

CC# 17705: A Pilot Study of Pembrolizumab and Liver-Directed Therapy or Peptide
Receptor Radionuclide Therapy for Patients with Well-Differentiated Neuroendocrine
Tumors and Symptomatic and/or Progressive Metastases

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Study Drug: Pembrolizumab

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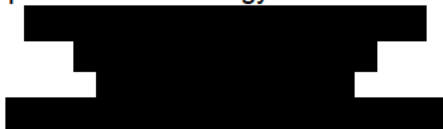
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PROTOCOL SIGNATURE PAGE

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Institutional Review Board (IRB), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable IRB requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572 or equivalent), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with IRB policies, Federal, state and local laws and regulations.

UCSF Principal Investigator

Printed Name

Signature

Date

ABSTRACT

Abbreviated Title	Pembrolizumab and liver-directed therapy or PRRT for patients with metastatic well-differentiated neuroendocrine tumors
Trial Phase	Pilot
Clinical Indication	Well-differentiated metastatic neuroendocrine tumors
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous (IV)
Trial Blinding	Unblinded open-label (subjects will be blinded to their molecular marker results)
Treatment Groups	Group 1: Pembrolizumab + ¹⁷⁷Lu DOTATATE *Group 2: Pembrolizumab + Transarterial embolization *Group 3: Pembrolizumab + Yttrium-90 radioembolization *as of 09/15/2022, Groups 2 and 3 are closed to enrollment
Number of trial subjects	32 subjects will be enrolled
Estimated enrollment period	36 months
Estimated duration of trial	Approximately 60 months from the time the first subject signs the informed consent form (ICF) until the last subject's last study-related office visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the ICF through the final contact. After a screening phase of up to 28 days, eligible subjects will receive study treatment. Treatment will continue until progressive disease (PD), unacceptable adverse events (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, subject receives 35 treatments (approximately 2 years) of pembrolizumab, or administrative reasons requiring cessation of treatment. Subjects who discontinue for reasons other than PD will have post-treatment follow-up for disease status until PD, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. After the end of treatment, each subject will be followed for 30 days for AE monitoring. Serious adverse events (SAE) and events of clinical interest (ECI) will be collected for 90 days after the end of treatment or for 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier.

LIST OF ABBREVIATIONS

Abbreviation/Term	Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
ASaT	All Subjects as Treated
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
β-HCG	Beta Human Chorionic Gonadotropin
CBC	Complete Blood Count
CB-CTA	Cone-beam computed tomography angiogram
CNS	Central Nervous System
CPI	Checkpoint Pathway Inhibitor
CR	Complete Response
CrCl	Calculated Creatinine Clearance
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Antigen-4
DCR	Disease Control Rate
DKA	Diabetic Ketoacidosis
DLT	dose limiting toxicity
DOR	Duration of Response
ECI	Events of Clinical Interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ERC	Ethics Review Committee
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
GCP	Good Clinical Practice
GI	Gastrointestinal
GFR	Glomerular Filtration Rate
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IND	Investigational New Drug

Abbreviation/Term	Definition
INR	International Normalized Ratio
IR	Interventional Radiologist
irAEs	Immune-related Adverse Events
irRECIST	Immune related RECIST (Modification of RECIST 1.1)
IRB	Institutional Review Board
ITIM	Immunoreceptor Tyrosine-based Inhibition Motif
ITSM	Immunoreceptor Tyrosine-based Switch Motif
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Integrated Web Response System
Kg	Kilogram
LCNEC	Large Cell Neuroendocrine Carcinoma
LDH	Lactate Dehydrogenase
LSF	Lung Shunt Fraction
MAA	Macroaggregated albumin
mAb	Monoclonal Antibody
mcL	Microliters
MDSC	Myeloid-derived Suppressor Cell
MEL	Melanoma
Mg	Milligram
Mg/kg	Milligram per Kilogram
mL	milliliter
MRI	Magnetic Resonance Imaging
mRNA	Messenger RNA
NA or N/A	Not Applicable
NCI	National Cancer Institute
NE	Neuroendocrine
NET	Neuroendocrine tumor
NGS	Next Generation Sequencing
NSAID	Non-Steroidal Anti-inflammatory Drug
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival
OTC	Over-the-counter
PD	Progressive Disease
PD-L1	Programmed Death Ligand 1
PD-NEC	Poorly-differentiated neuroendocrine carcinoma
PFS	Progression Free Survival
PK	Pharmacokinetic
PR	Partial Response
PRRT	Peptide receptor radionuclide therapy

Abbreviation/Term	Definition
PT	Prothrombin Time
PVA	Polyvinyl Alcohol
RE	Radioembolization
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	Radiofrequency Ablation
RNA	Ribonucleic Acid
RR	Response Rate
Q12W	Every 12 Weeks
SAE	Serious Adverse Events
SCC	small cell carcinoma
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOP	Standard Operating Procedures
SSTR	Somatostatin receptor
TAE	Transarterial embolization
TB	Bacillus Tuberculosis
TCR β	T Cell Receptor β
TIL	Tumor Infiltrating Lymphocytes
TKI	Tyrosine Kinase Inhibitor
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
UCSF	University of California San Francisco
WBC	White Blood Cell
WD-NET	Well-differentiated neuroendocrine tumor
Y90	Yttrium-90

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1.0 TRIAL DESIGN

1.1 Trial Design

This is a three arm, open-label non-randomized study in biomarker “unselected” subjects with previously treated well-differentiated metastatic neuroendocrine tumors. Subjects will be required to have a least one measureable lesion by Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) and at least one other lesion (primary or metastatic; intra- or extrahepatic) for response assessment.

All patients will receive one dose of IV pembrolizumab. Subsequent therapy will be based on group assignment. Group assignment will be based on burden of metastatic disease in the liver, according to the guidelines outlined below.

Patients assigned to **Group 1** will be treated with pembrolizumab and intravenous peptide receptor radionuclide therapy (PRRT) using ^{177}Lu -DOTA⁰-Tyr³-Octreotate (^{177}Lu -DOTATATE, Lutathera®) for up to four (4) sessions 8 ± 1 weeks apart. The first PRRT session would be 2-15 days following the first pembrolizumab dose. Subsequent PRRT sessions would be administered no fewer than 6 days prior to the subsequent pembrolizumab dose. Within 1 month prior to PRRT, an optional core biopsy of the safest percutaneously accessible lesion and peripheral blood samples will be obtained. Pembrolizumab will be administered at 3 week intervals. A repeat, optional core biopsy of the safest percutaneously accessible lesion (ideally, same lesion as the one targeted for first biopsy) and peripheral sampling will be repeated approximately 5 weeks after the first PRRT treatment.

Patients assigned to **Group 2** will be treated with segmental or subsegmental transarterial embolization (TAE) to at least one measurable liver lesion approximately 3-7 days following the first dose of pembrolizumab. The hepatic artery segmental branch supplying the liver segment with the highest volume ratio of tumor to normal liver tissue will be targeted for embolization. Tumor to normal tissue volume distribution will be determined with the help of cone beam CT angiography (CB-CTA) performed prior to TAE. Up to 12% of total liver volume would be treated during TAE. Target liver volume will be assessed immediately prior to TAE with the help of CB-CTA. CB-CTA is a technique, which involves administration of iodinated contrast through a catheter placed in a branch of the hepatic artery while imaging of the entire liver using cone-beam CT technique. As a result, the contrast-opacified liver parenchyma is equivalent in volume to the liver parenchyma perfused by the hepatic artery branch in which the catheter had been placed. CB-CTA reliably measures the relative volume of liver parenchyma perfused by any given hepatic artery branch. Prior to TAE, mandatory core biopsies of liver lesion tissue not targeted for embolization and blood samples of liver lesion tissue and peripheral blood samples will be obtained. Pembrolizumab will be administered at 3 week intervals for 3 additional doses. A repeat, optional core biopsy of a non-embolized liver lesion tissue (ideally, same lesion as the one targeted for first biopsy) and peripheral sampling will be repeated approximately 5 weeks after TAE.

Patients assigned to **Group 3** will undergo mapping visceral angiography, Tc-99m MAA liver perfusion scan, and treatment with segmental or subsegmental Yttrium-90 radioembolization (RE) to at least one measurable liver lesion approximately 3-15 days following the first dose of pembrolizumab. The hepatic artery segmental branch supplying the liver segment with the highest volume ratio of tumor to normal liver tissue will be targeted for RE. Tumor to normal tissue volume distribution will be determined with the help of cone beam CT angiography (CB-CTA) performed prior to RE. Up to 12% of total liver volume would be treated during radioembolization. Target liver volume will be assessed immediately prior to radioembolization with the help of cone-beam CT angiography. Prior to RE, mandatory core biopsies of liver lesion tissue not targeted for radioembolization and blood samples of liver lesion tissue and peripheral blood samples will be obtained. Pembrolizumab will be administered at 3 week intervals for 3 additional doses. A repeat, optional core biopsy of a non-radiated liver lesion tissue (ideally, same lesion as the one targeted for first biopsy) and peripheral sampling will be repeated approximately 5 weeks after RE.

After receiving 4 cycles of pembrolizumab, all patients will be evaluated by cross-sectional imaging (CT or MRI) to assess tumor response.

Subjects who attain confirmed **complete response** (CR) by 2 tumor imaging assessments at least 4 weeks apart and who have received at least 8 treatments (approximately 6 months) with pembrolizumab may discontinue treatment at the discretion of the investigator after receiving at least 2 treatments beyond the initial determination of a CR. Radiographic disappearance of all tumors would constitute complete response.

Group 1 (PRRT) Partial Response (PR) or Stable Disease (SD). Patients with **partial response** (PR) or **stable disease** (SD) by RECIST v. 1.1 after cycle 4 of pembrolizumab who were treated with PRRT (**group 1**) would continue to receive systemic IV administrations of ^{177}Lu -DOTATATE every 8 ± 1 weeks for up to four (4) treatments. Pembrolizumab will also continue to be administered every 3 weeks. PRRT sessions would be administered no fewer than 6 days prior to the subsequent pembrolizumab dose. Assessment with cross-sectional imaging and tumor markers will be repeated every 4 cycles of pembrolizumab (or 3 months, whichever comes first). After completion of four (4) PRRT treatments, pembrolizumab may be administered alone for up to 35 cycles.

Groups 2 and 3 (Liver-directed therapy) Partial Response (PR). Patients with **partial response** (PR) response by RECIST v. 1.1 in lesion(s) not targeted for liver-directed therapy (**groups 2 and 3**) will continue treatment with pembrolizumab alone for up to 35 cycles. Assessment with cross-sectional imaging and tumor markers will be repeated every 4 cycles (or approximately 3 months, whichever comes first).

In the event of disease progression (by RECIST v 1.1) in the group of patients who have experienced PR or CR following the combination of liver-directed therapy (**groups 2 and 3**) and pembrolizumab, liver-directed therapy may be repeated once

(according to the previous group assignment). If CR, PR, or SD response is recaptured in lesion(s) not targeted for liver-directed therapy following repeated liver-directed therapy, patients will be allowed to continue pembrolizumab alone for up to 35 cycles.

Groups 2 and 3 (Liver-directed therapy) Stable Disease. For patients assigned to groups 2 and 3 who demonstrate SD response in lesion(s) not targeted for liver-directed therapy, liver-directed therapy may be repeated with cycle 5 at the investigator discretion according to the previous group assignment if there are measurable liver lesions that have not been previously treated with liver-directed therapy. For patients assigned to TAE and radioembolization groups (Groups 2 and 3), repeat embolotherapy would target no more than 12% of the liver volume (same or different segment of the hepatic artery circulation, which would depend on liver tumor perfusion by the hepatic artery). The volume of targeted liver would be assessed prior to TAE and radioembolization using cone-beam CT angiography. The total volume of liver parenchyma targeted by two embolotherapy treatments (between cycles 1 and 2, and between cycles 5 and 6 of pembrolizumab) would represent no more than 25% of total liver volume. Research biopsies and blood sampling will not be repeated during cycles 5-8. In the event of SD or PR response in lesion(s) not targeted for liver-directed therapy after cycle 8, patients will be allowed to continue pembrolizumab alone for up to 35 cycles. Assessment with cross-sectional imaging and tumor markers will be repeated every 4 cycles (or approximately 4 months, whichever comes first).

Group 1 (PRRT) Progressive Disease (PD). Due to possible observation of “tumor flare” after PRRT and/or after pembrolizumab, in the event of demonstrated progressive disease (PD) response by RECIST v. 1.1 after cycle 4, patients assigned to **group 1** may continue treatment with pembrolizumab for one or two additional cycles. One additional PRRT treatment will be administered 8 ± 1 weeks following the preceding PRRT treatment. Confirmation of PD by imaging performed after cycle #5 or #6 of pembrolizumab would lead to discontinuation of study treatment as determined by the principle investigator.

Groups 2 and 3 (Liver-directed therapy) Progressive Disease (PD). Due to possible observation of “tumor flare” after pembrolizumab, in the event of demonstrated progressive disease (PD) response by RECIST v. 1.1 in lesion(s) not targeted for liver-directed therapy after cycle 4, patients assigned to **groups 2 and 3** may continue treatment with pembrolizumab for one or two additional cycles. Confirmation of PD by imaging performed after cycle #5 or #6 would lead to discontinuation of study treatment.

The primary objective of this trial is to evaluate the best observed **overall response rate** (ORR) according to RECIST 1.1. On study imaging assessments will be performed approximately every 3 months calculated from the date of the first pembrolizumab dose and independent of treatment delays. Following the first evidence of radiologic PD, treatment decisions may be made in adherence to immune-

related RECIST v. 1.0 in order to accommodate for the tumor response patterns seen with pembrolizumab treatment (e.g. tumor flare).

After completion of PRRT or liver-directed therapy, subjects will continue to be treated with pembrolizumab until PD, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, administrative reasons, or the subject has received 35 treatments with pembrolizumab (approximately 2 years). Subjects who discontinue treatment for reasons other than PD will have post-treatment follow-up for disease status until PD, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up.

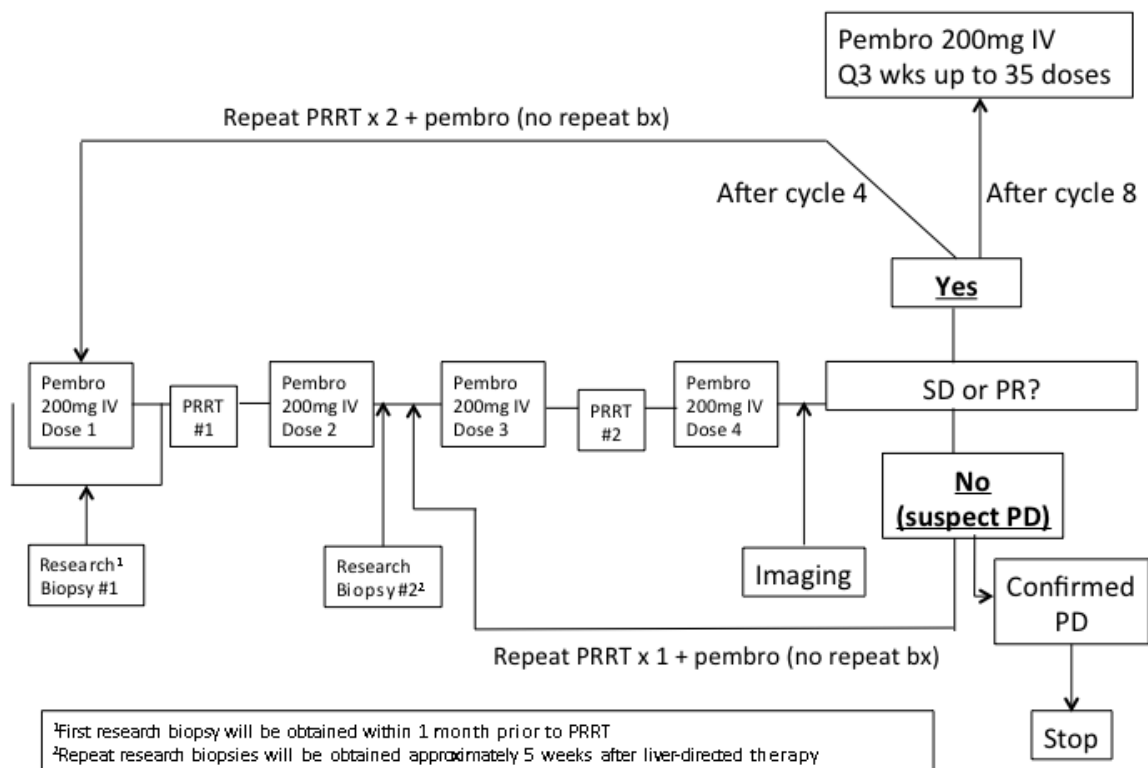
Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (Section 6.2.5). After the end of treatment, each subject will be followed for 30 days for AE monitoring. SAEs and events of clinical interest (ECIs) will be collected for 90 days after the end of treatment or for 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier.

This study will be conducted in compliance with Good Clinical Practice.

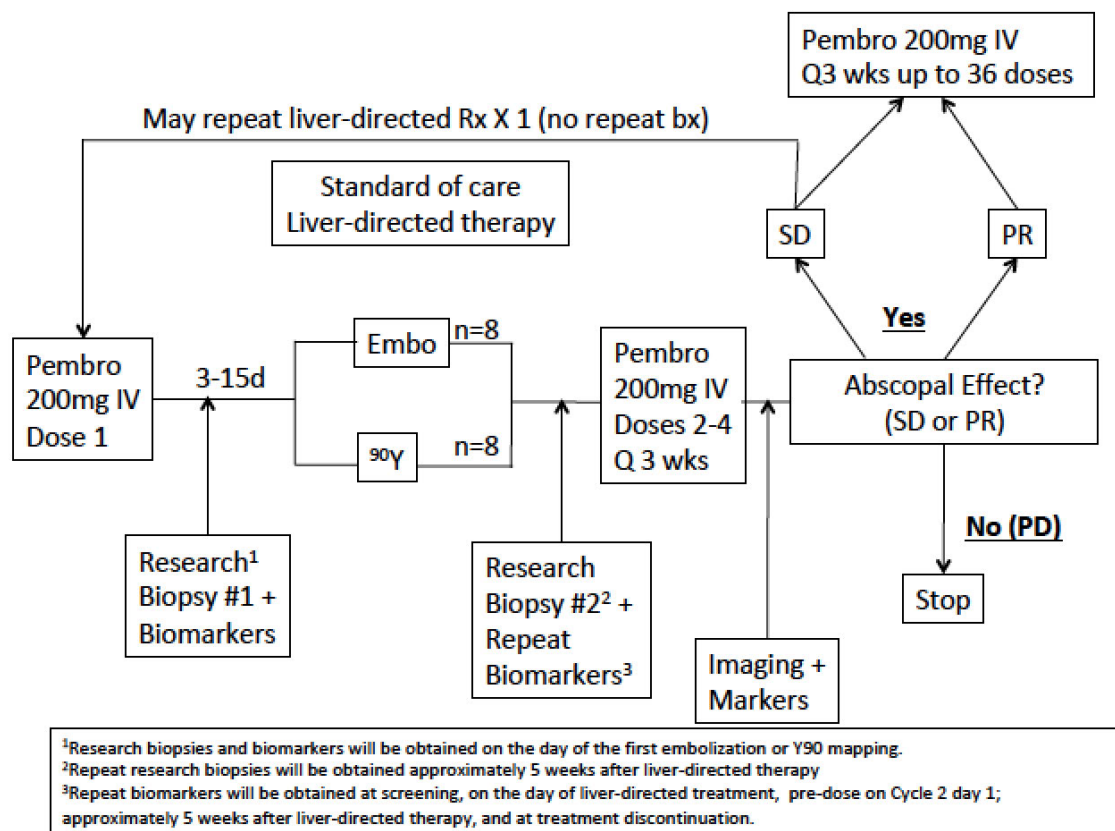
Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart (Section 5.0). Details of each procedure are provided in the Trial Procedures (Section 6.1). On-treatment biopsies are optional for group 1. For groups 2 and 3, the first on-treatment biopsy (during cycle 1) and the second on-treatment biopsy (about 5 weeks after liver-directed therapy) are both optional.

1.2 Trial Diagrams

1.2.1 Study Outline for Group 1

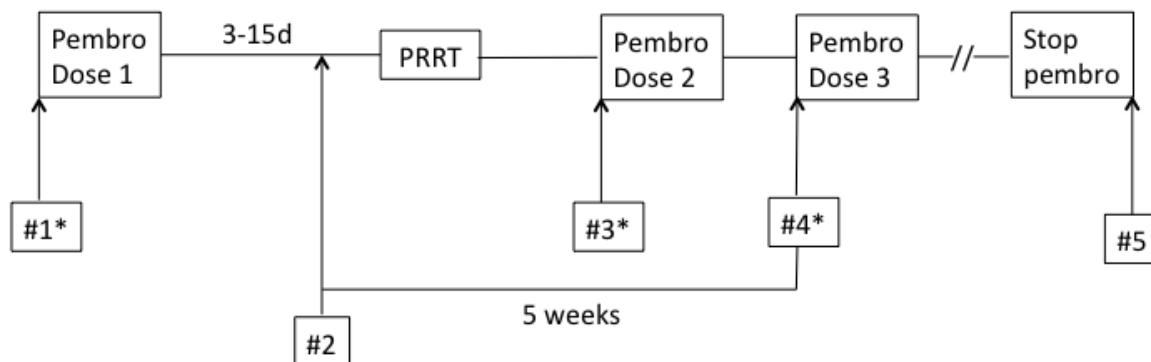


1.2.2 Study Outline for Groups 2 and 3



***as of 09/15/22, Groups 2 and 3 are closed to enrollment**

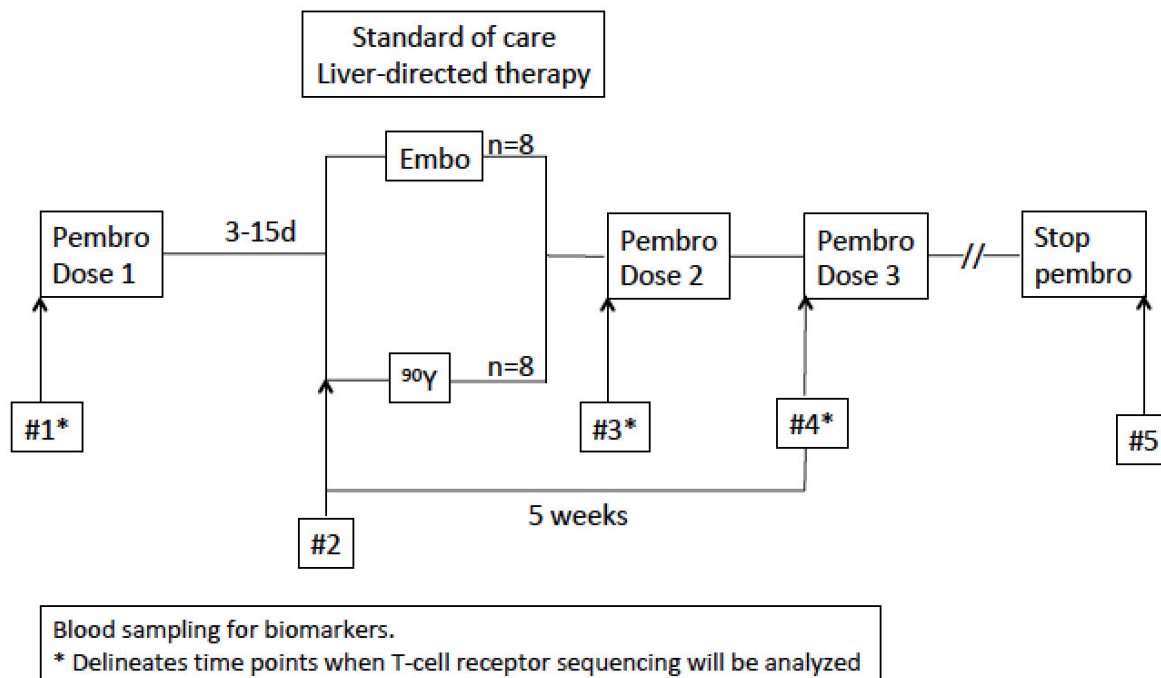
1.2.3 Biomarker Analysis Schedule for Group 1



Blood sampling for biomarkers.

* Delineates time points when T-cell receptor sequencing will be analyzed

1.2.4 Biomarker Analysis Schedule for Groups 2 and 3



2.0 OBJECTIVES & HYPOTHESES

2.1 Primary Objectives & Hypotheses

- (1) **Objectives:** A) To evaluate safety profile of pembrolizumab in combination with PRRT, transarterial embolization and radioembolization. B) To evaluate the best observed overall response rate (ORR) in lesion(s) *not* targeted for liver-directed therapy (abscopal effect) to pembrolizumab plus liver-directed therapy according to RECIST 1.1 for patients with metastatic WD-NET. C) To evaluate the best observed ORR to pembrolizumab plus PRRT according to RECIST 1.1 for patients with metastatic grade 2 and 3 WD-NET (Ki-67 index > 10%).
- (2) **Hypotheses:** A) Pembrolizumab is safe, well tolerated and produces abscopal responses when combined with local liver therapy in patients with WD-NETs. B) Pembrolizumab is safe, well tolerated and produces responses when combined with PRRT in patients with grade 2 and 3 WD-NET (Ki-67 index > 10%). C) Pretreatment biomarkers can be used to identify patients who are more likely to benefit from pembrolizumab-based therapy.

2.2 Secondary Objectives

- (1) **Objective:** to evaluate duration of response (DOR) in patients receiving pembrolizumab in combination with liver-directed therapies or PRRT.
- (2) **Objective:** to evaluate progression free survival (PFS) in subjects treated with pembrolizumab in combination with liver-directed therapies or PRRT.
- (3) **Objective:** best observed radiographic ORR per modified RECIST (mRECIST) in lesions targeted for liver-directed therapy.
- (4) **Objective:** duration of response in lesions targeted for liver-directed therapy by mRECIST.

2.3 Exploratory Objectives

- (1) **Objective:** to compare ORR, DOR, and PFS based on irRECIST with the same measures assessed by RECIST 1.1.
- (2) **Objective:** to correlate clinical outcomes (ORR, DOR, PFS) with baseline immune cell infiltration and PD-L1 staining in cycle 1 and cycle 5 tumor biopsies.
- (3) **Objective:** to assess the level of PD-L1 expression in tumor tissue prior to liver-directed therapy (prior to PRRT) and 5 weeks following liver-directed therapy (following PRRT). To compare pre-treatment and on-treatment PD-L1 expression in tumor tissue in patients with documented PR or CR response to patients with SD or PD response.

- (4) **Objective:** to assess T cell infiltration on the pre-LDT (pre-PRRT) and on the on-treatment tumor tissue biopsies. To use immunohistochemistry to assess the change in the ratio of tumor infiltrating CD8 and Treg cells (CD8/Treg) over time. To correlate pre-treatment and on-treatment CD8/Treg ratio in patients with documented PR or CR response to patients with SD or PD response.
- (5) **Objective:** to assess baseline circulating T cell receptor (TCR) repertoires and changes in TCR repertoires with treatment, and correlate baseline and turnover of repertoires to clinical outcomes.
- (6) **Objective:** to analyze the relationship between baseline tumor proliferative index (as measured by Ki67) and response to therapy.

3.0 BACKGROUND & RATIONALE

3.1 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on pembrolizumab.

3.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [2-6]. 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 tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an 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) [7, 8]. The structure of murine PD-1 has been resolved [9]. 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 CD3 ζ , PKC θ and ZAP70 which are involved in the CD3 T-cell signaling cascade [7, 10-12]. 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 [13, 14]. 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 [15, 16]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [17]. 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 tumors [13, 18-20]. 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 [13]. 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 tumor-specific T-cell expansion in subjects with melanoma (MEL) [21]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

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. KEYTRUDA® (pembrolizumab) has recently been approved in the United States for the treatment of patients with unresectable or metastatic melanoma, for first and second line therapy for non small cell lung cancer, and for head and neck cancer.

3.1.2 Preclinical and Clinical Trial Data

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

3.1.2.1 Preclinical Studies

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a mono-therapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a mono-therapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of INF- γ , granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [22-27]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a mono-therapy

as well as in combination with chemotherapy in syngeneic mouse tumor models (see the Investigator's Brochure [IB]).

3.1.2.2 Ongoing Clinical Trials

Clinical trials have demonstrated efficacy in subjects with advanced melanoma, non-small cell lung cancer, head and neck cancer, bladder cancer, Hodgkin's lymphoma, triple-negative breast cancer, and gastric adenocarcinoma. Pembrolizumab is now FDA approved for use in melanoma, non-small cell lung cancer and head and neck cancer.

Ongoing clinical trials of pembrolizumab are being conducted in multiple malignancies, including advanced melanoma, non-small cell lung cancer, and a number of other advanced solid tumor indications and hematologic malignancies. For study details please refer to the IB. Of note, studies are ongoing with pembrolizumab in combination with paclitaxel-based chemotherapy, as well as in combination with irinotecan (see <https://clinicaltrials.gov>).

3.2 Rationale

3.2.1 Rationale for the Trial and Selected Subject Population

Neuroendocrine (NE) neoplasms are a diverse group of rare neoplasms distinguished by site of origin, functional status, and degree of aggressiveness [28-31]. For unknown reasons, the incidence has increased 5-fold over the past 30 years [31]. In fact, taken together, gastrointestinal NE tumors (NETs) are the second most common gastrointestinal malignancies behind colorectal cancer. NETs are divided into morphologically well-differentiated neuroendocrine tumors (WD-NET) and poorly differentiated neuroendocrine carcinomas (PD-NEC). Neuroendocrine tumors are further subdivided according to Ki-67 index into grade 1 (Ki-67 < 2%), grade 2 (Ki-67 2-20%), and grade 3 (Ki-67 > 20%). Grade 1 and 2 tumors are considered well-differentiated. Differentiation of grade 3 tumors is based on cellular morphology, rather than on Ki-67 index alone. WD-NETs are relatively indolent, with a natural history that can evolve over years or decades. They are not associated with mutations common to the exocrine cancers that arise at the same organ site and are relatively genetically stable with a low somatic mutation rate [32].

Standard treatment for most types of WD-NETs is limited to somatostatin analogues [33, 34]. Somatostatin receptor positive (SSTR+) WD-NETs may benefit from treatment with peptide receptor radionuclide therapy (PRRT) using ¹⁷⁷Lu DOTATATE. The expected PFS for patients who demonstrated progression on a somatostatin receptor agonist was estimated to be 40 months for patients with grade 1 and 2 NET [35]. Conversely, patients with grade 3 NET (Ki-67 index 21-55%) were found to have lower duration of PFS than for grade 1 and 2 NET population, between 11 and 16 months [36-38].

According to the current NCCN, NANETS, and ENETS guidelines, patients with symptomatic and/or progressive liver-metastases may benefit from surgical debulking or liver-directed local therapy including radiofrequency ablation (RFA), transarterial embolization (TAE), transarterial chemoembolization (TACE), and transarterial radioembolization (RE) using Yttrium-90 microspheres [39, 40].

The role of immunotherapy with checkpoint pathway inhibitors (CPI) has not been established for WD-NETs. A recent study [41] has demonstrated that WD-NET tumor cells typically do not express PD-L1. Therefore, monotherapy with a PD-L1 antagonist may not result in an anti-tumor response. The intensity of anti-tumor immune response, however, can be enhanced by addition of local therapy against one or several of the lesions.

Immune system potentiating effects by multiple forms of local therapy have been documented in the literature. For instance, cryoablation was associated with a significantly higher increase in IL-6 levels compared to RFA and microwave ablation [42]. Arterial embolization leads to tumor cell death due to hypoxia, which in turn, may lead to an increase in PD-L1 expression on tumor cells [43, 44]. Delivery of localized ionizing radiation has also been described to activate anti-tumor immune responses in general [45], may increase tumor sensitivity to immune checkpoint inhibitors by upregulation of PD-L1 expression [46], and may result in distal abscopal responses [47-51]. In fact, abscopal responses have also been described for patients with metastatic melanoma when local radiotherapy was combined with CTLA-4 inhibitor ipilimumab after progression on ipilimumab monotherapy [52]. These findings suggest that various forms of local therapy as well as ionizing radiation may augment the immune response.

The value of checkpoint inhibitors for treatment of WD-NETs remains untested and unknown. Identification of activity in this population would potentially lead to fundamental changes in the treatment of these patients. Currently, approximately 15-20 patients with WD-NET undergo various forms of liver-directed therapy, and approximately 30 patients are treated with PRRT at UCSF per year. Of note, the cooperative groups have an excellent track record of accrual to multicenter trials in GI-NETs (including CALGB 80701, ECOG 2211, and A021202, a randomized phase II trial of pazopanib v placebo in carcinoid—Bergsland, PI). As such, pilot data from this study could potentially be used to inform the design of a randomized trial carried out by a consortium or cooperative group.

3.2.2 Rationale for Dose Selection/Regimen/Modification

Pembrolizumab: An open-label Phase I trial (Keynote 001) is being 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 every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement

and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. 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 data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic 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. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. 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 body weight 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 tumor burden on exposure. In addition, exposure was similar between the 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 tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 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 tumor burden or indication on distribution behavior 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 tumor 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 every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in

melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

Group 1. Peptide receptor radionuclide therapy using ^{177}Lu -DOTATATE (Lutathera®) will be offered to patients with somatostatin receptor positive (SSTR+) tumors with Ki-67 index > 10% (well-differentiated grade 2 or 3). Patients may have any number of liver and/or extrahepatic lesions with liver parenchyma replacement by tumor < 75%. 200±20 mCi of ^{177}Lu -DOTATATE will be administered intravenously per treatment on outpatient basis. Patients will receive a total of four treatments of ^{177}Lu -DOTATATE, administered every 8±1 weeks. Supportive measures including intravenous amino-acid solution and antiemetics will be provided, per standard of clinical care at UCSF. Patients will be discharged after an observation period of 4-6 hours.

Group 2. Transarterial embolization (TAE) will be offered to patients with any number of liver lesions, largest being no larger than 5 cm, who have < 75% liver parenchyma replacement by tumors. Anesthesia monitoring will be used for patients with hormonally active tumors. At the discretion of the investigator, anesthesia monitoring may be substituted for monitoring by an Interventional Radiology nurse under supervision of an IR physician for patients with hormonally inactive tumors.

Selective hepatic artery angiography will be performed in a standard fashion via a trans-femoral approach using commercially available sheaths, catheters, and guidewires. Embolization will be carried out via a microcatheter placed in a segmental or a sub-segmental hepatic artery branch using 70-150, 100-300, 300-500, 500-700, and/or 700-900 micron size spherical PVA microspheres (LC Bead™ or BeadBlock™, BTG International Inc., West Conshohocken, PA). Smallest size beads (70-150 micron) will be used preferentially at the beginning of the embolization. However, angiographic detection of significant hepatic artery to portal vein or to hepatic vein shunting would trigger use of larger particles. All patients will be admitted overnight for monitoring, per standard of care at UCSF.

Group 3. Yttrium-90 radioembolization (RE) will be offered to patients with any number of liver lesions, with the largest lesion measuring more than 5 cm, who have < 75% liver parenchyma replacement by tumors.

Mapping hepatic angiography will be performed 3-7 days following pembrolizumab dose #1. Anesthesia monitoring will be used for patients with hormonally active tumors. At the discretion of the investigator, anesthesia monitoring may be substituted for monitoring by an Interventional Radiology nurse under supervision of an IR physician for patients with hormonally inactive tumors. Hepatic artery angiography will be

performed in a standard fashion via a trans-femoral approach using commercially available sheaths, catheters, and guidewires. Protective embolization may be performed at the IR investigator discretion in order to prevent reflux of Y90 microspheres into extrahepatic circulation. Following mapping angiography, 1-2 mCi of Tc-99m MAA will be administered into the hepatic artery. Lung shunt fraction (LSF) is calculated as a ratio of total lung counts (sum of counts obtained over both lungs) divided by total body counts.

Yttrium-90 radioembolization will be performed approximately 1-10 days following the mapping angiogram (depending on timing of Y90 dose delivery, tumor vascularity, and rate of hepatic artery flow). Anesthesia monitoring will be used for patients with hormonally active tumors. At the discretion of the investigator, anesthesia monitoring may be substituted for monitoring by an Interventional Radiology nurse under supervision of an IR physician for patients with hormonally inactive tumors. Hepatic artery angiography will be performed in a standard fashion via a trans-femoral approach using commercially available sheaths, catheters, and guidewires. Radioembolization will be carried out using Yttrium-90 glass microspheres (TheraSphere®, BTG International Inc., West Conshohocken, PA).

Desired target tissue dose will be 120Gy. Yttrium-90 dose required will be calculated according to the following formulae:

$$\text{Activity Required (GBq)} = \frac{[\text{Desired Dose (Gy)}][\text{Mass of Selected Liver Target (kg)}]}{50}$$

The absorbed lung dose will be estimated by the following formula:

$$\text{Lung dose [Gy]} = 50 * \text{injected activity corrected for residual in vial} * \text{LSF}$$

Maximum allowable absorbed lung dose will be 15Gy for a single treatment (25Gy for a patient's lifetime). Target liver dose may be reduced to no less than 60Gy in order to comply with above absorbed lung dose requirements.

RE will target no more than 1 segment per treatment in order to minimize damage to the normal hepatic parenchyma. All patients will be admitted overnight for monitoring, per standard of care at UCSF.

3.2.3 Rationale for Endpoints

3.2.3.1 Efficacy Endpoints

3.2.3.1.1 Primary Endpoint

The primary efficacy objective of this study is to evaluate the ORR in lesions *not* targeted for liver-directed therapy (i.e. lesions located outside the liver, in the opposite liver lobe or in a segment not targeted by liver-directed therapy; abscopal effect) from

combination treatment consisting of pembrolizumab and liver-directed therapy for patients in **groups 2 and 3**. Since the PRRT is a systemic form of therapy, ORR irrespective of lesion location will be assessed for patients assigned to **group 1**. Best observed ORR per RECIST version 1.1 will be used as the primary endpoint (investigator-reported).

3.2.3.1.2 Secondary Endpoints

The secondary efficacy objectives of this study are to evaluate safety and tolerability, DOR and PFS of pembrolizumab in combination with liver-directed therapy or PRRT per RECIST v. 1.1.

3.2.3.2 Safety Endpoints

The safety objective of this study is to characterize the safety and tolerability of pembrolizumab in combination with liver-directed therapy or PRRT in subjects with metastatic WD-NETs. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE, v5.0 (Section 6.2.5). The attribution to drugs, procedures, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific immune-related adverse events (irAEs) will be collected and designated as immune-related events of clinical interest (ECIs) as described in Section 6.2.3.2.

3.2.3.3 Biomarker Research (Exploratory)

3.2.3.3.1 Ki67 Proliferation rate in tumor: Ki67, a tumor proliferative biomarker, is determined by immunohistochemistry (IHC) of the tumor tissue. The relationship between baseline tumor proliferative index (as measured by Ki67) and response to immunotherapy is uncertain and will be assessed.

3.2.3.3.2 Baseline and on-treatment expression of PD-L1 in tumor: The level of PD-L1 expression in tumor tissue prior to and following liver-directed therapy and PRRT is not known. Tissue from serial biopsies will be evaluated for changes in PD-L1 expression. PD-L1 expression in the cycle 1 and cycle 5 tumor biopsy will be assessed by IHC (UCSF Cancer Immunotherapy Lab, CIL) and correlated with ORR, PFS, and DOR.

3.2.3.3.3 Characterization and quantification of tumor-infiltrating immune cells: The extent of well-differentiated neuroendocrine tumor infiltration by cytotoxic and regulatory lymphocytes is unknown. Liver-directed therapy and/or PRRT may increase the number of tumor infiltrating lymphocytes. Relative ratio of CD8⁺ to regulatory T cells in tissue may correlate with clinical outcomes and with response to immune checkpoint inhibitors. Thus, a low CD8⁺ to regulatory T cell ratio within tumor tissue has been

associated with poor clinical outcome for patients with ovarian cancer [53]. A high CD8⁺ to regulatory T cell ratio within tumor tissue has been associated with favorable prognosis in ovarian cancer [54] and with response to cisplatin-based neoadjuvant therapy for patients with muscle invasive urothelial carcinoma of the bladder [55]. Furthermore, a high CD8⁺ to regulatory T cell ratio within tumor tissue has been found to be predictive of response to immune checkpoint inhibitor in combination with trastuzumab and docetaxel for patients with breast cancer [56]. The amended exploratory objectives have included assessment of T cell infiltration on the pre-liver-directed therapy (and pre-PRRT) and on the on-treatment tumor tissue biopsies. Our team also plans to use immunohistochemistry to assess the change in the ratio of tumor infiltrating CD8 and Treg cells (CD8/Treg) over time on pre-treatment and on-treatment tumor biopsies. Pre-treatment and on-treatment CD8/Treg ratio in patients with documented PR or CR response will be compared to to patients with SD or PD response.

3.2.3.3.4 Baseline tumor immune profile: will be assessed by quantifying the number of infiltrating T cells subsets, including cytotoxic CD8⁺, helper CD4⁺FOXP3⁻, and regulatory CD4⁺FOXP3⁺ T cells. The ratio of CD8⁺ to regulatory T cells will be determined. The proportion of activated T cells (e.g. PD1⁺ and Ki67⁺) will also be analyzed, as will myeloid-derived suppressor cells (e.g. M2 CD68/Arg-1, M1 CD68/iNOS). Immune cell characterization will be performed by the UCSF CIL.

3.2.3.3.5 T cell receptor (TCR) sequencing (blood and tumor biopsy): T cell receptor (TCR) sequencing can also be used to track immunotherapy induced changes in T cell repertoire and T cell clonotypes in the blood and tumor tissue. T cells see antigen through their TCR, which is comprised of two subunits, α and β . Each is generated by a VDJ recombination event resulting in a broad range of T cell clones with different specificities. The β subunit has greater clonal diversity. Next-generation sequencing (NGS) of the T cell receptor β chain (TCR β) has been used to define the diversity and frequency of T cell clones in the blood and tumor tissue of cancer patients after immunotherapy treatment and has been shown to associate with clinical response and OS [57, 58]. Fong, et al. performed TCR next-generation sequencing (NGS) on serial blood (PBMC) samples and prostatectomy samples from sipuleucel-T treated patients [59]. Changes in TCR sequence frequency and diversity showed that sipuleucel-T treatment narrows the TCR repertoire in the blood while increasing the TCR diversity in prostate tissue. The increase in common TCR sequences (clonotypes)

between tumor and blood supports the notion of treatment-induced T cell migration into prostate tissue.

Using established techniques (UCSF CIL), NGS will be used to quantify the T cell immune response induced by pembrolizumab. TCR clonotypes will be characterized at baseline (blood and cycle 1 tumor biopsy), as will changes in the T cell immune response over time (blood). The data may inform optimal use of therapies in the patient population under study and identify candidate biomarkers of response, resistance or toxicity.

- 3.2.3.3.6 Characterization of peripheral immune cell subsets (blood): Circulating immune cells will be assessed by multiparameter flow cytometry on peripheral blood samples. T cell activation status will be characterized.

4.0 METHODOLOGY

4.1 Entry Criteria

4.1.1 Diagnosis/Condition for Entry into the Trial

Subjects with metastatic well-differentiated neuroendocrine tumors of any primary site (including unknown primary site) who have at least one measurable disease site will be eligible to participate.

Subject Inclusion Criteria

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

1. Be willing and able to provide written informed consent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Have a histologically proven well-differentiated neuroendocrine tumor (WHO grade 1, grade 2, or morphologically and/or clinically well-differentiated grade 3) of any primary site, including unknown primary site.
 - a. For group 1, only well-differentiated grade 2 or 3 tumors with Ki-67 index $> 10\%$ that demonstrate somatostatin receptor expression on DOTA or In-111 Octreoscans will be allowed.
4. Radiographic, biochemical, or clinical evidence of tumor progression over a period of up to 12 months in at least one site.
 - a. Group 1:

- i. At least one symptomatic and/or progressive somatostatin receptor positive (SSTR+) lesion over a period of up to 12 months.
 - ii. Have at least one measurable lesion based on RECIST v. 1.1.
- b. Groups 2 and 3:
 - i. At least one symptomatic and/or progressive liver lesion over a period of up to 12 months.
 - ii. Have at least two measurable lesions in the liver or at least one measurable lesion in the liver and another measurable lesion elsewhere, based on RECIST v. 1.1.
- 5. Have a performance status of 0 or 1 on the ECOG Performance Scale.
- 6. Have a life expectancy of greater than 3 months.
- 7. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 30 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	$\geq 1,500$ /mcL
Platelet count	$> 75,000$ /mcL
Hemoglobin	≥ 9 g/dL ^b
Renal	
Serum creatinine OR Measured or calculated ^a creatinine clearance (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 institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN OR Direct bilirubin $\leq$ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 5 X ULN
Albumin	≥ 2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
^a Creatinine clearance should be calculated per institutional standard.	
^b For group 1 only. There is no hemoglobin cut-off level for groups 2 and 3.	

8. Female subject of childbearing potential should have a negative urine or serum pregnancy within 30 days prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
9. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 4.8.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
10. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy 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.

4.1.2 Subject Exclusion Criteria

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

1. Has had prior thermal ablation, embolotherapy, radioembolization, or external beam radiation within 30 days of initiation of study therapy.
2. Has had prior peptide receptor radionuclide therapy (**group 1 only**).
3. Has had biliary tract intervention that resulted in compromise to the Ampulla of Vater or a biliary-enteric anastomosis (**groups 2 and 3 only**).
4. Has greater than 75% liver parenchyma replacement by tumor (determined by radiologist investigator).
5. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
6. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
7. Has a known history of active TB (Bacillus Tuberculosis).
8. Hypersensitivity to pembrolizumab or any of its excipients.

9. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., $\leq$ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
10. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., $\leq$ Grade 1 or at baseline) from adverse events due to a previously administered agent.
 - Note: Subjects with $\leq$ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
 - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
 - Concurrent somatostatin analog therapy is allowed.
11. 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.
12. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
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 (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
14. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or current pneumonitis/interstitial lung disease.
15. Has an active infection requiring systemic therapy.
16. Has liver fibrosis either determined by imaging or laboratory testing (i.e. total serum bilirubin > 1.5 times ULN, AST and ALT > 5 times ULN, INR > 1.5 times ULN, albumin < 2.0 mg/dl).

17. 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 investigator.
18. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
19. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
20. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
21. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
22. Has known active untreated Hepatitis B.
23. Has received a live vaccine or live-attenuated vaccine within 30 days prior to the first dose of study drug. Administration of killed vaccines is allowed.

4.2 Trial Treatments

The treatment to be used in this trial is outlined below in **Table 2**

Table 2 Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 21 day cycle	Experimental

Guidelines for group assignment is provided in Table 3.

Table 3 Patient Selection Guidelines

	1. PRRT	2. TAE	3. Y-90 RE
Liver disease burden	Any	< 75% replacement	< 75% replacement
Largest liver lesion size	Any	≤ 5 cm	> 5 cm
WHO grade	2 or 3 (Ki-67 ≥ 10%)	Any*	Any*
SSTR status	+	Any	Any
Prior PRRT	Not allowed	Allowed	Allowed

*Patients who are not candidates for PRRT, patients who had progressed on PRRT, or patients with Ki-67 index < 10% who have not been treated with PRRT.

Group 1. Peptide receptor radionuclide therapy (PRRT) using Lu-177 DOTATATE (Lutathera, Novartis AG, New York, NY) will be offered to patients with somatostatin receptor positive (SSTR+) tumors with Ki-67 index $\geq 10\%$ (well-differentiated grade 2 and 3). Patients may have any number of liver and/or extrahepatic lesions with liver parenchyma replacement by tumor < 75%. 200 $\pm$ 20 mCi of ^{177}Lu DOTATATE will be administered intravenously per treatment on outpatient basis approximately 8 $\pm$ 1 weeks apart for up to 4 (four) doses. PRRT treatments 2, 3, and 4 may be delayed up to 8 weeks in order to allow for resolution of intercurrent illnesses or treatment-related toxicities. PRRT sessions would be administered no fewer than 6 days prior to the subsequent pembrolizumab dose. Supportive measures including intravenous amino-acid solution and antiemetics will be provided, per standard of clinical care at UCSF.

Patients who demonstrate PR or SD response by RECIST v. 1.1 after cycle 4 of pembrolizumab will be offered four (4) additional cycles of pembrolizumab and additional PRRT treatments (approximately 8 $\pm$ 1 weeks apart for up to four doses total). Due to prior observation of “tumor flare,” patients who demonstrate PD response by RECIST v. 1.1 after cycle 4 will be eligible to receive one or two additional cycles of pembrolizumab and one additional PRRT treatment approximately 8 $\pm$ 1 weeks after the preceding PRRT treatment before reassessment of tumor response.

Group 2. Transarterial embolization (TAE) using 70-150 micron, 100-300 micron, 300-500 micron, 500-700 micron, and/or 700-900 micron size BeadBlock (BTG International Inc., West Conshohocken, PA) microspheres. TAE will be offered to patients with any number of liver lesions, largest being no larger than 5 cm, who have < 75% liver parenchyma replacement by tumors. Smallest size beads (70-150 micron) will be used preferentially at the beginning of the embolization. However, angiographic detection of significant hepatic artery to portal vein or to hepatic vein shunting would trigger use of larger particles. TAE will be performed under anesthesia monitoring. TAE will target no more than 1 segment per treatment in order to minimize damage to the normal hepatic parenchyma. All patients will be admitted overnight for monitoring, per standard of care at UCSF.

Group 3. Yttrium-90 radioembolization (RE) using glass microspheres (TheraSphere®, BTG International Inc., West Conshohocken, PA) will be offered to patients with any number of liver lesions, and the largest lesion measuring more than 5 cm, who have < 75% liver parenchyma replacement by tumors. RE will target no more than 1 segment per treatment in order to minimize damage to the normal hepatic parenchyma. Patients with hormonally active WD-NETs will be admitted overnight for monitoring, per standard of care at UCSF.

Whether subjects receive additional liver-directed therapy after cycle 5 of pembrolizumab will depend on the radiographic response after cycle 4 and on the treatment toxicity profile. Patients with stable disease response by RECIST v. 1.1 and

favorable toxicity profile (no grade 3 or worse AE during cycles 1-4) will be eligible to receive one additional liver-directed treatment (same group assignment). However, the decision to proceed with additional liver-directed treatment will be based on investigators' discretion and patient preference.

4.3 Dose Selection/Modification

4.3.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 3.2.2.

Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Pharmacy Manual.

4.3.2 Dose Modification

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

Table 4 below.

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to the combination, to PRRT, TAE or RE, alone or to pembrolizumab alone, for adverse events listed in Table 4, both interventions must be held according to the criteria in Table 4 Pembrolizumab Dose Modification Guidelines for Drug-Related Adverse Events and Combination Therapy.

Holding Study Interventions:

When study interventions are administered in combination, if the AE is considered immune-related, both interventions should be held according to recommended dose modifications.

Restarting Study Interventions:

Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in Table 4.

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.
- If the toxicities do resolve and conditions are aligned with what is defined in Table 4, the combination of ¹⁷⁷Lu DOTATATE or Transarterial embolization or Yttrium-90 radioembolization, and pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to ¹⁷⁷Lu DOTATATE or Transarterial embolization or Yttrium-90 radioembolization, alone, re-initiation of pembrolizumab as a monotherapy may be considered at the principal investigator's discretion.

See Section 4.7.1 and Investigator's Brochure for supportive care guidelines, including use of corticosteroids.

Table 4 Pembrolizumab Dose Modification Guidelines for Drug-Related Adverse Events and Combination Therapy

General instructions: 1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. 2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤ 10 mg/day within 12 weeks of the last study intervention treatment. 3. The corticosteroid taper should begin when the irAE is $\leq$ Grade 1 and continue at least 4 weeks. 4. If study intervention has been withheld, study intervention may resume after the irAE decreased to $\leq$ Grade 1 after corticosteroid taper.				
irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Diarrhea/Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	- Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) - Participants with $\geq$Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis - Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT Elevation or Increased Bilirubin	Grade 2 ^a	Withhold	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	Grade 3 ^b or 4 ^c	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia ^a	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β -cell failure	Withhold ^d	- Initiate insulin replacement therapy for participants with T1DM - Administer antihyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold permanently discontinue ^d or		
Hyperthyroidism	Grade 2	Continue	Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold permanently discontinue ^d or		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2, 3 or 4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
All Other irAEs	Persistent Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event ^e		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

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

^a AST/ALT: >3.0 to 5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

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

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

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

^e Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (e.g. vasculitis and sclerosing cholangitis).

4.3.3 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 5.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks for 24 months or 35 administrations. Given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

4.3.4 Timing of Liver-directed Therapy and PRRT

PRRT using ^{177}Lu DOTATATE will be administered every 8 ± 1 weeks, and no fewer than 6 days prior to the subsequent dose of pembrolizumab.

Transarterial embolization will be performed approximately 3-7 days following the first dose of pembrolizumab.

Mapping visceral angiography and Tc-99m MAA lung shunt study will be performed approximately 1-5 days following the first dose of pembrolizumab, whereas administration of Y90 microspheres will be performed approximately 1-10 days following the mapping procedure, depending on patient-specific dosimetry and radiation dose ordering deadlines.

4.3.5 Duration of therapy

Subjects will continue to be treated with pembrolizumab until PD, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, administrative reasons, or the subject has received 35 treatments pembrolizumab (approximately 2 years).

For a clinically stable subject with first radiologic evidence of PD (e.g. unconfirmed), it is at the discretion of the investigator to continue treating the subject with pembrolizumab until PD is confirmed at least 4 weeks from the date of the first tumor

imaging suggesting PD. If radiologic PD is confirmed by the subsequent tumor imaging, the subject should be discontinued from treatment.

Subjects who attain CR by 2 tumor imaging assessments at least 4 weeks apart and who have received at least 8 treatments (approximately 6 months) with pembrolizumab may discontinue treatment at the discretion of the investigator after receiving at least 2 treatments beyond the initial determination of a CR.

4.3.6 Trial Blinding/Masking

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

4.4 Randomization or Treatment Allocation

All enrolled subjects will be allocated to receive pembrolizumab 200 mg IV Q3W in combination with liver-directed therapy or PRRT. The choice of the second treatment modality will be according to the guidelines presented in Section 23 (

Table 4).

Whether subjects receive additional liver-directed therapy (groups 2 and 3) after cycle 4 of pembrolizumab will depend on the radiographic response after cycle 4 and on the treatment toxicity profile. Patients with SD response by RECIST v. 1.1 and favorable toxicity profile (no grade 3 or worse AE during cycles 1-4) will be eligible to receive one additional liver-directed treatment (same group assignment). However, the decision to proceed with additional liver-directed treatment will be based on investigators' discretion and patient choice.

The number of PRRT treatments (group 1) after cycle 4 of pembrolizumab will depend on the radiographic response assessment after cycle 4 and on the treatment toxicity profile. Patients who demonstrate PR or SD response by RECIST v. 1.1 after cycle 4 will be offered four (4) additional cycles of pembrolizumab and additional PRRT treatments approximately 8+/-1 weeks apart, up to four total. Due to prior observation of "tumor flare," patients who demonstrate PD response by RECIST v. 1.1 after cycle 4 will be eligible to receive one or two additional cycles of pembrolizumab and one additional PRRT treatment administered 8±1 weeks after the second PRRT treatment before reassessment of tumor response. Confirmation of PD by imaging would lead to discontinuation of study treatment.

4.5 Stratification

No stratification based on age, sex, or other characteristics will be used in this trial.

4.6 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

4.6.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period,



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documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 6.2.

For patients in group 1, somatostatin receptor analogues (octreotide, lanreotide) may be administered up to 3 weeks prior to the first PRRT treatment. For patients in groups 2 and 3, somatostatin receptor analogues may be administered while on study.

4.6.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy (except for somatostatin analogues and ¹⁷⁷Lu DOTATATE for patients assigned to group 1).
- Immunotherapy not specified in this protocol.
- Chemotherapy.
- Investigational agents other than pembrolizumab.
- External-beam radiation therapy.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids unless used as a premedication for chemotherapy or 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 principle investigator.
 - Note: Inhaled steroids are allowed for the management of asthma.
 - Note: Use of prophylactic corticosteroids to avoid allergic reactions (e.g., to IV contrast dye) is permitted.
- Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial.
- Subjects may receive other medications that the investigator deems to be medically necessary.

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

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

4.7 Rescue Medications & Supportive Care

4.7.1 Supportive Care Guidelines

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

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 4.3 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. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

- **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.

- **Diarrhea/Colitis:**

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

- All subjects who experience diarrhea/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 diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous 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.
- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, 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 hyperglycemia associated with metabolic acidosis or ketonuria.
 - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- **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.
- **Hyperthyroidism or Hypothyroidism:**

Thyroid disorders can occur at any time during treatment. Monitor patients 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 and 3 hypothyroidism):**
 - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.

- In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, 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.
- **Hepatic:**
 - For **Grade 2 or 3** events that occur within 7 days of liver-directed therapy, monitor liver function tests more frequently until returned to baseline values (consider weekly). Withhold pembrolizumab until toxicity returns to Grade 1 or better.
 - For **Grade 4** events that occur within 7 days of liver-directed therapy, treat with intravenous corticosteroids for 24 to 48 hours (e.g. equivalent of prednisone 1-2 mg/kg/d). When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
 - For **Grade 2** events that occur more than 7 days after liver-directed therapy, monitor liver function tests more frequently until returned to baseline values (consider weekly). Withhold pembrolizumab until toxicity returns to Grade 1 or better.
 - For **Grade 3-4** events that occur more than 7 days after liver-directed therapy, treat with intravenous corticosteroids for 24 to 48 hours (e.g. equivalent of prednisone 1-2 mg/kg/d). When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- **Renal Failure or Nephritis:**
 - For **Grade 2-4** 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.
- **Gastrointestinal ulceration:**
 - All patients treated with radioembolization will be asked to take H2 blocker or proton pump inhibitor starting at least 3 days prior to radioembolization and continuing for at least 30 days following radioembolization
 - **Grade 1-2** events will be managed with diet modifications and medical therapy (PPI, karafate)
 - **Grade 3** events will be managed with medical therapy and may require total parenteral nutrition

- **Grade 4** events may require medical therapy, total parenteral nutrition, and surgical intervention
- **Cholecystitis:**
 - **Grade 2** events will be managed with supportive measures (antibiotics, analgesics, antiemetics, dietary change)
 - **Grade 3-4** events may require operative intervention or percutaneous cholecystostomy placement in addition to the above supportive measures.
- **Bowel perforation:**
 - **Grade 2** events will be managed with supportive measures (antibiotics, analgesics, antiemetics, percutaneous drainage of fluid collection(s))
 - **Grade 3-4** events may require operative intervention in addition to the above supportive measures.
- **Carcinoid storm:**
 - All patients with hormonally-active tumors will be monitored by an anesthesiologist during liver-directed treatments.
 - Medical prophylaxis with additional IV and/or subcutaneous somatostatin analogues, H1, and H2 blockers will be used on case-by-case basis at investigators' discretion.

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 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 5 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
<u>Grade 1</u> 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
<u>Grade 2</u> 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 investigator.	Subject may be premedicated 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).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	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. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.	
<u>Grades 3 or 4</u> 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 subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. Subject is permanently discontinued from further trial treatment administration.	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

4.8 Diet/Activity/Other Considerations

4.8.1 Diet

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

4.8.2 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. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥ 45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 6.2.2. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

4.8.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours to the Sponsor and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator 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. 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 and to Merck and followed as described above and in Section 6.2.2.

4.8.4 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, subjects who are breast-feeding are not eligible for enrollment.

4.9 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment 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 Section 6.1.4.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression

Note: For unconfirmed radiographic disease progression, please see Section 4.3.5

- Unacceptable adverse experiences as described in Section 4.3.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.

Note: 24 months of study medication is calculated from the date of first dose.

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 5.0 (Protocol Flow Chart) and Section 6.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 6.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up.

4.9.1 Discontinuation of Study Therapy after Complete Response (CR)

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Radiographic disappearance of tumors that have not been targeted for liver-directed therapy would constitute complete response.

4.10 Subject Replacement Strategy

All patients who receive any liver-directed therapy will be analyzed for safety and efficacy. Subjects who discontinue from study participation prior to receiving liver-directed study therapy may be replaced after discussion with the principal investigator. Subjects who have received liver-directed study therapy will not be replaced. Patients who do not complete radioembolization treatment (not suitable candidates due to technical factors) may be offered transarterial embolization instead if Group 2 (TAE) has not been completely accrued. Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related AEs to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. However, they will not be replaced.

4.11 Stopping Rule

A stopping rule for safety will halt accrual to the study and prompt reevaluation of each group's combination treatment strategy if unacceptable treatment-related toxicity (defined as any Grade 4 toxicity, any recurrent Grade 3 toxicity, or any Grade 3 toxicity persisting more than 4 weeks) is observed at a frequency of $\geq 33\%$ in any treatment group. Because pembrolizumab is generally well tolerated, this safety review will occur after a total of 5 subjects have been accrued in a given treatment group.

4.12 Clinical Criteria for Early Trial Termination

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

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug
5. In the event of Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

5.0 TRIAL FLOW CHARTS

5.1 Trial Flow Chart for Group 1

Trial Period:	Screening Phase	Treatment Cycles								End of Treatment	Post-Treatment	
Treatment Cycle/Title:		1	2	3	4	To be repeated beyond 8 cycles				Discon	Safety Follow-up	Follow Up Visits
						5	6	7	8			
Scheduling Window (Days):	Study Screening -30 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 3-6 months post discon
Administrative Procedures												
Informed Consent	X											
Inclusion/Exclusion Criteria	X											
Demographics and Medical History	X											
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	
Post-study anticancer therapy status											X	X
Clinical Procedures/Assessments												
Pembrolizumab ^a		X	X	X	X	X	X	X	X			
PRRT ^b		X			X ^b			X ^b				
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X									X		
Directed Physical Examination		X	X	X	X	X	X	X	X			
Vital Signs, Weight and Height ^c	X	X	X	X	X	X	X	X	X	X		
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X		
Electrocardiogram	X											
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory												
Pregnancy Test – Urine or Serum β-HCG	X ^d											

Trial Period:	Screening Phase	Treatment Cycles								End of Treatment	Post-Treatment	
Treatment Cycle/Title:	Study Screening -30 to -1	1	2	3	4	To be repeated beyond 8 cycles				Discon	Safety Follow-up	Follow Up Visits
Scheduling Window (Days):						5	6	7	8			
PT/INR ^e	X		X	X	X	X	X	X	X	X	X	
CBC with Differential ^e	X		X	X	X	X	X	X	X	X	X	X
Comprehensive Metabolic Panel ^e	X		X	X	X	X	X	X	X	X	X	X
T3, FT4 and TSH ^e	X		X		X		X		X	X	X	
Tumor markers (blood and/or urine)	X				X				X	X		X
Efficacy Measurements												
Tumor Imaging	X ^f	X ^g								X ^h		X
Tumor Biopsies/Correlative Studies Blood												
Newly Obtained Tissue Collection ^k		X ^j		X ^j								
Correlative Studies Blood Collection ⁱ	X	X	X	X						X		

- a. The window for each visit is ± 3 days unless otherwise noted.
- b. Peptide receptor radionuclide therapy will be performed 8 ± 1 weeks apart for up to four (4) treatments. PRRT treatments will be performed 8 ± 1 weeks apart. The first PRRT treatment would be performed 2-15 days after the first pembrolizumab dose. PRRT sessions would be administered no fewer than 6 days prior to the subsequent pembrolizumab dose. PRRT treatments 2, 3, and 4 may be delayed up to 8 weeks in order to allow for resolution of intercurrent illnesses or treatment-related toxicities. Patients who demonstrate PR or SD response by RECIST v. 1.1 after cycle 4 will be offered four (4) additional cycles of pembrolizumab and additional PRRT treatments 8 ± 1 weeks apart (up to 4 total). Due to prior observation of "tumor flare," patients who demonstrate PD response by RECIST v. 1.1 after cycle 4 will be eligible to receive one or two additional cycles of pembrolizumab with one additional PRRT treatment that will be performed 8 ± 1 weeks after the preceding PRRT treatment before reassessment of tumor response. Confirmation of PD by imaging would lead to discontinuation of study treatment.
- c. Height will be measured at Visit 1 only

- d. For women of reproductive potential, a serum or urine pregnancy test should be repeated within 72 hours prior to first dose of trial treatment. A negative pregnancy test between 30 and 3 days prior to treatment initiation is acceptable for study enrollment. Pregnancy tests (urine or serum) should be repeated if required by local guidelines.
- e. After cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. Thyroid function tests to be performed every other cycle.
- f. Screening tumor imaging will be performed within 60 days prior to C1D1. Acceptable studies include multiphase CT or MRI. Contrast required unless contraindicated due to allergy or renal dysfunction in which case noncontrast scan allowed if radiology has confirmed pt still has measureable disease
- g. The first on-study imaging time point will be performed at 12 weeks (84 ± 7 days) calculated from C1D1 and will continue to be performed approximately every 3 months (84 ± 7 days) thereafter, or earlier if clinically indicated. Weeks are in reference to calendar week, and should not be adjusted for treatment dosing delays
- h. In subjects who discontinue study therapy without confirmed PD per RECIST, tumor imaging should be performed at the time of treatment discontinuation (± 4 weeks). If previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then additional tumor imaging at treatment discontinuation is not required.
- i. Whole blood samples for correlative studies should be collected at screening, prior to treatment on the day of PRRT, pre-dose on Day 1 of Cycle 2, approximately 5 weeks after PRRT, and again at treatment discontinuation. Blood will be collected in seven 10mL BD Sodium Heparin^N (NH) 158 USP Units Plus Blood Collection Tubes (green-top) and sent to the Immune Monitoring Core at UCSF (See Section 6.1.3.3.2).
- j. Optional, on-treatment tissue biopsies will be performed at the following time points:
 - 1) after dose #1 of pembrolizumab and before PRRT.
 - 2) approximately 5 weeks after the first PRRT treatment.
- k. See section 6.1.3.3.1 for details regarding specimen collection and processing

5.2 Trial Flow Chart for Groups 2 and 3

Trial Period:	Screening Phase	Treatment Cycles								End of Treatment	Post-Treatment	
Treatment Cycle/Title:		1	2	3	4	To be repeated beyond 8 cycles				Discon	Safety Follow-up	Follow Up Visits
						5	6	7	8			
Scheduling Window (Days):	Study Screening -30 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 3-6 months post discon
Administrative Procedures												
Informed Consent	X											
Inclusion/Exclusion Criteria	X											
Demographics and Medical History	X											
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	
Post-study anticancer therapy status											X	X
Clinical Procedures/Assessments												
Pembrolizumab ^a		X	X	X	X	X	X	X	X			
Liver-directed therapy ^b		X				X						
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X									X		
Directed Physical Examination		X	X	X	X	X	X	X	X			
Vital Signs, Weight and Height ^c	X	X	X	X	X	X	X	X	X	X		
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X		
Electrocardiogram	X											
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory												
Pregnancy Test – Urine or Serum β-HCG	X ^f											
PT/INR ^e	X		X	X	X	X	X	X	X	X	X	
CBC with Differential ^e	X		X	X	X	X	X	X	X	X	X	X

Trial Period:	Screening Phase	Treatment Cycles								End of Treatment	Post-Treatment	
Treatment Cycle/Title:	Study Screening -30 to -1	1	2	3	4	To be repeated beyond 8 cycles				Discon	Safety Follow-up	Follow Up Visits
						5	6	7	8			
Scheduling Window (Days):			± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 3-6 months post discon
Comprehensive Metabolic Panel ^f	X		X	X	X	X	X	X	X	X	X	X
T3, FT4 and TSH ^f	X		X		X		X		X	X	X	
Tumor markers (blood and/or urine)	X				X				X	X		X
Efficacy Measurements												
Tumor Imaging	X ^f	X ^g								X ^g		X
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood												
Newly Obtained Tissue Collection ^k		X ^j		X ^j								
Correlative Studies Blood Collection ⁱ	X	X	X	X						X		

- The window for each visit is ± 3 days unless otherwise noted.
- Liver-directed therapy based on group assignment (transarterial embolization or radioembolization) will be performed 3-15 days after starting cycle 1. Whether subjects receive additional liver-directed therapy after cycle 5 of pembrolizumab will depend on the radiographic response after cycle 4 and on the treatment toxicity profile. Patients with stable disease response by RECIST v. 1.1 and favorable toxicity profile (no grade 3 or worse AE during cycles 1-4) will be eligible to receive one additional liver-directed treatment (same group assignment). However, the decision to proceed with additional liver-directed treatment will be based on investigators' discretion and patient choice.
- Height will be measured at Visit 1 only
- For women of reproductive potential, a serum or urine pregnancy test should be repeated within 72 hours prior to first dose of trial treatment. A negative pregnancy test between 30 and 3 days prior to treatment initiation is acceptable for study enrollment. Pregnancy tests (urine or serum) should be repeated if required by local guidelines.
- After cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. Thyroid function tests to be performed every other cycle.

- f. Screening tumor imaging will be performed within 60 days prior to C1D1. Acceptable studies include multiphase CT or MRI. Contrast required unless contraindicated due to allergy or renal dysfunction in which case noncontrast scan allowed if radiology has confirmed pt still has measureable disease
- g. The first on-study imaging time point will be performed at 12 weeks (84 ± 7 days) calculated from C1D1 and will continue to be performed approximately every 3 months (84 ± 7 days) thereafter, or earlier if clinically indicated. Weeks are in reference to calendar week, and should not be adjusted for treatment dosing delays
- h. In subjects who discontinue study therapy without confirmed PD per RECIST, tumor imaging should be performed at the time of treatment discontinuation (± 4 weeks). If previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then additional tumor imaging at treatment discontinuation is not required.
- i. Whole blood samples for correlative studies should be collected at screening, pre-procedure on the day of TAE, or RE, pre-dose on Day 1 of Cycle 2, approximately 5 weeks after liver-directed therapy, and again at treatment discontinuation. Blood will be collected in seven 10mL BD Sodium Heparin^N (NH) 158 USP Units Plus Blood Collection Tubes (green-top) and sent to the Immune Monitoring Core at UCSF (See Section 6.1.3.3.2).
- j. On-treatment tissue biopsies will be performed at the following time points:
 - 1) Optional: after dose #1 of pembrolizumab and before liver-directed therapy. The first biopsy may be performed on the day of TAE or on the day of mapping or Y90 radioembolization procedure
 - 2) Optional: approximately 5 weeks after liver-directed therapy
- k. See section 6.1.3.3.1 for details regarding specimen collection and processing

6.0 TRIAL PROCEDURES

6.1 Trial Procedures

The Trial Flow Chart - Section 5.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

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

6.1.1 Administrative Procedures

6.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

6.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject'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 subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB requirements, applicable laws and regulations and Sponsor requirements.

6.1.1.2 Inclusion/Exclusion Criteria Review

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

6.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease (high grade NEC) for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

6.1.1.4 Prior and Concomitant Medications Review

6.1.1.4.1 Prior Medications

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

6.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 6.2.

6.1.1.5 Disease Details and Treatments

6.1.1.5.1 Disease Details

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

6.1.1.5.2 Prior Treatment Details

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

6.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit may occur before the first dose of the new therapy.

6.1.1.6 Assignment of Screening Number

All patients who are consented will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements. All patients will have a unique screening identification number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

6.1.1.7 Trial Compliance (Medication/Diet/Activity/Other)

Interruptions from the protocol specified treatment for greater than 12 weeks between pembrolizumab doses due to non-drug-related or administrative reasons require consultation between the investigator and Principal Investigator and written documentation of the collaborative decision on subject management.

The total volume of pembrolizumab infused will be compared to the total volume prepared to determine compliance with each dose of pembrolizumab administered. The instructions for preparing and administering pembrolizumab are provided in the Pharmacy Manual. Compliance with scheduled chemotherapy will also be tracked.

6.1.2 Clinical Procedures/Assessments

6.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0 (Section 6.2.5). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see Section 4.7 regarding the identification, evaluation and management of potential irAEs.

Please refer to section 6.2 for detailed information regarding the assessment and recording of AEs.

6.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening.

6.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

6.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 5.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

6.1.2.5 12-Lead Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed one time during screening using local standard procedures. Clinically significant abnormal findings should be recorded as medical history. Additional time points may be performed as clinically necessary.

6.1.2.6 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 1 at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

6.1.2.7 Tumor Imaging and Assessment of Disease

Radiographic evaluations and tumor measurements will be performed at screening (within 60 days prior to the first dose of pembrolizumab), and then approximately every 3 months (+/- 7 days) thereafter. Off study, frequency of imaging will be every 3-6 months, at the discretion of the treating medical oncologist. Weeks and months are in reference to calendar week or month, and should not be adjusted for treatment dosing delays.

Imaging should include multiphase CT abdomen/pelvis with contrast (or MRI abdomen/pelvis with contrast). Chest CT+/- contrast-at will be at physician discretion. When possible, the same imaging modality should be used throughout the study in given patient.

RECIST v1.1 will be used to determine radiographic response for primary endpoint (See Appendix 2). However, Immune-related response criteria (irRC) will also be assessed (See Appendix 3).

6.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 6.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 28 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

Tumor markers (24-hour urine 5-HIAA, chromogranin A, pancreatic hormones) will be evaluated approximately every 3 months if their levels were elevated at the time of study entry.

Unresolved abnormal labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of the treatment if labs are within normal range.

Table 6 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Urine pregnancy test †	Serum β -human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	24-hour urine 5-HIAA*	(β -hCG)†
Platelet count	Alanine aminotransferase (ALT)		PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)		
Red Blood Cell Count			Total triiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡		Free tyroxine (T4)
Absolute Lymphocyte Count	(CO ₂ or biocarbonate)		Thyroid stimulating hormone (TSH)
	Calcium		
	Chloride		Chromogranin A*
	Glucose		Pancreatic hormones**
	Creatinine		Blood for correlative studies
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin (<i>If total bilirubin is elevated above the upper limit of normal</i>)		
	Total protein		
	Blood Urea Nitrogen		
† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. ‡ If considered standard of care in your region * For patients with baseline elevation **Pancreatic hormone levels found to be elevated at study entry			

6.1.3.1 Serum/Urine β -hCG

All women who are being considered for participation in the trial, and who are not surgically sterilized or postmenopausal, will be tested for pregnancy within 72 hours of receiving the first dose of study medication, and must be excluded in the event of a positive or borderline-positive test result. If a urine test is positive or borderline a serum β -hCG test will be required. Pregnancy tests (urine or serum) should be repeated per local guidelines. The results of the pregnancy testing will not be recorded.

6.1.3.2 Post-study Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-cancer therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit may occur before the first dose of the new therapy.

6.1.3.3 Tumor Tissue Collection and Correlative Studies Blood Sampling

6.1.3.3.1 Fresh Tumor Biopsy for Correlative Studies

Subjects in groups 1-3 will undergo biopsy of metastatic liver lesion during the time interval between pembrolizumab dose #1 and TAE, RE, or PRRT. Subjects will undergo biopsy of a second metastatic liver lesion (or of a viable region of a partially treated metastatic liver lesion) approximately 5 weeks after liver-directed therapy or PRRT.

Five core biopsies will be obtained:

1. Formalin fixed paraffin embedded (FFPE): Fresh tissue sample will be placed into a 60 mL pre-filled polypropylene container that contains 30 mL of 10% neutral buffered formalin (NBF) WITHIN 1 MINUTE of collection. After 16-24 hours, sample will be processed and paraffin-embedded.
2. Fresh frozen: Freshly harvested tissues should be flash frozen in liquid nitrogen or an ethanol/dry ice bath. Flash freezing the sample immediately helps to prevent sample degradation. Tissues should be stored at -80°C or in liquid nitrogen until ready for shipping.
3. Formalin fixed paraffin embedded (FFPE): Fresh tissue sample will be placed into a 60 mL pre-filled polypropylene container that contains 30 mL of 10% neutral buffered formalin (NBF) WITHIN 1 MINUTE of collection. After 16-24 hours, sample will be processed and paraffin-embedded.
4. Fresh frozen: Freshly harvested tissues should be flash frozen in liquid nitrogen or an ethanol/dry ice bath. Flash freezing the sample immediately helps to prevent sample degradation. Tissues should be stored at -80°C or in liquid nitrogen until ready for shipping.

5. Formalin fixed paraffin embedded (FFPE): Fresh tissue sample will be placed into a 60 mL pre-filled polypropylene container that contains 30 mL of 10% neutral buffered formalin (NBF) WITHIN 1 MINUTE of collection. After 16-24 hours, sample will be processed and paraffin-embedded.

Additional biomarker research to identify factors important for pembrolizumab therapy may also be pursued. Samples will be sent to the Cancer Immunotherapy Lab (CIL) at UCSF:

Cancer Immunotherapy Lab



University of California, San Francisco



Additional details regarding tissue processing will be provided in the accompanying biospecimen collection manual.

6.1.3.3.2 Blood collections for Correlative Studies

Research blood samples will be collected at four time points. Each time, seven 10mL BD Sodium Heparin^N (NH) 158 USP Units Plus Blood Collection Tubes (green-top) will be collected and sent to the UCSF CIL:

Cancer Immunotherapy Lab



University of California, San Francisco



Correlative studies will be performed as outlined in Section 3.2.3.3. Additional biomarker research to identify factors important for pembrolizumab therapy may also be pursued.

Circulating immune cells (e.g. T cell, B cell, NK cells):

Preferred specimen: 60 (sixty) mL whole blood in green-top (heparinized) tubes

Transport temp: Ambient

Specimen Stability: Room temperature: 24 hours

Assessment of TCR clonotypes by NGS:

Preferred specimen: 6 (six) mL whole blood in green-top (heparinized) tube
Transport temp: Ambient
Specimen Stability: Room temperature: 24 hours

Note that blood samples must ship within 24 hours. If the blood is drawn on a Friday or prior to a holiday please check with the UCSF CIL to ensure appropriate staff are present to accession the sample.

Additional details to be provided in the biospecimen collection manual.

6.1.4 Other Procedures

6.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 6.2 - Assessing and Recording Adverse Events. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 6.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 6.1.5.3.2).

6.1.4.2 Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

6.1.5 Visit Requirements

Visit requirements are outlined in Section 5.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 6.1 - Trial Procedures.

6.1.5.1 Screening

Approximately 28 days prior to treatment allocation, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 4.0. Screening procedures may be repeated.

Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of trial treatment except for the following:

- For women of reproductive potential, a serum pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. A urine test may be considered if serum test is not appropriate.

Subjects may be rescreened after initially failing to meet the inclusion/ exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of repeat screening test if performed within the specified time frame and the inclusion/ exclusion criteria is met. Subjects who are rescreened will retain their original screening number.

6.1.5.2 Treatment Period

Visit requirements are outlined in the Trial Flow Chart (Section 5.0). Specific procedure related details are provided above in the Trial Procedures (Section 6.0).

6.1.5.3 Post-Treatment Visits

6.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

6.1.5.3.2 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed according to the accepted standard of care for patients with WD NET by radiologic imaging to monitor disease status every 3-6 months. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, or end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

6.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product, is also an adverse event.

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

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

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

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 6.2.3.1.

6.2.1 Definition of an Overdose for this Protocol and Reporting of Overdose to the Sponsor and to Merck

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

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. [REDACTED]

6.2.2 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects 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 serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. [REDACTED]

6.2.3 Immediate Reporting of Adverse Events to Merck

6.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is another important medical event

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

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety [REDACTED]

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. [REDACTED] at the time of submission to FDA.

All subjects with serious adverse events must be followed up for outcome.

6.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. [REDACTED]
ECI for this trial include:

1. An overdose of Merck product, as defined in Section 6.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

3. Immune-Related Adverse Events (irAEs): An irAE is defined as a clinically significant AE of any organ that is associated with study drug exposure, is of unknown etiology, and is consistent with an immune-related mechanism. If an irAE is suspected, a thorough evaluation should be conducted in an effort to possibly rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes prior to diagnosing an irAE. Serological, immunological, and histological (biopsy) data should be considered to support the diagnosis of an immune-related toxicity.

ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. [REDACTED] regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

6.2.4 Immediate Reporting of Adverse Events to Boston Scientific

Adverse Event Data Collection

The following variables will be collected for each SAE to be reported to BSC:

- AE (verbatim)
- The maximum CTCAE severity grade reported
- Investigator causality rating with respect to the device, or procedures and if the AE is a SAE, provide Seriousness criteria
- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Date of hospital admission and discharge, if applicable
- Clinical description of the SAE (brief narrative)
- Investigation performed and results
- Treatment provided
- Outcome (and type of resolution (with/without sequelae))
- Date of resolution
- Probable cause of death, if applicable
- Date of death, if applicable
- Whether an autopsy was performed, if applicable

The grading scales found in the revised NCI CTCAE version 5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 5.0 can be downloaded from the Cancer Therapy Evaluation Program website (<http://ctep.cancer.gov>).

Signs and symptoms that directly relate to the progression of disease will not be reported as AEs.

Causality Collection

The Investigator must assess the relationship of the reportable AE to the devices (TheraSphere), (Bead Block, LC Bead), or procedure.

The Investigator will assess the causal relationship between the event and the devices as:

Related the event is associated with the investigational device or with procedures

Possible (causality is weak and other causes may explain the event, or there is no documentation available to assess the relatedness) or

Probable (causality is weak but no other cause could explain the event and additional information needed)

Not related No temporal relationship, other cause

See below for further information

6.2.4.1 Criteria for Assessing Relationship of Study Devices or Procedure to an AE

Classification	Description
Not Related <i>Ref: MEDDEV 2.7/3</i>	Relationship to the device or procedures can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the investigational device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Possibly Related <i>Ref: MEDDEV 2.7/3</i>	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related <i>Ref: MEDDEV 2.7/3</i>	The relationship with the use of the investigational device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.
RELATED Causal Relationship <i>Ref: MEDDEV 2.7/3</i>	The event is associated with the investigational device or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedures; - the event involves a body-site or organ that -the investigational device or procedures are applied to;-the investigational device or procedures have an effect on;

Classification	Description
	- the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the investigational device used for diagnosis, when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

6.2.4.2 AEs based on diagnosis or signs and symptoms

SAEs Based On Diagnosis

When collecting SAEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. Provide the diagnosis as the SAE term and in the narrative, provide the related sign and symptoms, (i.e. angiocholitis (the related symptoms, are described in the narrative of the SAE: fever, abdominal pain). If deterioration in a laboratory value/vital sign is associated with a SAE these associated laboratory result/vital sign will be considered as additional information and must be reported.

Serious Adverse Events Based On Examinations And Tests

In the absence of clinical signs or symptoms, deterioration as compared to baseline in protocol-mandated and non mandated laboratory values, vital signs, should therefore only be reported as SAE criteria if they fulfill a seriousness criteria or are the reason for discontinuation of study treatment.

Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g. anemia versus low hemoglobin value). clinically relevant deteriorations in non-mandated parameters should be reported as SAE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an SAE unless unequivocally related to the disease under study.

Abnormal Liver Function Test

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq 3 \times \text{ULN}$ together with total bilirubin $\geq 2 \times \text{ULN}$ may need to be reported as SAEs.

Disease-under Study (DUS)

Symptoms of DUS are those which might be expected to occur as a direct result of NET. Events which are unequivocally due to DUS should not be reported as an AE during the study unless they meet SAE criteria (i.e. tumor bleeding) or lead to discontinuation of the investigational product. However, death due to NET should not be reported as an SAE.

Disease Progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the study treatments are being studied.

It may be an increase in the severity of the DUS and/or increases in the symptoms of the disease. Any events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

Deaths

All deaths that occur during the study treatment period, or within the protocol-defined follow-up period after the administration of the last dose of study drug, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease (PD) under study, the AE causing the death must be reported to the Study Monitor/Physician as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign main and contributory causes of death.

- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in the eCRF. Every effort should be made to determine a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to BSC or its representative within the usual timeframes.

Deaths occurring after the protocol defined safety follow-up period after the administration of the last dose of study drug should be documented in the Statement of Death page. If the death occurred as a result of an event that started post the defined safety follow-up period and the event is considered to be due to a late onset toxicity to study drug then it should also be reported as an SAE.

6.2.4.3 Device Deficiencies

Device deficiencies will be collected for the devices and will be documented and reported to iCardioQAcomplaints@bsci.com. If possible, the device(s) should be returned to BSC for analysis, unless it contains radioactive material (Y-90 glass microspheres). Device deficiencies should also be documented in the patient's source records.

Device deficiencies are not AEs. However, an AE that results from a device deficiency would be recorded as an AE on the appropriate eCRF.

Any device deficiency that might have led to an SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.

Device deficiencies may include, but are not limited to the following:

- Packaging or labelling deficiency
- Difficulty or inability to inject glass microspheres through the catheter

Safety reporting and medical management

It is the responsibility of the investigator to assess and report to BSC any event which occurs in any of following categories:

- All device related SAEs
- Pregnancy
- Device administration Error
- All Investigational Device Deficiencies
- Unanticipated Serious Adverse Device Effects
- New findings/updates in relation to already reported events

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device or procedure, it should be submitted as an adverse event and/or device deficiency.

Events will be graded using standard grading criteria (National Cancer Institute – Common Terminology Criteria or Adverse Events – Version 5.0 (NCI-CTCAE v5.0))

Reporting of serious adverse events

All SAEs have to be reported, whether causally related to study device, or to the study procedure(s) to iCardioQAcomplaints@bsci.com.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate Sponsor representatives within one day (i.e. immediately but **no later than 24 hours** of when he or she becomes aware of it).

The designated Sponsor representative works with the Investigator to ensure that all the necessary information is provided to BSC data entry site **within 1 calendar day** of initial receipt for all SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform BSC of any follow-up information on a previously reported SAE within one calendar day (i.e. immediately but **no later than 24 hours** of when he or she becomes aware of it).

Pregnancy

Pregnancy information will be collected from the time of the patient receives their first dose of study treatment until the follow up period is completed (or for 90 days after TheraSphere administration. All pregnancies and outcomes of pregnancy should be reported to BSC except if the pregnancy is discovered before the study patient has received any study treatment.

If a pregnancy is reported, the Investigator should inform BSC within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Maternal exposure

Female patients of childbearing potential should refrain from pregnancy for 90 days after TheraSphere administration.

If a patient becomes pregnant during the course of the study, study treatment should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs BSC within 1 day (i.e. immediately but **no later than 24 hours** of when he or she becomes aware of it).

The same timelines apply when outcome information is available.

Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 5 months after the last dose of durvalumab or for 90 days after TheraSphere administration (if patient is on the control arm only).

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner.

Patients who are permanently discontinued from further receipt of study treatment, regardless of the reason, will be identified as having permanently discontinued treatment and will enter follow-up.

Treatment administration error

If a device treatment error occurs in the course of the study, then the Investigator or other site personnel informs BSC to iCardioQAcomplaints@bsci.com, within 1 day (i.e. immediately but no later than 24 hours of when he or she becomes aware of it).

Device Malfunctions

The Institution and/or the Sponsor-Investigator shall report all device malfunctions and/or quality complaints to iCardioQAcomplaints@bsci.com within one business day of becoming aware of the issue.

6.2.5 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0 (<http://ctep.cancer.gov/reporting/ctc.html>). Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

Table 7 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V5.0 CTCAE Grading	Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
	Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
	Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
	Grade 4	Life threatening consequences; urgent intervention indicated.
	Grade 5	Death related to AE
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	† Results in death ; or	
	† Is life threatening ; or places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	† Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or	
	† Results in or prolongs an existing inpatient hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	† Is a congenital anomaly/birth defect (in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a new cancer ; (that is not a condition of the study) or	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Merck product to be discontinued?	
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. The following components are to be used to assess the relationship between the Merck product and the AE ; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck product (continued)	The following components are to be used to assess the relationship between the test drug and the AE: (continued)	
	Dechallenge	Was the Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Merck product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE MERCK PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck product relationship).	
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.	
No, there is not a reasonable possibility Merck product relationship	Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)	

6.2.6 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/ERCs and investigators in accordance with all applicable global laws and regulations.

7.0 STATISTICAL ANALYSIS PLAN

7.1 Statistical Analysis Plan Summary

Demographic and baseline characteristics including weight, vital status, time since diagnosis of disease, time since most recent disease progression, and prior cancer treatment will be summarized with descriptive statistics.

The point estimate and 90% confidence interval of overall response rate will be obtained for each of the three groups separately. For Group 1 (PRRT) assuming the overall response rate (RECIST v. 1.1) is 25% for each patient group, with **26** patients in the group, there is **99%** of power to detect partial response rate significantly different from 1% at alpha of 0.05 by a **two-sided** binomial test.

Analyses of safety endpoints will consist of tabulations and descriptive summaries of adverse events and laboratory test results, and will be based on all patients who receive at least one dose of study regimen. Verbatim description of treatment-related adverse events will be mapped to thesaurus terms. Adverse events assessed as related to study drug and serious adverse events will be summarized similarly. Adverse events leading to treatment discontinuation will also be summarized. Safety analysis will include a tabulation of all toxicities by grade. The frequency of toxicities will be tabulated separately for each cohort.

7.1.1 Primary objectives (efficacy and safety)

Objectives and hypotheses of the study are stated in Section 2.0.

The primary efficacy endpoint will be best observed Overall Response Rate (ORR) by RECIST 1.1 (investigator reported). ORR is defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR).

Safety will be evaluated for Group 1. A minimum of 4 patients will be entered into Group 1, with expansion of the cohort to 26. If ≥ 2 patients in the first 4 patients develop unacceptable treatment-related toxicity (defined as any Grade 4 toxicity, any recurrent Grade 3 toxicity, or any Grade 3 toxicity persisting more than 4 weeks), then this cohort will stop enrollment. Only after acceptable tolerance has been demonstrated in the first four patients treated in Group 1, will the cohort be expanded up to 26 patients in order to evaluate more fully safety and efficacy for the corresponding cohort.

7.1.2 Secondary Endpoints

- Duration of Response (DOR) – RECIST 1.1 assessed by investigator

For subjects who demonstrated CR or PR, response duration is defined as the time from the date of first response (CR or PR) until the date of disease progression or death.

- Progression free Survival (PFS) – RECIST 1.1 assessed by investigator

PFS is defined as the time from first day of study treatment to the first documented disease progression or death due to any cause, whichever occurs first.

- Safety and Tolerability

The safety objective of this trial is to characterize the safety and tolerability of pembrolizumab therapy in subjects with previously treated WD-NET. The safety analysis will be based on subjects who experienced toxicities as defined by CTCAE, version 5.0 criteria (Section 6.2.5). The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific immune-related adverse events (irAEs) will be collected and designated as immune-related events of clinical interest (ECIs) as described in Section 6.2.3.2.

7.2 Statistical Analysis Plan

7.2.1 Analysis populations

Efficacy: The All Subjects as Treated (ASaT, ITT) population will be used for the analysis of ORR, PFS and OS. The ASaT population consists of all subjects who received at least one liver-directed therapy procedure (TAE, radioembolization,) or at least one dose of PRRT following at least one dose of pembrolizumab.

The analysis population for DOR consists of responders.

Safety: The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all allocated subjects who received at least one liver-directed therapy procedure (TAE, radioembolization) or at least one dose of ¹⁷⁷Lu DOTATATE following at least one dose of pembrolizumab.

At least one liver-directed therapy procedure (TAE, radioembolization) or at least one dose of ¹⁷⁷Lu DOTATATE following at least one dose of pembrolizumab is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

7.2.2 Primary Efficacy Objective: Overall Response Rate

The point estimate and 95% confidence interval of overall response rate will be obtained for each of the three groups (PRRT, TAE, TARE) separately.

Group 1 (PRRT). The point estimate and 90% confidence interval of overall response rate will be obtained for each of the three groups separately. Assuming the overall response rate (RECIST v. 1.1) is 25% for the PRRT group, with 26 patients in the group, there is 99% of power to detect partial response rate significantly different from 1% at alpha of 0.05 by a bi-directional binomial test.

Groups 2 and 3 (Liver-directed therapy). The point estimate and 90% confidence interval of overall response rate will be obtained for each of the three liver-directed therapy groups separately. Assuming the abscopal response rate (RECIST v. 1.1) is 25% for each patient group, with 8 patients in each group, there is 80% of power to detect partial response rate significantly different from 1% at alpha of 0.1 by a directional binomial test.

7.2.3 Secondary Efficacy Objectives:

DOR: Duration of Response is defined as the time from the date of first response (CR or PR) until the date of disease progression or death. Kaplan-Meier method will be used to summarize DOR. Median DOR and its 95% confidence interval will be obtained for each of the three groups separately.

PFS: Progression free survival is defined as the time from the first day of study treatment with protocol therapy to the date of documented tumor progression or death due to any cause, whichever occurs first, as determined by irRC for irPFS and RECIST v1.1 for PFS. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Kaplan-Meier method will be used to summarize progression free survival; median irPFS and PFS will be estimated with 95% confidence interval for each of the three groups separately.

7.2.4 Statistical Methods for Safety Analyses

All subjects will be evaluated for toxicity from the time of the first treatment with pembrolizumab. Adverse events occurring from the start of treatment until 30 days after the end of treatment will be summarized by maximum toxicity grade. Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, and vital signs. The toxicity grade for laboratory data will be calculated using CTCAE v5.0 and the lab data will be summarized according to the subjects' baseline grade and maximum grade for each cycle of therapy. All treatment related adverse events will be graded using NCI CTCAE v5.0.

Verbatim description of treatment-related adverse events will be mapped to thesaurus

terms. Adverse events assessed as related to study drug and serious adverse events will be summarized similarly. Adverse events leading to treatment discontinuation will also be summarized. Safety analysis will include a tabulation of all toxicities by grade. The frequency of toxicities will be tabulated separately for each cohort. Count and percentage of AE will be provided.

7.3 Statistical Analysis Plan Summary: Exploratory Objectives

7.3.1 Immune Infiltration

Immune cell subsets and localization will be assessed by immunohistochemistry (IHC) in cycle 1 tissue biopsy samples. Markers will include CD3, CD8 and FoxP3. Wilcoxon rank-sum test will be used to assess whether there is a relationship between any of the immune cell subsets and objective response, and with long/short-term survivors. Furthermore, Cox-proportional hazard models will be applied to assess if there is relationship between any of the immune cell subsets and ORR, DOR, and PFS, respectively.

7.3.2 PD-L1 staining and Ki67 staining

PD-L1 IHC will be performed by Qualtek (CLIA-certified) on cycle 1 tumor biopsies using Merck's 22C3 antibody. Descriptive statistics will be used to summarize PD-L1 scores. Wilcoxon rank-sum test will be used to assess whether there is a relationship between PD-L1 score and objective response, and with long/short-term survivors. Furthermore, Cox-proportional hazard models will be applied to assess if there is relationship between PD-L1 score and ORR, DOR, PFS, respectively.

Ki67 proliferative index will be assessed using commercially available techniques. Descriptive statistics will be used to summarize Ki67 proliferative index. Wilcoxon rank-sum test will be used to assess whether there is a relationship between Ki67 proliferative index and objective response, and with long/short-term survivors. Furthermore, Cox-proportional hazard models will be applied to assess if there is relationship between a Ki67 proliferative index and ORR, DOR, and PFS, respectively.

7.3.3 T Cell Receptor (TCR) Repertoires

For each subject, blood will be collected at screening, prior to liver-directed therapy, on C2D1, approximately 5 weeks following liver-directed therapy, and at progression. T cell repertoire before, during and after treatment will be assessed by next-generation sequencing. Besides the number of unique clonotypes and read depth, the TCR repertoire diversity will be assessed by Clonality diversity index and clonality. Repertoire overlap will be measured by Baroni-Urbani and Buser index, and changes in clonotypes counts between sequencing experiments will be measured using Morisita's distance. The diversity index will be compared by paired-Wilcoxon rank-sum test between baseline and the post-treatment time point. Wilcoxon rank-sum test will

also be used to assess whether the diversity index is different between responders vs. non-responders (defined by objective response).

7.3.4 Circulating Immune Cells

For each subject, blood will be collected at screening, prior to liver-directed therapy, on C2D1, approximately 5 weeks following liver-directed therapy, and at progression. Flow cytometry will be performed to assess changes in circulating immune cell subsets with treatment, including effector T cells, regulatory T cells, and myeloid cells. The Wilcoxon rank-sum test will be used to assess differences in immune subsets in responders vs. non-responders (defined by objective response). Changes in immune cell subsets in individual subjects with treatment will be assessed using paired Wilcoxon Signed-rank test.

8.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

8.1 Investigational Product

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

Clinical Supplies will be provided by Merck as summarized in Table 8.

Table 8 Product Descriptions

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

All other supplies not indicated in Table 8 above will be provided locally by the trial site. For any commercially available product that is provided by the trial site. The trial site is responsible to record the lot number, manufacturer and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

8.2 Packaging and Labeling Information

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

8.3 Clinical Supplies Disclosure

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

8.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

8.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

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

8.6 Liver-directed Therapy and PRRT

8.6.1 Peptide Receptor Radionuclide Therapy

PRRT will be performed using the 200±20 mCi of commercially available ¹⁷⁷Lu DOTATATE [REDACTED] Administration of PRRT and supportive medications will be in accordance with standard of care at UCSF.

8.6.2 Transarterial Embolization.

Target hepatic artery branch catheterization and angiography will be performed via femoral artery approach using commercially available French vascular sheaths, catheters, and guidewires. Embolization will be carried out using commercially available BeadBlock (BTG International, Inc) available in sizes of 70-150, 100-300, 300-500, 500-700, and 700-900 microns.

8.6.3 Radioembolization

Target hepatic artery branch catheterization and angiography will be performed via femoral artery approach using commercially available French vascular sheaths, catheters, and guidewires. Radioembolization will be performed using commercially-available Yttrium-90 glass microspheres (TheraSphere®, BTG International, Inc).

9.0 ADMINISTRATIVE AND REGULATORY DETAILS

9.1 Confidentiality

9.1.1 Confidentiality of Data

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

9.1.2 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

9.2 Compliance with Financial Disclosure Requirements

For all Principal Investigators and Sub-Investigators listed on the FDA 1572, Financial Disclosure Forms, CVs, MD Licenses, Drug Enforcement Agency (DEA) Licenses, and Staff Training Documents (i.e. Collaborative Institute Training Initiative (CITI), etc.) will be provided as required.

9.3 Compliance with Law, Audit and Debarment

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered “serious”. The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 4 for additional information regarding UCSF’s data and safety monitoring plan.

9.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, <http://www.clinicaltrials.gov>. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

9.5 Study Management

9.5.1 Pre-Study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

9.5.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will

be reviewed and approved by the UCSF Institutional Review Board. Prior to obtaining IRB approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

9.5.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

9.5.4 Changes in the Protocol

Once the protocol has been approved by the UCSF IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five (5) working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

9.5.5 Handling and Documentation of Clinical Supplies

The UCSF Principal Investigator and each participating site will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The Principal Investigator shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the Principal Investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

9.5.6 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered "serious". The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 4 for additional information regarding UCSF's data and safety monitoring plan.

9.5.7 Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

9.6 Case Report Forms (CRFs)

The Principal Investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Study Chair, the Trial Statistician, and the Protocol Project Manager.

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11.0 APPENDICES

APPENDIX 1: ECOG PERFORMANCE STATUS

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

APPENDIX 2: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST)

1.1 CRITERIA FOR EVALUATING RESPONSE IN SOLID TUMORS

RECIST version 1.1* will be used in this study for assessment of tumor 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 tumors: 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.

APPENDIX 3: IMMUNE-RELATED RESPONSE CRITERIA (IRRC) FOR EVALUATION OF IMMUNE THERAPY ACTIVITY IN SOLID TUMORS

Immune-related response criteria (irRC)* will also be used in this study for assessment for tumor response.

* As published in Clinical Cancer Research:

J.D. Wolchok, A. Hoos, S. O'Day, J.S. Weber, O. Hamid, C. Lebbe, M. Maio, M. Binder, O. Bohnsack, G. Nichol, R. Humphrey, S.F. Hodi . Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009 Dec;15(23): 7412-7420.

APPENDIX 4: DATA AND SAFETY MONITORING PLAN

Data and Safety Monitoring Plan for a Phase II or III Institutional Trial

1. Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for auditing data quality and participant safety for all HDFCCC institutional clinical trials. A summary of DSMC activities for this trial includes:

- Semiannual auditing (depending on trial accrual)
- Review of serious adverse events
- Minimum of biennial regulatory auditing

2. Monitoring and Reporting Guidelines

Investigators will conduct a continuous review of data and participant safety at monthly site committee meetings where the results of each participant's treatment are discussed and documented in the site committee minutes.

All institutional Phase II and III therapeutic trials are audited on a semiannual basis, with all data from twenty percent of the enrolled participants audited by the DSMC Monitor/Auditor. The assigned DSMC Monitor/Auditor will review no more than a total of 10 participant charts during the course of auditing this trial. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the auditing visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

Auditing of all enrolled participants in these trials will be complete after 20% of enrolled participants have been audited through five cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 adverse events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the use of the investigational agent(s) or study procedure, will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events

are further given an assignment of attribution or relationship to investigational agent or study procedure. Attribution categories are:

- Definite** – The adverse event is clearly related to the investigational agent(s) or study procedure.
- Probable** – The adverse event is likely related to the investigational agent(s) or study procedure.
- Possible** – The adverse event may be related to the investigational agent(s) or study procedure.
- Unrelated** – the adverse event is clearly not related to the investigational agent(s) or study procedure.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and attribution assignment.

3.2 Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e., results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Permanent or significant disability/incapacity
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:

<https://irb.ucsf.edu/adverse-event>

Med Watch forms and information:

www.fda.gov/medwatch/getforms.htm

All serious adverse events are entered into OnCore®, as well as submitted to the IRB (per IRB guidelines). The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at

DSMC meetings, which take place every six weeks. The date the SAE is sent to all required reporting agencies will be documented in OnCore®.

If the SAE involves a subject death, and is determined to be possibly, probably or definitely related to the investigational drug or any research related procedure, the event must be reported to the DSMC Chair (or Vice Chair) and DSMC Director within one business day.

3. **Review of Adverse Event Rates**

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Principal Investigator will notify the DSMC via report at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Investigator voluntarily holds enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and the DSMC Director must be notified within one business day and the IRB must be notified as per IRB reporting regulations.

Data and Safety Monitoring Committee Contacts:

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