycles and up to 17						
Treatment Cycle Nos Week Nos	Screening		Day 1	1[1], 10 Wk 0, 27	2 & 11 Wk 3, 30	3, 12 Wk 6, 33	4, 13 Wk 9, 36	5, 14 Wk 12, 39	6, 15 Wk 15, 42	7, 16 Wk 18, 45	8, 17 Wk 21, 48	9 Wk 24	Discontinuation	Safety Follow-up (SFU)	Tel Follow Up Visits[10]
Scheduling Window (Days):	Pre- TACE -28 to -1		N/A	Post TACE 30 + 3 (Part 1) Or Post TACE 45 + 3 (Part 2)	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	30 ± 7 post EOT	Q8W ± 7 post SFU
Informed Consent	X														
Demographics and Medical History	X														
Tumour Imaging (mRECIST)[2] (Chest CT and dual phase CT or contrast enhanced MRI scan of the abdomen)	X							X				X	X		
Assessment of Child-Pugh Score	X			X	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X														
Directed Physical Examination				X	X	X	X	X	X	X	X	X	X	X	
Vital Signs, Weight & Height[12]	X[12]			X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X			X	X	X	X	X	X	X	X	X	X	X	
12 – Lead ECG	X														
QoL Assessment: EORTC QLQ-C30 and QLQ-HCC18	X			X				X				X	X		
Pregnancy Test – Urine or Serum beta-HCG	X			X*											
Hepatitis Serology[3]	X														
Viral Load (HBV DNA, HCV RNA)[4]	X			X[1]				X				X	X		
PT/INR and aPTT	X			X[1]	X	X	X	X	X	X	X	X	X	X	
Alpha fetoprotein	X			X	X	X	X	X	X	X	X	X	X	X	
Haematology[5]	X			X[1]	X	X	X	X	X	X	X	X	X	X	

	Screening	TACE		Treatment Cycles[1]									End of Treatment	Post-Treatment	
									To be repeated beyond 9 cycles and up to 17						
Treatment Cycle Nos Week Nos	Screening		Day 1	1[1], 10 Wk 0, 27	2 & 11 Wk 3, 30	3, 12 Wk 6, 33	4, 13 Wk 9, 36	5, 14 Wk 12, 39	6, 15 Wk 15, 42	7, 16 Wk 18, 45	8, 17 Wk 21, 48	9 Wk 24	Discontinuation	Safety Follow-up (SFU)	Follow Up Tel Visits[10]
Scheduling Window (Days):	Pre- TACE -28 to -1		N/A	Post TACE 30 + 3 (Part 1) Or Post TACE 45 + 3 (Part 2)	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	30 ± 7 post EOT	Q8W ± 7 post SFU
Biochemistry[6]	X			X[1]	X	X	X	X	X	X	X	X	X	X	
Urinalysis[7]	X			X	X	X	X	X	X	X	X	X	X	X	
T3, T4 and TSH	X			X[1]	X	X	X	X	X	X	X	X	X	X	
Cortisol	X			X[1]	X	X	X	X	X	X	X	X	X	X	
TACE administration[8]			X												
Pembrolizumab Administration				X	X	X	X	X	X	X	X	X			
Archival Tissue Collection	X														
Biomarker Biopsy Sample [9]	X												X		
Record of Concomitant Medications	X			X	X	X	X	X	X	X	X	X	X	X	
AE Assessment (NCI-CTCAE v4.03)	X			X	X	X	X	X	X	X	X	X	X	X	X‡
Survival and Post-study anticancer therapy status															X[11]
Optional Biomarker Blood Sample[11]	X			X				X				X	X		
Optional Research Blood Sample – Circulating Tumour Cells (CTCs)[11]	X			X[11]									X		
Optional Biomarker Urine Sample [11]	X			X				X				X	X		
Optional Biomarker Stool Sample [11]	X												X		

A serum pregnancy test will be performed a maximum of seven days before pembrolizumab administration

‡ *AEs/SAEs will be recorded and reported up to 130 days after last study drug administration. Following completion of 130 days period, AE/SAE monitoring will be stopped and patients will continue to be followed up every eight weeks for survival status and commencement of other anti-cancer therapies.*

1. *In Parts I & II visits should occur on Day 1 (± 3 days) of every 21 day cycle. In Parts I & II Cycle 1 only, participants will need to come in for weekly visits (± 2 days) for blood samples.*
2. *Tumour assessments may be performed by chest CT and dual phase CT or contrast enhanced MRI scan of the abdomen during screening and every 12 weeks thereafter. Baseline CT/MRI scans do not need to be repeated if obtained within 35 days of first dose. Tumour assessment only needs to be conducted during EOT visit if participant has come off study for reason other than disease progression and has not had a scan in the previous 6 weeks.*
3. *Hepatitis serology is required at screening. This includes HBV DNA, HBsAg, HBeAg, HBCT (anti-HBV core total IgG/IgM), HBeAb (anti-HBV e antibody), HBSab (anti-HBV Surface Antibody) as well as full Hepatitis C Virus profile including HCQB (HCV quantitative RNA) and anti-HCV antibodies (IgG)*
4. *Participants in part 1 of the study who carry a background of chronic active hepatitis B and/or C will have weekly monitoring of viral load (HCV RNA and/or HBV DNA as appropriate in Cycle 1 only). In part 2 only of the study viral load monitoring will be performed every 4 cycles of treatment and at discontinuation of Pembrolizumab.*
5. *Haematology includes: Haematocrit, Haemoglobin, Platelet count, White Blood Cell (WBC, total and differential) Red Blood Cell (RBC) Count, Absolute Neutrophil Count, Absolute Lymphocyte Count*
6. *Biochemistry includes: Albumin, Alkaline phosphatase, ALT, AST, Lactate dehydrogenase (LDH), C-reactive protein (CRP), Uric Acid, Calcium, Chloride, Glucose, Phosphate, Potassium, Sodium, Magnesium, Total Bilirubin, Direct Bilirubin (If total bilirubin is elevated above the ULN) Total protein, Blood Urea Nitrogen,*
7. *Urinalysis includes: Blood, Glucose, Protein Specific gravity, Microscopic exam (If abnormal)*
8. *Participants who fail to achieve complete tumour devascularisation after the first session of TACE as assessed by follow-up contrast-enhanced scan may be allowed up to 1 further TACE. Re-screening is not required. Conventional and DEB-TACE are both considered accepted modalities for TACE treatment.*
9. *The 2-incision tumour biopsy samples at screening and end of treatment are optional.*
10. *Participants should be followed up until the last participant comes off study for disease progression, intolerance, withdrawal or completes 1 year of treatment*
11. *All other biomarker samples (bar the screening biomarker tumour sample) are optional. All samples taken during treatment cycles are predose. Urine and stool collections are -3 days.*
    CTCs to be taken at screening, cycle 1 and discontinuation visits only.
    Stool sample to be taken at screening and discontinuation visits only.
12. *Height will be measured at screening only.*

5.1.1 Administrative Procedures

5.1.1.1 Informed Consent

The PI or qualified designee must obtain written informed consent from each potential participant prior to any study specific procedures are performed.

Consent must be documented by the participants dated signature on a consent form along with the dated signature of the PI or qualified designee conducting the consent discussion. A copy of the signed and dated consent form should be given to the participant and placed in the participant's medical notes. The original form should be stored in the investigator site file (ISF).

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject will have received the Health Research Authority (HRA)/Research Ethics Committees (REC) approval/favourable opinion (where required) in advance of use. Participants should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature.

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

5.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the PI or qualified designee to ensure that the participant is eligible to enter the trial.

5.1.1.3 Medical History

A medical history will be obtained by the PI or qualified designee. Medical history will include all active conditions, and any condition diagnosed that are considered to be clinically significant by the PI or delegate. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history however under disease status.

5.1.1.4 Prior and Concomitant Medications Review

5.1.1.4.1 Prior Medications

The PI or qualified designee will review prior and current medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject at screening. Treatment for the disease for which the participant has enrolled in this study will be recorded under prior cancer treatments and not listed as a prior medication.

5.1.1.4.2 Concomitant Medications

The PI or qualified designee will record all medication taken by the participant from screening through to SFU. All medications related to reportable Serious Adverse Events (SAEs) and Event of Clinical Interest (ECIs) should be recorded as defined in Section 7.

5.1.1.5 Disease Details and Treatments

5.1.1.5.1 Disease Details

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

5.1.1.5.2 Prior Treatment Details

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

5.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The PI or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of IMP. If a participant initiates a new anti-cancer therapy within 30 days after the last dose of IMP, the SFU visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the participant will move into survival follow-up.

5.1.2 Clinical Procedures/Assessments

5.1.2.1 Adverse Event (AE) Monitoring

The PI or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the visit schedule and more frequently if clinically indicated. Adverse events will be graded and recorded from informed consent until safety follow up according to NCI CTCAE Version 4.0 (see Appendix 3). Toxicities will be characterised by seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with Pembrolizumab exposure should be evaluated to determine if it is possibly an ECI of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see section 6.8.24 regarding the identification, evaluation and management of potential irAEs.

Please refer to section 7 for detailed information regarding the assessment and recording of AEs and ECIs.

5.1.2.2 Full Physical Exam

The PI or qualified designee will perform a complete physical exam at screening. Clinically significant abnormal findings should be recorded as medical history.

5.1.2.3 Directed Physical Exam

At all other times as indicated in the visit schedule, the PI or qualified designee will perform a directed physical exam as clinically indicated prior to IMP administration as specified in the visit schedule. Clinically significant abnormal findings should be recorded as an AE.

5.1.2.4 Vital Signs

The PI or qualified designee will take vital signs as indicated in the visit schedule. Vital signs will be taken predose on treatment cycles. Vital signs will include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

5.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The PI or qualified designee will assess ECOG status (see Appendix 2) as indicated in the visit schedule.

5.1.2.6 Tumour Imaging and Assessment of Disease

Tumour imaging may be performed by chest CT, dual phase CT or contrast enhanced MRI scan of the abdomen at screening and every 12 weeks thereafter. Baseline CT/MRI scans do not need to be repeated if obtained within 35 days of TACE. Tumour imaging only needs to be conducted during the EOT if participant has come off study for reason other than disease progression and has not had a scan in the previous 6 weeks.

Tumour imaging will be assessed centrally as per mRECIST criteria.

5.1.2.7 Tumour Tissue Collection and Correlative Studies Specimen Sampling

Optional 2 incision tumour tissue samples will be collected from participants at screening and EOT. Leftover tumour tissue will be snap frozen in liquid nitrogen and preserved at -80 °C until genomic analysis (for details of sample collection procedures, please refer to the study Laboratory Manual). Parallel next generation DNA and RNA sequencing will be performed in paired clinical samples and correlated with response to treatment. Paraffin-embedded diagnostic tissue blocks will be processed for immune-histochemical expression of putative markers of immune response including PD-L1.

All other biomarker samples will be optional. Blood sampling will include prospective collection of serum, plasma and PBMC. A subset of peripheral blood samples collected at baseline and disease progression will undergo CTC enumeration and phenotypic characterization using a standardised Food & Drug Administration (FDA)-approved CellSearch system (Janssen Diagnostics). On treatment cycles, all samples will be collected predose.

Further correlative studies will be performed on urine samples to characterise the metabolomics determinants underlying anticancer immune response. Stool samples will be collected to characterise dynamic changes in the host's microbiome throughout treatment. Urine and stool collections may be collected within 3 days of the study's visit.

Laboratory tests will be performed as defined in the schedule of study assessments (Table 4). Samples will be analysed by the local study site laboratory using standard methods for routine tests. The following variables (Table 4) will be measured:

Table 4: Laboratory Tests

Haematology	Biochemistry	Urinalysis	Other
• Haematocrit • Haemoglobin • Platelet count • White Blood Cell (WBC -total and differential) • Red Blood Cell Count (RBC) • Absolute Neutrophil Count (ANC) • Absolute Lymphocyte Count	• AlbuminAlkaline phosphatase • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Lactate dehydrogenase (LDH) • C-reactive protein (CRP) • Uric Acid • Calcium • Chloride • Glucose • Phosphate • Potassium • Sodium • Magnesium • Total Bilirubin • Conjugated Direct Bilirubin (If total bilirubin is elevated above the upper limit of normal) • Total protein • Blood Urea Nitrogen • Cortisol	• Blood • Glucose • Protein • Specific gravity • Microscopic exam (If results abnormal) • Urine pregnancy test †	• Serum β-human chorionic gonadotropin† • PT (INR) • aPTT • Total thriiodothyronine (T3) • Free tyroxine (T4) • Thyroid stimulating hormone (TSH) • Alpha- fetoprotein
† *Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.* A serum pregnancy test will be performed a maximum of seven days before pembrolizumab administration			

Laboratory tests will be performed as indicated in the visit schedule. In Part I Cycle 1 only, participants will need to come in for weekly visits (± 2 days) for blood samples. Samples will be taken pre-dose on Day 1 of each Cycle. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Safety lab results (FBC & LFTs) must be reviewed by the PI or qualified designee and found to be acceptable prior to each dose of IMP.

Participant treatment and overall management decisions will be based on local laboratory data. Laboratory values that are considered to be of clinical concern must be recorded as an AE as described in section 7. Unless explained by a clinical condition, these tests must be followed up at appropriate intervals until they reach a level deemed acceptable by the PI or delegate.

5.2.1 Guidance on the interpretation of hepatitis serology for the purpose of eligibility.

Participants will require a full hepatitis serology screen prior to enrolment into the study. This will include a full Hepatitis B Virus profile (HBV DNA, HBsAg, HBeAg, HBCT (anti-HBV core total IgG/IgM), HBeAb (anti-HBV e antibody), HBSab (anti-HBV Surface Antibody) as well as a full Hepatitis C Virus profile including HCQB (HCV quantitative RNA) and anti-HCV antibodies (IgG). Participants are eligible to the trial if they fulfil the following serological criteria illustrated in Table 5.

Table 5. Interpretation of hepatitis serology.

Test	Participant Status	Eligibility	Any HBV Treatment Needed?
HBsAg (–) Total anti-HBc (+) HBsAb (+)	Immune after natural infection	Yes	No
HBsAg (–) Total anti-HBc (–) HBsAb (+)	Immune after vaccination	Yes	No
HBsAg (+) Total anti-HBc (+) IgM anti-HBc (+) HBsAb (–)	Acute infection	No	—
HBsAg (+) Total anti-HBc (+) IgM anti-HBc (–) HBsAb (–)	Chronic infection	Yes	Yes, need to be on a HBV treatment for at least 12 weeks prior to start of treatment Exclude if: (a) <12 weeks of therapy; (b) HBV viral load not under control during this time frame; (c) Documented HBV flare in the past 12 weeks
HBsAg (–) Total anti-HBc (+) IgM anti-HBc (–) HBsAb (–) HBV viral load (negative)	Unclear. Could be: Resolved infection False positive anti-HBc Low level infection Resolving acute infection	Yes	No
HBsAg (–) Total anti-HBc (+) IgM anti-HBc (–) HBsAb (–) HBV viral load (+)	Low level infection Resolving acute infection	Yes	Yes (as above)

5.2.2 Total Blood Volume

The total volume of blood that will be drawn from each participant in Part I and Part II are shown in Table 6 a: Part I Volume of blood to be drawn from each participant for the duration of the trial; calculations based

on 1 year on treatment including screening, end of treatment visit and post- treatment safety visit. These include optional biomarker samples.

	Approximate Sample volume (mL)	**No. of samples**	**Approximate Total volume (mL)**
Haematology (including coagulation)	10[1]	22	220
Biochemistry	8[1]	22	176
Total			396
Biomarker CTC Sample (optional)	10	3	30
Biomarker Blood Sample (optional)	6	5	30
Total:			456[2]

Table 6 a: Part I Volume of blood to be drawn from each participant for the duration of the trial; calculations based on 1 year on treatment including screening, end of treatment visit and post- treatment safety visit. These include optional biomarker samples.

	Approximate Sample volume (mL)	**No. of samples**	**Approximate Total volume (mL)**
Haematology (including coagulation)	10[1]	20	200
Biochemistry	8[1]	20	160
Total			360
Biomarker CTC Sample (optional)	10	3	30
Biomarker Blood Sample (optional)	6	5	30
Total:			420[2]

Table 6 b: Part II Volume of blood to be drawn from each trial participant for the duration of the trial; calculations based on 1 year on treatment including screening, end of treatment visit and post- treatment safety visit. These include optional biomarker samples.

[1] *Blood volumes for haematology and biochemistry may vary according to local practice*

[2] *The total volume of blood drawn from each participant for the duration of the trial depends on the time to progression for each participant.*

5.3 Treatment

All participants enrolled on the study will receive Pembrolizumab every Q3W until disease progression, occurrence of unacceptable toxicities, withdrawal or the participant has completed 1 year of IMP administration. Scheduled visits are described within the visit schedule (Table 4). Observations and assessments required during the study visits are also summarised in visit schedule (Table 4).

Time windows for visits are listed in the Visit Schedule. Assessment days will all be relative to the start of IMP administration, i.e.Cycle 1 Day 1. .

5.4 Post Treatment Follow-up

5.4.1 Safety Follow-Up Visit

There will be an early and a late Safety Follow-Up (SFU) visit. The early SFU should be conducted approximately 30 days (± 7 days) after the last dose of IMP or before the initiation of a new anti-cancer treatment, whichever comes first. A late SFU visit will 130 days after the last dose of the IMP (+/-7 days) by a telephone call. All AEs that occur prior to the SFU Visit should be recorded. Participants with on-going AE's at the SFU visits should be followed up by PI or delegate until resolution or stabilisation of the event but there will be no further need to record details of the AE, whichever comes first, including all study assessments to monitor the event.

5.4.2 Follow-up Visits

Participants who discontinue will move into the Follow-Up Phase and should be assessed by telephone follow up every 8 weeks (+/-7 days) to collect information regarding disease status, survival status, and details of new anti-cancer therapy initiated. For up to 130 days post last dose, their AE/SAE will be followed up as well.

Follow-up will continue until the last participant has completed the study, either with disease progression, unacceptable toxicities, withdrawal or completion of 1 year of treatment.

6.0 TREATMENT

Treatment will consist of a maximum of 1 year of Pembrolizumab Q3W following TACE.

6.1 TACE.

TACE will be performed as per SOC and will classify as a NIMP for the purpose of this study. Treatment will consist in the infusion of cytotoxic chemotherapy after arterial hepatic angiogram, followed by either selective or super-selective embolization of the arterial vascular bed perfusing the tumour. The procedure will be standardised across sites and will consist of conventional transcatheter arterial chemoembolization (conventional TACE) or drug-eluting beads TACE (DEB TACE) approach. The chemotherapeutic agent of choice will be doxorubicin delivered intra-arterially at the fixed dose of 60 mg for patients who receive conventional TACE. In patients receiving DEB TACE, the dose of doxorubicin will be ranging from 75-150 mg depending on the size of the tumour and according to the standard of care. Doxorubicin should be stored, prepared and disposed of in accordance with the relative Summary of Product Characteristics (SmPC) and hospital procedures. In addition to conventional TACE, drug-eluting beads (DEB) TACE is also considered an acceptable modality for TACE treatment. The local study team site personnel will maintain a dispensing record for each participant. Doxorubicin will be sourced for use in this clinical trial as per normal hospital procedures. Poly-vinyl alcohol particles will be the embolizing agent of choice. TACE is normally administered as a short elective inpatient treatment to allow for monitoring of immediate post-procedural complications. Contrast-enhanced CT or MRI scan will be performed approximately 30 days after TACE as part of SOC. Reports will be recorded.

Participants who fail to achieve complete tumour devascularisation after the first session of TACE as assessed

by follow-up contrast-enhanced scan may be allowed up to 1 further TACE session as per EASL/EORTC clinical guidelines unless clinical or technical factors preclude repeat treatment. In participants requiring re-treatment, time intervals for commencement of Pembrolizumab and subsequent DLT window will remain unchanged. No re-screening is required.

6.2 Investigational Medicinal Product Details

The IMP for this study is Pembrolizumab. A potent and highly-selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab potentiates existing immune responses only in the presence of antigen and does not non-specifically activate T-cells.

Pembrolizumab will be manufactured by MSD according to Good Manufacturing Practice (GMP) and will be provided in the formulation as described in Table 7. Additional information about the IMP can be found in the IB.

Table 7: IMP Product Description

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

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

6.2.1 Product Preparation

The IMP will be prepared as per the Pharmacy Manual.

6.3 Labelling and Packaging

Pembrolizumab will be supplied by MSD as specified in table 7; ready for injection. Pembrolizumab will be packaged, labelled and delivered to the participating sites by MSD. 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 GMP Annex 13. As a minimum the labels will include the following information:

a. name of the Sponsor;
b. name of drug, dose, quantity of dose units and route of administration;
c. batch number to identify the contents and packaging operation;
d. blank space for recording the trial ID;
e. directions for use;
f. PI name;
g. trial EudraCT number and protocol number;
h. storage conditions;
i. expiry date;
j. “for clinical trial use only”;
k. “keep out of reach of children”.

6.4 Storage and Dispensing

6.4.1 Storage

Details on storage of the IMP can be found in the pharmacy manual.

6.4.2 Handling

Further details on the preparation of the drug product can be found in the pharmacy manual.

At each site the PI/designee e.g. pharmacist is responsible for ensuring that all IMP is stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of the IMP must be recorded by an authorised person at the trial site. IMP may not be used for any purpose other than that stated in the protocol.

6.4.3 Returns and Reconciliation

The PI/designee is responsible for keeping accurate accountability records for Pembrolizumab including the amount dispensed to and returned for each participant and the amount remaining on site at the conclusion of the trial. Upon completion or termination of the study, it is the PI/designee responsibility to ensure all unused drug is returned to MSD and partially used IMP 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 ISF.

6.5 Dosage, Duration and Compliance

In Part 1 of the study, participants will be recruited to the safety run-in phase of the trial and will receive the IMP after having received prior TACE as per SOC. Participants will receive 200mg of Pembrolizumab Q3W with an interval from TACE of at least 30 days. If there are zero DLTs and no other safety concerns Part II with be undertaken using the standard 200 mg Q3W dose 30 days post TACE. If there is one to two DLTs, the IDSMC will then advise to continue with either 200 mg dose Q3W 30 days post TACE or to consider increasing the TACE-pembrolizumab interval prior to Cycle 1 to 45 days for the expansion cohort based on general safety profile. If three or more DLTs are observed in the six participants of the safety run-in the trial will be stopped.

In Part 2 of the study, participants will be recruited prior to TACE and prospectively followed up. Participants will be recruited at the schedule determined in part 1 with either a 30 or a 45-days (+3 days) interval from TACE to the first cycle of pembrolizumab. Pembrolizumab will be administered at the standard dose of 200 mg Q3W until disease progression, unacceptable toxicities, withdrawal or completion of 1 year of treatment.

6.5.1 Timing of Dose Administration

Pembrolizumab will be administered on an outpatient basis on Day 1 (± 3 days) of every 21 day cycle after all procedures/assessments have been completed as detailed on the schedule of study assessments (Table 4).

Pembrolizumab will be administered as a 30 minute IV infusion (treatment cycle intervals or infusion length may be increased due to toxicity). Due to the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

6.5.2 Trial Blinding/Masking

This is an OL trial; therefore, the Sponsor, CI, PI and participant will know the IMP is being administered.

6.6 Dose Modifications for Toxicity

Adverse events (both non-serious and serious) associated with Pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 8 below. See Section 6.8 for supportive care guidelines, including use of corticosteroids.

Treatment discontinuation for AST, ALT deterioration in participants who present with Grade 2 AST or ALT will be triggered only if AST or ALT increases by greater than or equal to 50% relative to the measurement taken at initiation of systemic treatment (Cycle 1 Day 1) and lasts for at least 1 week.

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhoea/ Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycaemia	T1DM or 3-4	Hold Pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume Pembrolizumab when participants are clinically and metabolically stable
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with Pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with Pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with Pembrolizumab can be continued while thyroid replacement therapy is instituted

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

[a] For participants who begin treatment with Grade 2 AST or ALTat Cycle 1 Day 1 of treatment, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then participants should be discontinued.

[b] If symptoms resolve within one hour of stopping IMP infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be pre-medicated for the next scheduled dose.

[c] Participants with intolerable or persistent Grade 2 drug-related AE may hold study medication at PI/delegate discretion. Permanently discontinue IMP for persistent Grade 2 adverse reactions for which treatment with IMP has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Table 8: Dose Modification Guidelines for Drug-Related Adverse Events

6.7 Drug interactions/Precautions

6.7.1 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are also not allowed during the on-going trial. If there is a clinical indication for one of these or other prohibited medications or vaccinations then discontinuation from the study may be required. The PI/delegate should discuss any questions regarding this with the CI/designee. The final decision on any supportive therapy or vaccination rests with

the CI and/or the participant's primary physician. However, the decision to continue the participant on the study requires the mutual agreement of the PI/delegate, CI/designee, and the participant.

6.7.2 Acceptable Concomitant Medications

All treatments that the PI/delegate considers necessary for a participant's welfare may be administered at the discretion of the PI/delegate in keeping with the community standards of medical care. All concomitant medication will be recorded including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date will be documented. Drugs to be recorded where possible using World Health Organisation Drug Dictionary (WHO DD) classification.

All concomitant medications received from screening until discontinuation should be recorded.

6.7.3 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the screening and treatment cycles:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than Pembrolizumab
- Live vaccines within 30 days prior to the first IMP administration and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor & CI/delegate.

Participants who, in the assessment by the PI/delegate, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Participants may receive other medications that the PI/delegate deem to be medically necessary. The exclusion criteria describes other medications which are prohibited in this trial. There are no prohibited therapies during the follow-up phase.

6.8 Rescue Medications & Supportive Care

6.8.1 Supportive Care Guidelines

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

supportive care. The treatment guidelines are intended to be applied when the PI/delegate determines the events to be related to Pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the PI/delegate does not need to follow the treatment guidance (as outlined below). Refer to Section 6.6 for dose modification.

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

6.8.1.1 Pneumonitis:

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

6.8.1.2 Diarrhoea/Colitis:

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

- All participants who experience diarrhoea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhoea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2 diarrhoea/colitis,** administer oral corticosteroids.
- For **Grade 3 or 4 diarrhoea/colitis,** treat with i.v. steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

6.8.1.3 Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycaemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)

- For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycaemia associated with metabolic acidosis or ketonuria.
    - Evaluate participants with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

6.8.1.4 Hypophysitis:

- For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no

less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

6.8.1.5 Hyperthyroidism or Hypothyroidism:

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

- **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
- **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

6.8.1.6 Hepatic:

- Comprehensive guidance on the diagnosis and management of hepatic events of interest are reported in Section 6.8.3.
- For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
- For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

6.8.1.7 Renal Failure or Nephritis:

- For **Grade 2** events, treat with corticosteroids.
- For **Grade 3-4** events, treat with systemic corticosteroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

6.8.1.8 Immune-related adverse events:

Please see Section 6.8.2 below regarding diagnosis and management of adverse experiences of a potential immunologic etiology.

6.8.1.9 Management of Infusion Reactions:

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

Table 9 below shows treatment guidelines for participants who experience an infusion reaction associated with administration of Pembrolizumab.

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the PI. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further IMP administration.**	Participant may be pre-medicated 1.5h (± 30 minutes) prior to infusion of Pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the participant	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	is deemed medically stable in the opinion of the PI. Hospitalisation may be indicated. **Participant is permanently discontinued from further IMP administration.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

Table 9: Infusion Reaction Treatment Guidelines

6.8.2 Supportive Care Guidelines for Immune-related Adverse Event (irAE) and Immune-related Events of Clinical Interest (irECI).

Immune-related Adverse events (IrAEs) may be defined as an AE of unknown etiology, associated with IMP exposure and is consistent with an immune phenomenon. IrAEs may be predicted based on the nature of the Pembrolizumab compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of IMP.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labelling an AE as an irAE. Participants who develop a Grade 2 or higher irAE should be discussed immediately with the CI/designee.
Recommendations to managing irAEs not detailed elsewhere in the protocol are detailed in Table 10.

irAE	Withhold/Discontinue Pembrolizumab?	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold Pembrolizumab	Consider systemic corticosteroids in addition to appropriate symptomatic treatment. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.
Grade 3 and Grade 4	Withhold Pembrolizumab Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 12 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.

Table 10: General Approach for Handling irAEs

Details for managing specific irAEs are summarised below:

Immune-mediated pneumonitis

Monitor participants 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 Pembrolizumab for moderate (Grade 2) pneumonitis, and permanently discontinue Pembrolizumab for severe (Grade 3) or life-threatening (Grade 4) pneumonitis.

Immune-mediated colitis

Monitor participants for signs and symptoms of colitis. Exclude other causes of colitis, and manage treatment in accordance with the guidelines above. Administer corticosteroids, withhold Pembrolizumab for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue Pembrolizumab for life-threatening (Grade 4) colitis.

Immune-mediated hepatitis

Monitor participants for changes in liver function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of hepatitis. Exclude other causes of hepatitis, and manage treatment in accordance with the guidelines above. Administer corticosteroids and, based on severity of liver enzyme elevations, withhold or discontinue Pembrolizumab.

Immune-mediated nephritis

Monitor participants for changes in renal function. Exclude other causes of nephritis, and manage treatment in accordance with the guidelines above. Administer corticosteroids, withhold Pembrolizumab for moderate (Grade 2), and permanently discontinue Pembrolizumab for severe (Grade 3) or life-threatening (Grade 4) nephrits.

Immune-mediated endocrinopathies

Monitor participants for signs and symptoms of hypophysitis (including hypopituitarism and secondary adrenal insufficiency). Exclude other causes of hypophysitis, and manage treatment in accordance with the guidelines above. Administer corticosteroids, withhold Pembrolizumab for moderate (Grade 2), withhold or discontinue Pembrolizumab for severe (Grade 3) and for life-threatening (Grade 4) hypophysitis.

Monitor participants for hyperglycaemia or other signs and symptoms of type 1 diabetes. Exclude other causes of diabetes. Administer insulin for type 1 diabetes, and withhold Pembrolizumab in cases of severe hyperglycaemia until metabolic control is achieved.

Thyroid disorders have been reported in participants receiving Pembrolizumab and can occur at any time during treatment; therefore, monitor participants for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders. Administer corticosteroids, withhold Pembrolizumab for severe (Grade 3) hyperthyroidism, and permanently discontinue Pembrolizumab for life-threatening (Grade 4) hyperthyroidism. Treat symptoms of hyperthyroidism as appropriate. Isolated hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids. For participants with severe (Grade 3) or life-threatening (Grade 4) endocrinopathy that resolved and is controlled with hormone replacement, continuation of Pembrolizumab may be considered.

Other immune-mediated adverse events

Across clinical studies with Pembrolizumab in approximately 5000 participants, the following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% of participants: uveitis and severe skin reactions.

In addition a set of irAEs have also been classified as immune-related events of clinical interest (irECI) a full list of these can been found in Table 12 in section 7.4. Participants with symptomatic irECIs should immediately stop receiving Pembrolizumab and be evaluated to rule out non treatment related causes of the event. All irECIs irrespective of relationship to the IMP should be reported within 24 hours of the PI/delegate being aware to the Sponsor/CI who will in turn notify MSD. If the irECI is determined to be associated please refer to section 6.8.3. If the event is not considered to be related with the IMP the PI/delegate should exercise individual clinical judgment on the event management based on the participant. Any additional questions of the collection or information on management of irECIs should be directed to the CI/delegate.

6.8.3 Guidance for Diagnosis and Management of Hepatic Events of Clinical Interest.

In addition to overdose, hepatic ECIs will include any of the following events. All of these events will require holding Pembrolizumab treatment, notification of the Sponsor, CI/delegate within 24 hours, and a hepatology consultation. Refer to Section 7 for reporting guidelines.

All cases of retreatment and permanent discontinuation must be reported to the Sponsor, CI/delegate and recorded in the eCRF.

a. ALT:
   i. Among participants with Day 1 ALT <2×ULN: ALT ≥5×ULN
   ii. Among participants with Day 1 ALT ≥2×ULN: ALT >3× the Day 1 level
   iii. ALT >500 U/L regardless of baseline level

b. AST:
   i. Among participants with Day 1 AST <2×ULN: AST ≥5×ULN
   ii. Among participants with Day 1 AST ≥2×ULN: AST >3× the Day 1 level
   iii. AST >500 U/L regardless of baseline level

c. Total Bilirubin:
   i. Among participants with baseline levels <25.65 µmol/L : a value of >34.2 µmol/L .
   ii. Among participants with baseline levels that are ≥25.65 µmol/L : a value ≥2× the baseline level
   iii. Total bilirubin >51.3 µmol/L regardless of baseline level

d. Regardless of laboratory values, hepatic decompensation diagnosed clinically, including:
   i. New onset clinically detectable ascites
   ii. Gastrointestinal bleeding suggestive of portal hypertension (e.g., esophageal or gastric varices)
   iii. Encephalopathy

(Participants with clinically apparent ascites or encephalopathy, or untreated varices are not eligible for enrolment)

Immediate assessment

All participants

- All participants should be evaluated according to directions below within 72 hours of alert for non-overdose ECI
- Procedures:
  - Obtain a consultation with a hepatologist

- Obtain a work-up for hepatitis if there is no underlying hepatitis, including hepatitis A, B,C, D, E, Epstein-Barr virus, and cytomegalovirus
- Assess for ingestion of drugs/supplements with hepatotoxic potential
- Assess for alcohol ingestion
- Assess for potential bacterial infection, biliary obstruction, or occult gastrointestinal bleeding
- Repeat ALT, AST, Tbil, Dbil, ALP, γ-glutamyl transpeptidase (GGT), INR, and FBC with differential
- Other laboratories or imaging studies as clinically indicated
- Consider liver biopsy if indicated by hepatologist

Hepatitis C-Infected Subjects (including subjects who previously achieved SVR 12)

- In addition to the above, measure HCV RNA viral load

Hepatitis B-infected Subjects

- HBV DNA, HBsAg, HBeAg, HBCT (anti-HBV core total IgG/IgM), HBeAb (anti-HBV antibody), HBSab (anti-HBV Surface Antibody)
- Participants should be questioned about compliance with the use of anti-viral agents.

Permanent Discontinuation Criteria for Subjects with Non-overdose Hepatic ECI

Therapy should also be permanently discontinued for any of the following:

- ALT >20×ULN
- Child-Pugh score of ≥9 points
- Gastrointestinal bleeding suggestive of portal hypertension (e.g., esophageal or gastric varices)
- New onset clinically detectable ascites
- Encephalopathy
- Recurrence of a severe or life-threatening event, or of any of the laboratory abnormalities listed above, that are presumed to be immune-related.

Other participants may be eligible for treatment interruption (and potential re-start) of Pembrolizumab after discussion with the Sponsor, CI/delegate.

Diagnosis and Management of Non-Overdose Hepatic ECIs

HCC subjects are at risk for a range of complications that can cause hepatic laboratory abnormalities with or without clinical decompensation. Those with a history of chronic HCV or HBV infection also have the potential to experience virologic flares. Immune-related hepatitis has been observed in ~1% of subjects who received Pembrolizumab. The following section provides further guidance on the diagnosis and management of potential hepatic complications among HCC subjects.

a. Hepatitis B Flare

Hepatitis B flares are characterized by rapid elevations of ALT and AST to >5×ULN and/or >3× baseline. ALT elevation to ≥10×ULN is common. In the absence of hepatic decompensation, ALT/AST elevations are typically isolated (i.e. limited/no elevations of bilirubin/ALP). participants who are compliant with anti-viral therapy should have continued suppression of HBV DNA at the time of flare; thus, detection of HBV DNA should prompt questioning of subjects for compliance. Laboratory abnormalities secondary to flare are typically observed for 3-5 weeks.

Among participants with HBV, a flare should be considered if this pattern is observed and there is no evidence of an alternative etiology. Guidelines for participants with a diagnosis of HBV flare are as follows:

- Care should be instituted in consultation with a hepatologist.
- For participants who have detectable HBV DNA, re-institute anti-viral therapy.
- If the participant is clinically stable, Pembrolizumab dosing may be interrupted for up to 12 weeks. Subjects should undergo weekly laboratory tests including: AST, ALT, ALP, Tbil, Dbil, INR, HBsAg, HBV DNA (if detected at the onset of the flare). Obtain anti-HBe, anti-HBs, and HBV DNA levels (if not detected at the onset of the flare) every 2-3 weeks.
- If ALT returns to normal or Grade 1 (if normal at baseline), or to baseline grade (if Grade 2 at baseline) within 12 weeks, and participants are clinically stable, participants may restart Pembrolizumab treatment. If these conditions are not met, then Pembrolizumab treatment should be permanently discontinued.

b. Hepatitis C Recurrence or Flare

Participants who achieved a sustained virologic response at 12 weeks on specific antiviral treatment (SVR 12) and subjects with on-going HCV infection are eligible for enrolment. In rare circumstances, HCV participants who achieve SVR 12 may relapse at later time points. Relapse is characterised by detection of HCV RNA, often accompanied by ALT elevations to >5×ULN. In the absence of hepatic decompensation, ALT/AST elevations are typically isolated (i.e., limited/no elevations of bilirubin/ALP).

Among participants with uncontrolled hepatitis C, virologic flares are possible. Hepatitis C flares are characterized by rapid elevations of ALT and AST to >5×ULN and/or >3× baseline along with a rise in HCV RNA. ALT elevation to ≥10×ULN and a 1 log elevation in HCV RNA level are common. In the absence of hepatic decompensation, ALT/AST elevations are typically isolated (i.e., limited/no elevations of bilirubin/ALP). Laboratory abnormalities secondary to flare or recurrence are typically observed for 3-5 weeks.

Guidelines for participants with recurrent HCV infection or an HCV flare are described below:

i. Recurrent HCV infection:

If the participant entered the study with an HCV RNA test of "Target not Detected" and has confirmed detectable HCV RNA (2 specimens, 1 week apart), then the subject has experienced a late HCV relapse or a recurrent infection.

- Question the participant about use of injection or inhalation drugs
- At the time of first detection of HCV RNA, send a specimen for HCV genotyping
- Measure AST, ALT, ALP, Tbil, Dbil, and INR weekly
- Measure HCV RNA levels every 2 weeks
- Therapy with HCV anti-viral treatments should be strongly considered.

ii. HCV Flare:

- At the time of first detection of HCV RNA, send a specimen for HCV genotyping
- Measure AST, ALT, ALP, Tbil, Dbil, INR weekly
- Measure HCV RNA levels every 2 weeks
- Therapy with HCV anti-viral treatments should be strongly considered.

iii. For both recurrent infection and HCV flare: if ALT returns to normal or Grade 1 (if normal at baseline), or to baseline grade (if Grade 2 at baseline) within 12 weeks, and the participants are clinically stable, participants may restart Pembrolizumab treatment. If these conditions are not met, then Pembrolizumab treatment should be permanently discontinued.

c. Immune-related hepatitis

i. Description: Immune-related hepatitis due to Pembrolizumab should be suspected if any of the following is seen:

- AST or ALT baseline values are less than 2×ULN, and AST or ALT laboratory values increase to ≥5×ULN
- Among participants with Day 1 ALT or AST ≥2×ULN, levels increase to >3× the Day 1 level
- AST/ALT >500 U/L regardless of baseline level
- Among participants with Day 1 Tbil levels <1.5 mg/dL: a value of >2.0 mg/dL
- Among participants with Day 1 Tbil levels that are ≥1.5 mg/dL: a value of ≥2× the Day 1 level
- Total bilirubin >51.3 µmol/L regardless of baseline level.

Immune-related hepatitis is a diagnosis made after excluding other possible etiologies for the change. Viral flare (if applicable), biliary or vascular obstruction, infection, medications, and alcohol use must be ruled out (see below).

ii. Management

- Interrupt Pembrolizumab treatment and alert the sponsor/CI or delegateas per ECI criteria above for ALT, AST, bilirubin, and hepatic decompensation.
- Start IV corticosteroid (methylprednisolone 125 mg) followed by oral corticosteroid (1-2 mg/kg/day).
- Monitor with biweekly laboratory tests including AST, ALT, Tbil, Dbil, ALP, and INR.
- If symptoms and laboratory tests resolve to Grade ≤1 or baseline (if abnormal at baseline), taper steroids over 28 days. Pembrolizumab treatment may be restarted after steroid treatment has been tapered to prednisone ≤10 mg/day (or equivalent dose of another agent). Treatment and laboratory results must be documented.
- If laboratory abnormalities do not resolve within 3 weeks, or steroids cannot be lowered to ≤10 mg/day (or prednisone equivalent) within 12 weeks, or participants show evidence of decompensation to Child-Pugh C status or have esophageal or variceal bleeding at any point, treatment must be permanently discontinued. This must be documented.

d. Other Hepatic Events of Clinical Interest

- Infection needs to be ruled out with cultures of blood, urine, and ascites (if possible), as well as chest x-ray and abdominal imaging if relevant. If an infection is found, antibiotics should be started.
- If Tbil is elevated above baseline, magnetic resonance cholangiopan-creatography or ultrasound with doppler should be obtained to rule out vascular compromise, biliary obstruction, and/or tumour progression. If biliary obstruction is present, consultation with a gastroenterologist and/or an interventional radiologist should be obtained to see if the obstruction may be relieved.
- A careful review of drugs, including herbal and alternative medications, should be obtained, and alcohol use should be ruled out.

- For all of these cases, participants may resume Pembrolizumab treatment if they are clinically stable after appropriate therapy or discontinue the causative agent, as long as laboratory values have returned to Grade 1 or baseline (if normal or Grade 1 at start) or to baseline grade within 3 weeks.
- Treatment must be permanently discontinued if the participant is off Pembrolizumab therapy for infection, obstruction, or drug/alcohol-related toxicity for more than 3 weeks, or if they have oesophageal bleeding, or become Child-Pugh C at any point.

6.9 Diet/Activity/Other Considerations

6.9.1 Diet

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

6.9.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if Pembrolizumab has transient adverse effects on the composition of sperm. For this trial, male participants will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female participants will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of IMP by complying with one of the following:

(1) practice abstinence[†] from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (oestrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the participants preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

Participants should be informed that taking the IMP may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study participants of childbearing potential must adhere to the contraception requirement (described above) from the day of IMP administration (or 14 days prior to the initiation of study medication for oral contraception) for the duration of the study and for 120 days after the last dose of IMP. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

6.9.3 Use in Pregnancy

If a participant inadvertently becomes pregnant while on treatment with Pembrolizumab, the participant will immediately be removed from the study. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor, CI/delegate without delay and within 24 hours if the outcome is a SAE (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The Sponsor, CI/delegate will notify MSD of all events within 48 hours. The PI will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor, CI/delegate. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor, CI/delegate and followed as described above and in Section 7. If the pregnancy continues to term, the outcome (health of infant) must also be reported for up to 3 months.

6.9.4 Use in Nursing Women

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

6.10 Overdose of IMP

For purposes of this trial, an overdose of Pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of Pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. Details of reporting an overdose can be seen in section 7.6.

6.11 Permanent Discontinuation of Study Treatment and Withdrawal from Study

6.11.1 Permanent discontinuation of study treatment

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

- The participant withdraws consent.
- Confirmed radiographic disease progression

  Note: For unconfirmed radiographic disease progression.

  Note: A participant may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved. IMP will be provided off-study and as a special.
- Unacceptable AEs.
- Intercurrent illness that prevents further administration of IMP
- PI's decision to withdraw the participant
- The participant becomes pregnant
- Noncompliance with trial treatment or procedure requirements
- Administrative reasons

Trial participants will not be replaced once completing 21 days of treatment or enrolled more than once. The primary reason for discontinuation should be recorded. Once the trial medication has been discontinued the participant should complete the end of treatment and safety follow-up visit procedures as listed in the schedule of study assessments (Table 3). After the end of treatment, participants will continue to be assessed for AE and SAE monitoring until the SFU visit.

Participants will continue onto follow-up after the safety follow up, their details will be reviewed every 8 weeks ± 7 days for details of disease status, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. Follow-up will continue until the last participant has completed treatment or comes off study for disease progression or unacceptable toxicities.

6.11.2Withdrawal from Study

Withdrawal from the study refers to discontinuation of IMP and study procedures and can occur for the following reasons:

- Participant decision
- Loss to follow-up
- Death
- PI/delegate Decision

Participants may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the PI/delegate should any untoward effect occur. In addition, a participant may be withdrawn by the PI/delegate or the Sponsor if enrolment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in below.

6.11.3 Procedures for Withdrawal from Study

When a participant withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any AEs which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 7

6.12 Non-IMP details

Trans-arterial chemoembolization will be performed as a background treatment and as such is classed as a NIMP for the purpose of this study

7.0 PHARMACOVIGILANCE

7.1 Adverse Event (AE)

An AE is defined as any untoward medical occurrence in a participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the IMP, whether or not considered related to the IMP.

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 Pembrolizumab and/or radiotherapy, is also an AE.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered AEs.

7.1.1 Disease Progression

Disease progression of the cancer under study is not considered an AE unless the investigator deems that it is at least possibly related to the Pembrolizumab.

7.1.2 New Cancers

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

7.1.3 Abnormal Laboratory Test Results

All clinically significant abnormal laboratory test results occurring during the study will be recorded as AEs from after first administration of the IMP until for at least 30 days following the last dose of IMP or the discontinuation visit; whichever is the sooner. The clinically significant abnormal laboratory tests will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the PI/delegate, or until a diagnosis that explains them is made.

Note: AEs seen at screening should be recorded as part of the participant's medical history.

7.1.4 Pregnancy and Lactation

Pregnancy and lactation are not considered AEs, however these events should be reported to the CI/delegate and subsequently to the Sponsor following guidance in below section.

7.2 Adverse Event recording

All AEs will be recorded from the time of signing the consent form and will be followed up for up to130 days following the last dose of IMP. All adverse events will be recorded in the electronic Case Report Form (eCRF).

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

If a PI/delegate learns of any SAEs, including death, at any time after a participant has completed the study and he/she considers there is a reasonable possibility that the event is related to Pembrolizumab, the PI/delegate should notify the Sponsor and CI/delegate

The following details will be collected for each AE:

- AE description / diagnosis
- Date and time of onset and resolution (if applicable)
- NCI-CTCAE grade (including any changes)
- Seriousness
- PI/delegate causality rating against the IMP
- Action taken with regard to IMP
- Outcome

7.2.1 Evaluating Adverse Events

AEs will be evaluated by a medically qualified physician.

7.2.1.1 Determining AE Severity and Grade

AE severity and grade will be evaluated according to the NCI CTCAE version 4.0. Any AE which changes CTCAE grade over the course of a given episode should be closed at the date and time the severity changed and a new AE recorded from the date and time of the new NCI CTCAE grade.

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

7.2.1.2 Determining AE Causality

The PI/delegate 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 the IMP. This may require instituting supplementary investigations of significant AEs based on their clinical judgement of the likely causative factors and/or include seeking a further opinion from a specialist in the field of the AE.

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

Definite:	• There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Probable:	• There is evidence to suggest a causal relationship and the influence of other factors is unlikely
Possible:	• There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after IMP administration. However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Unlikely:	• There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Not related:	• No evidence of any causal relationship.
Not assessable:	• There is insufficient or incomplete evidence to make a clinical judgement of the causal relationships

Table 11: Assessment of Causality between AE and exposure to the IMP.

7.2.2 Reporting of Pregnancy and Lactation

It is the responsibility of PI/delegate to report any pregnancy or lactation in a participant (spontaneously reported to them), including the pregnancy of a male participant's female partner that occurs during the trial or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier. All participants and female partners of male participants who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as SAEs. Consent to report information regarding these pregnancy outcomes from female partners of any males who took IMP will be obtained from the mother. If the pregnancy continues to term, the outcome (health of infant) must also be reported for up to 3 months.

Such events must be reported within 24 hours of learning of its occurrence to the Sponsor and CI/delegate who will subsequently inform MSD.

7.3 Serious Adverse Events (SAE)

7.3.1 Definition of 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 participant, in the view of the PI/delegate, at immediate risk of death from the event as it occurred[1]

- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalisation[2];
- Is a congenital anomaly/birth defect(in offspring of participant 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 AE associated with an overdose is considered a SAE.
- 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 jeopardise the participant 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 causality (without admission).*

7.4 Definitions of Events of Clinical Interest (ECI)

Selected non-serious and SAE can also be classified as ECI and must be reported as described in the below section.

Events of clinical interest for this trial include:

1. An overdose of Pembrolizumab, as defined in Section 7.6 that is not associated with clinical symptoms or abnormal laboratory results.
2. A Drug induced liver injury defined as elevated AST or ALT lab value that is greater than or equal to 3X the ULN

AND / OR

An elevated total bilirubin lab value that is greater than or equal to 2X ULN **AND / OR**
An alkaline phosphatase lab value that is less than 2X ULN, 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 ir-ECI. A detailed narrative of the event should be documented:

Pneumonitis - ***(reported as ECI if ≥ Grade 2)***		
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 (ALT and/or AST)
Infusion reactions - ***(reported as ECI for any grade)***		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic - ***(reported as ECI for any grade)***		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndromw		

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	Percarditis
Vasculitis	Sclerosing cholangitis	
Any other grade 3 event which is considered immune-related by the physician.		

Table 12: Immune related AEs considered ECIs.

Participants should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and participants should be asked for signs and symptoms suggestive of an immune-related event. Participants 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 ir 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.

7.4.1 Reporting of SAEs

Any SAE whether or not related to Pembrolizumab, occurring from informed consent until 130 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 Sponsorand CI/delegate who will then inform MSD.

Please find below Sponsor details:
Imperial College Joint Research Compliance Office
Email address: jrco.ctimp.team@imperial.ac.uk

All SAEs regardless of causality, pregnancy or overdose 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 worsening of the grade is to be recorded.

If new or amended information on a previously reported SAE becomes available, the PI or delegate should update the SAE and report this to the Sponsor, CI/delegate. Follow up information about a previously reported SAE must be reported within 24 hours of receiving it. If the SAE has not been reported within the specified timeframes, a reason for lateness must be included when sending the SAE.

Additionally, any SAE, considered by a PI/delegate who is a qualified physician to be related to Pembrolizumab that is brought to the attention of the PI at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and CI. The CI/delegate will then inform the MSD.

These AEs will be followed up until resolved or stabilised at a level acceptable to the CI even if this is after the study reporting period.

7.4.2 Events exempt from being reported as SAEs

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

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.

7.4.3 Determining SAE Causality and Expectedness

Assessment of causality and expectedness for all SAEs will be made by the PI/designee against the current approved version of the IB. If updated versions of the IB are released during the course of the trial then assessment of expectedness will be made against the current regulatory approved version.

7.5 Reporting of ECIs

Any ECIs whether or not related to the Pembrolizumab, 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 log and reported using the eCRF report form within 24 hours of the PI/designee becoming aware of the event to the CI or delegate who will then inform MSD.

7.6 Reporting of an Overdose

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

If an AE(s) is associated with ("results from") the overdose of Pembrolizumab, the AE(s) should be recorded on the AE eCRF and reported as a SAE, 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 and reported as a non-serious ECI, using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose either SAE or ECI must be reported within 24 hours of the PI/ designee becoming aware of the event to the Sponsor, CI/delegate by email who will inform MSD.

7.7 Definition of a Serious Adverse Reaction (SAR)

A SAR is defined as a SAE that is judged to be related to any dose of the IMP administered to the participant.

7.8 Definition of Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any SAR that is NOT consistent with the applicable product information as set out in the IB.

7.9 Reporting of SUSARs

The Investigator and local study team will report all SUSARs to the Sponsor, CI/delegate within 24 hours of becoming aware of the event.

The Sponsor, CI/delegate will ensure that SUSARs are notified to the appropriate regulatory authority, the relevant Independent Research Ethics Committee (REC), MSD and the participating PIs in accordance with regulatory requirements and within the timelines specified in legislation (SI 2004/1031 as amended).

The Sponsor has delegated the responsibility for notifying the MHRA and REC of all SUSARs occurring during the study to the CI/delegate. All SAEs and SUSARs must be reported in accordance with local regulatory guidelines:

*Life threatening SUSARs should be reported to the MHRA and REC n*o later than **7 days** after the CI has first knowledge of the minimum criteria for expedited reporting. Further relevant information should be given within a further 8 days.

*Non-fatal and non-life threatening SUSARs should be reported to the MHRA and REC n*o later than **15 days** after the CI has first knowledge of the minimum criteria for expedited reporting. Further relevant information should be given as soon as possible.

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

7.10 Annual Reporting of Serious Adverse Events

Annual reports will be submitted to regulatory authorities and REC by the CI or delegate in accordance with all applicable global laws and regulations. Copies will be forwarded to the Sponsor.

8.0 STATISTICAL ANALYSES

8.1 Sample Size and power considerations

Since this is the first time that Pembrolizumab is given to participants with chronic viral infection and limited functional liver reserve, we designed the study as a safety-oriented trial and considered enrolling a subsequent cohort of up to 26 participants following an initial safety run-in of 6 subjects to: 1) satisfy the safety aims of the study; 2) preliminarily document the efficacy of treatment to inform subsequent efficacy-testing in a future adequately powered trial; 3) obtain adequate information regarding the disease-modulating effects from treatment reflected by the proposed translational endpoints.

With primary endpoints being safety, no power calculation for hypothesis testing is required to formally power the study: the upper 95% confidence interval for toxicity events will inform the decision to proceed to a future, adequately powered phase II trial. Using the rule of three, if zero events are observed in 26 participants the upper 95% confidence interval will be 15%.

8.2 Data Analysis

The clinical data will be entered and stored in InForm™ database. Statistical analysis will be conducted.

A safety review will be conducted by the IDSMC after Part I. A final analysis will be conducted at the end of the study. Analyses will include an intent to treat (ITT) analysis including all participants enrolled and a per protocol analysis using all participants who complete the study without major protocol violations.

Histograms and boxplots will be used to check the distribution and possible outliers for continuous variables. Continuous variables that follow a normal distribution will be summarised using means and standard deviations. Skewed continuous variables will be summarised using medians and inter-quartile ranges. Categorical variables will be summarised using frequencies and percentages.

8.3 Primary and Secondary Endpoint Analysis

All participants who receive at least one dose of Pembrolizumab will be included in the safety analysis set.

The frequency of AEs will be assessed for severity (NCI CTCAE v4), expectedness, seriousness and causal relationship to IMP. In addition, AEs will be summarised by toxicity type, impact on IMP and by timing.
All participants who receive at least one dose of Pembrolizumab and undergo disease re-evaluation as per protocol will be included in the efficacy analysis.

Due to sample size constraints, for the primary outcome of assessing the safety and tolerability of Pembrolizumab following TACE and secondary outcomes of ORR every 3 months and QOL, we will use descriptive measures such as frequencies and percentages for categorical variables and means and standard deviations for normally distributed continuous variables, as specified above in section 8.1.

The secondary endpoint of PFSR will be estimated by the Kaplan-Meier method. This rate estimates the proportion of participants who do not progress and are alive at a given time of 12 weekly timepoints. The PFSR is calculated from the start of Imp administration until the date of progression or death from any cause.

Univariate models will be performed for all demographic and other study variables, as statistically appropriate, as well as to test for confounding due to sample size constraints, with models such as Fisher's exact test or the Chi-square test utilised for categorical variables and t-tests or the Wilcoxon test (if the continuous variable does not follow a normal distribution) for continuous ones. For all estimates, 95% confidence intervals will be calculated.

8.4 Exploratory Endpoint Analysis

The sample collection will be used for future ethically approved research. For the translational/exploratory endpoints, appropriate descriptive measures as well as univariate models will be shown as dependent on whether the relevant measure is categorical or continuous, whether the test is paired or not and whether is it normally or non-normally distributed as indicated above.

9.0 REGULATORY, ETHICAL AND LEGAL ISSUES

9.1 Declaration of Helsinki

The CI will ensure that this study is conducted in full conformity with the principles of the 1964 Declaration of Helsinki and any subsequent revisions.

9.2 Good Clinical Practice

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines).

9.3 Research Ethics Committee Approval

9.3.1 Initial Approval

Prior to the shipment of IMP and the enrolment of subjects, the REC must provide written approval of the conduct of the study at named sites, the protocol and any amendments, the Participant Information Sheet (PIS) and Informed Consent Form (ICF), any other written information that will be provided to the participants.

9.3.2 Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the HRA/REC and Medicines Healthcare Regulatory Agency (MHRA) (as required) for approval as instructed by the Sponsor.

Amendments that are intended to eliminate an apparent immediate hazard to participants may be implemented prior to receiving Sponsor or REC approval. However, in this case, approval must be obtained as soon as possible after implementation.

9.3.3 Annual Progress Reports

The REC will be sent annual progress reports in accordance with national requirements.

9.3.4 Annual Safety Reports and End of Trial Notification

The REC will be sent annual safety updates in order to facilitate their continuing review of the study (reference. ICH GCP E6 Section 3.1.4) and will also be informed about the end of the trial, within the required timelines.

9.4 Regulatory Authority Approval

The study will be performed in compliance with the regulatory requirements of the UK.
Clinical Trial Authorisation from the appropriate Regulatory Authority will be obtained prior to the start of the study. In addition, the Regulatory Authority must approve amendments (as instructed by the Sponsor), receive Suspected Unexpected Serious Adverse Reactions (SUSAR) reports, Development Safety Update Reports and be notified of the end of the trial.

9.5 Insurance and Indemnity

Imperial College holds Public Liability ("negligent harm") and Clinical Trial ("non-negligent harm") insurance policies which apply to this trial.

9.6 Trial Registration

The study will be registered on the *clinicaltrials.gov* trial database in accordance with requirements of the International Committee of Medical Journal Editors (ICMJE) regulations.

9.7 Informed Consent

The PI/delegate at each site will:

• Ensure that each participant is given full and adequate oral and written information about the study including the background, purpose and risks/benefits of participation

• Ensure that each participant is notified that they are free to withdraw from the study at any time

• Ensure that each participant is given the opportunity to ask questions and allowed sufficient time to read and understand the ICF

• Ensure each participant provides signed, dated ICF before undergoing any study specific procedure

• Ensure the original copy of the signed, dated ICF is stored in the ISF and a copy is also filed in the participant's medical records

• Ensure that each participant receives a copy of the signed, dated ICF

9.8 Contact with General Practitioner

It is the PI/delegate responsibility to inform the participant's General Practitioner by letter that the participant is taking part in the study provided the participant agrees to this, and information to this effect is included in the PIS and ICF.

9.9 Subject Confidentiality

The PI/delegate must ensure that the subject's confidentiality is maintained. On all documents submitted to the Sponsors, participants will be identified by a trial ID number only. Documents that are not submitted to the Sponsor (e.g. signed ICF) should be kept in a strictly confidential file by the PI/delegate.

The PI/delegate shall permit direct access to participant's records and source document for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, Regulatory Authorities and RECs.

9.10 Data Protection

Precautions will be taken to ensure that participant confidentiality is preserved at all times. The PI/delegate will identify those individuals who will require access to participant data and identifiable details and obtain appropriate permission from the consenting participant.

9.11 End of Trial

The EOT is defined as the last participant last visit (LPLV).

9.12 Study Documentation and Data Storage

The PI must retain essential documents until notified by the Sponsor, and for at least 25 years after study completion. Participant files and other source data (including copies of protocols, original reports of test results, IMP dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be retained. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the CI/delegate. 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 & CI/delegate.

10.0 DATA MANAGEMENT

10.1 Source Data

All original records and certified copies of original records of clinical findings, observations, or other activities 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, participant's 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, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial.

10.2 Language

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

10.3 Database & Data Management

Data will be recorded using the InForm electronic data capture (EDC) and management system where possible.

AE data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT), and CTCAE v4.0 grade.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trial.

10.4 Data Collection

Details of procedures for eCRF completion will be provided in a study manual.

11.0 STUDY MANAGEMENT STRUCTURE

11.1 Independent Data & Safety Monitoring Committee

This study will employ an Independent Data Safety Monitoring Committee (IDSMC)

The IDSMC is an independent body that will act in an advisory capacity to monitor the safety of participants participating in this study. The IDSMC will review the safety data and recommend modifications to the protocol to ensure participant safety, or recommend early termination of the study if major concerns arise about the participant's safety at any time during the course of the study. The IDSMC will review the safety profile of the IMP at the completion of Study Part 1 and should any SUSAR occur during the course of the study. The roles and responsibilities of the IDSMC will be outlined in a separate charter agreed to by each of the members of the IDSMC.

11.2 Trial Management Group

A Trial Management Group (TMG) will consist of the Chief Investigator, PIs, the Trial Statistician and Trial Coordinator. Other key study personnel may be invited to join the TMG as appropriate to ensure representation from a range of sites and professional groups.

Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the TMG will have operational responsibility for the conduct of the trial.

11.3 Early Discontinuation of the Study

Early trial termination can occur for well-documented reasons.

Further recruitment of participants will not take place under the following conditions:

- Premature termination of the trial.
- Drug-related events, i.e. SUSARs, emerging adverse effects that are serious and the risk/benefit ratio is unacceptable.
- Procedure-related events, i.e., the recruitment rate is too low or the number of dropouts for administrative reasons is too high

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

11.4 Risk Assessment

A study-specific risk assessment will be performed by the Sponsor prior to the start of the study to assign a risk category of 'low', 'medium' or 'high' to the trial. The risk assessment will consider all aspects of the study and will be used to guide the monitoring plan.

11.5 Monitoring

The study will be monitored periodically by monitors in the UK to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data.
Monitoring procedures and requirements will be documented in a Monitoring Plan. Monitoring will be proportionate to the objective, purpose, design, size, complexity, blinding, endpoints and risks associated

with the clinical trial. The appropriate level and nature of monitoring required for the clinical trial will be assessed by undertaking a formal risk assessment analysis of the study.

11.6 Quality Control and Quality Assurance

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

11.7 Disclosure of Data and Publication

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The CI may use this information for the purposes of the study only.

It is understood by the CI that the Sponsor will use information developed in this clinical study in connection with the development of the IMP and, therefore, may disclose it as required to other clinical investigators and to Regulatory Authorities. In order to allow the use of the information derived from this clinical study, the CI understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

Therefore all information obtained as a result of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the CI is completed.

The results may be published or presented by the CI/delegate(s).

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Appendices

Appendix 1: Diagnostic Criteria for HCC.

The diagnosis of HCC may be confirmed by biopsy or by application of the following non-invasive diagnostic criteria that have been proposed by the American Association for the Study of the Liver (AASLD), last updated in 2011*.

1. Nodules between 1 and 2 cm found on ultrasound screening of a cirrhotic liver should be characterized further with two dynamic studies, either multi-detector CT scan or MRI with contrast. If the imaging appearances are typical of HCC (i.e. hypervascular, arterial enhancement followed by washout in the portal/venous phase) in two independent techniques, then the lesion should be treated as HCC. If the findings are not characteristic or the vascular profile is not coincidental among techniques the lesion should be biopsied.

2. If the nodule is larger than 2 cm at initial diagnosis and has the typical features of HCC on one dynamic imaging technique, biopsy is not necessary for the diagnosis of HCC. However, if the vascular profile on imaging is not typical of HCC or if the nodule is detected in a non-cirrhotic liver, biopsy should be performed to confirm the diagnosis.

*As published in: Bruix J, Sherman M; Management of hepatocellular carcinoma: an update. Hepatology. 2011 Mar; 53(3):1020-2.

Appendix 2: ECOG Performance Status

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

Appendix 3: Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

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

Appendix 4: Modified Response Evaluation Criteria in Solid Tumours (mRECIST*) Criteria for Evaluating Response in Hepatocellular Carcinoma.

Modified RECIST version criteria will be used in this study for assessment of tumour response. CT is the preferred imaging technique in this study.

* As published in:

- Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular Carcinoma. Semin Liver Dis 2010; 30:52-60

Appendix 5: Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumours

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

* As published in the European Journal of Cancer:

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

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

Imperial College London

SIGNATURE PAGE 1 (CHIEF INVESTIGATOR)

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: A phase Ib study of Pembrolizumab following Trans-Arterial chemoembolization in primary Liver carcinoma (PETAL).

Signed: _____

Dr David James Pinato
MD MRes MRCP (UK) PhD

Date: _____

Imperial College London

SIGNATURE PAGE 2 (SPONSOR)

The signatures below constitute approval of this protocol by the signatory.

Study Title: A phase Ib study of Pembrolizumab following Trans-Arterial chemoembolization in primary Liver carcinoma (PETAL).

Signed: _____

Name of Sponsor's Representative
Title
Sponsor name

Date: _____

Imperial College London

SIGNATURE PAGE 3 (PRINCIPAL INVESTIGATOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: A phase Ib study of Pembrolizumab following Trans-Arterial chemoembolization in primary Liver carcinoma (PETAL).

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____