NCT03844750

A Phase 2 Study of Perioperative Immunotherapy in Patients with Colorectal Cancer and Resectable Hepatic Metastases

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Protocol Signature Page

1. I agree to follow this protocol version as approved by the University of California San Francisco (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), 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 / Study Chair

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Printed Name

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Signature Date

Principal Investigator **Site**

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Printed Name

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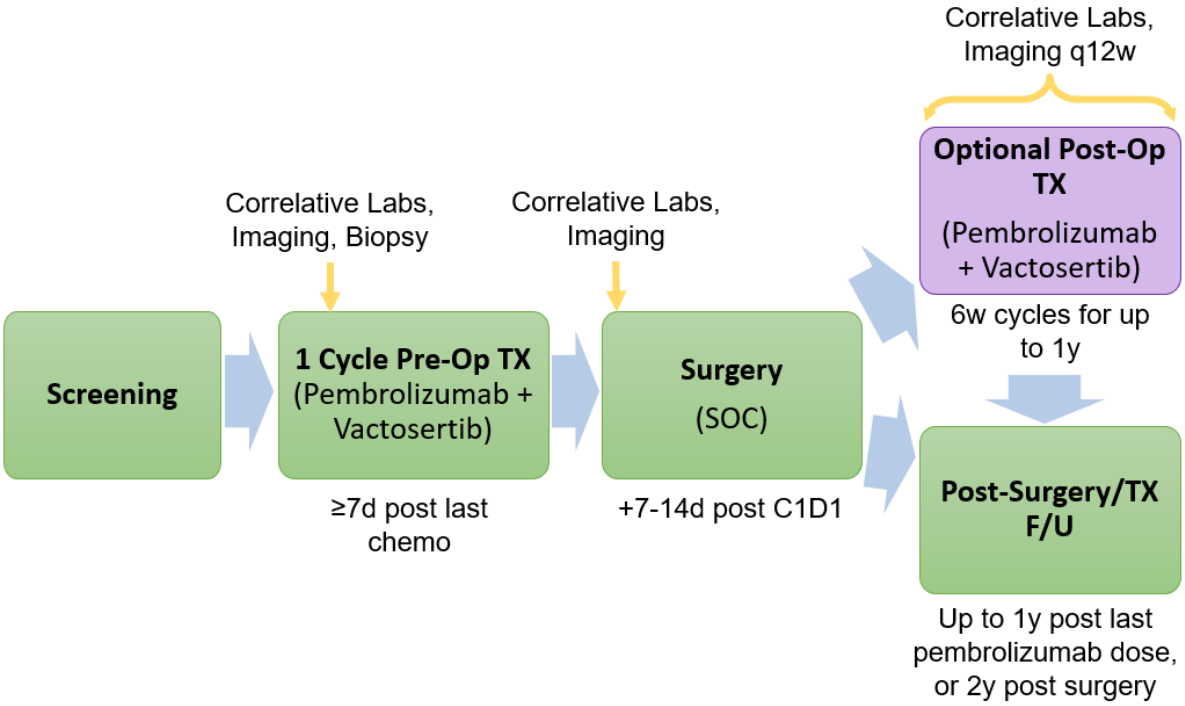
Signature Date

Abstract

Title	A Phase 2 Study of Preoperative Immunotherapy in Patients with Colorectal Cancer and Resectable Hepatic Metastases
Patient population	Patients with colorectal cancer (CRC) with liver-dominant or liver-only metastases who have received prior 5-fluorouracil (5-FU), leucovorin, and oxaliplatin (FOLFOX) chemotherapy and are appropriate candidates for resection of liver metastases.
Rationale for Study	We hypothesize that pembrolizumab plus vactosertib will increase tumor-infiltrating lymphocytes (TILs) and promote response without increasing perioperative complications.
Primary Objective	To characterize the change in the populations of TILs induced by neoadjuvant pembrolizumab plus vactosertib in patients with metastatic CRC.
Secondary Objectives	To establish the safety/toxicity profile of pembrolizumab-based treatment in the perioperative setting for patients with CRC with potentially resectable hepatic metastases, including rates of perioperative complications. To explore the efficacy of this strategy in this patient population. Clinical outcome measures will include response to pembrolizumab plus vactosertib as measured by R0 resection rate; pathologic response; and 1-year and 2-year relapse-free survival (RFS).
Study Design	Phase 2, single-site, open-label prospective clinical trial. See schema below. Additional cohorts exploring novel pembrolizumab-based combinations during this same perioperative window (e.g., pembrolizumab in combination with other immuno- or molecularly targeted agents, following FOLFOX) may be added and enrolled to in sequential fashion via a protocol amendment.
Number of patients	Up to 19 patients will be enrolled in the initial cohort (17 evaluable patients with paired pre-treatment biopsy and post-pembrolizumab plus vactosertib analyzable tumor specimens).
Duration of Therapy	Patients will receive a single cycle of pembrolizumab plus vactosertib prior to planned hepatic metastasectomy. Additionally, up to 8 cycles of adjuvant pembrolizumab plus vactosertib may be administered after hepatic metastasectomy.
Duration of Follow up	Patients will be followed for up to 1 year after the last dose of pembrolizumab is administered or 2 years after surgery (whichever is longer).
Duration of study	The study will reach completion 3 years from the time the study opens to accrual.
Study Drugs	Neoadjuvant pembrolizumab will be administered at a fixed dose of 200 mg (IV) for 1 cycle plus 200 mg vactosertib (PO QD, 5 days per week x 2 weeks). Adjuvant pembrolizumab (400 mg IV) + vactosertib (200 mg PO QD Cycle 1, 5 days per week, Cycles 2 and beyond 200 mg BID, 5 days per week) will be administered for up to eight 6-week cycles.

Safety Assessments	Safety assessments will include adverse events, clinical laboratory evaluations, and vital signs.
Efficacy Assessments	Objective response rate, pathologic response rate, R0 resection rate, and 1-year and 2-year RFS.
Unique Aspects of this Study	This is the first study to evaluate the safety and efficacy of pembrolizumab plus vactosertib following FOLFOX chemotherapy in patients with metastatic CRC undergoing liver resection with curative intent. Biopsy of a liver metastasis prior to administering pembrolizumab plus vactosertib and resection of the liver metastases following 1 cycle of pembrolizumab plus vactosertib will enable extensive scientific correlatives.

Study Schema



The above timeline is approximate with further guidelines below:

- A screening computed tomography (CT) chest/abdomen/pelvis with intravenous (IV) contrast must be performed and reviewed to confirm candidacy for hepatic resection prior to study entry.
- If chemotherapy is a direct lead-in to study enrollment, then liver resection surgery should be performed within 4-6 weeks of the final chemotherapy administration. During this 4-6 week window, 1 cycle of pembrolizumab plus vactosertib will be administered approximately 2 weeks (minimum 1 week) after the last dose of chemotherapy, and surgery will occur approximately 2 weeks (minimum 1 week) after C1D1.
- Labs, including liver function testing will be performed after C1D1, as close to surgery as possible.

- In the event that the surgery is canceled, and the first liver biopsy yielded adequate tumor material, a second liver biopsy will be requested (same lesion as the first biopsy preferred).
- Participants will be followed for up to 2 years after surgery or will be offered optional adjuvant treatment (described below).

Optional Adjuvant Treatment

- Participants who meet study eligibility criteria (Section 3.3) and have adequately recovered from toxicity or complications of a surgery or other procedure, per the assessment of the treating investigator will be offered participation in the adjuvant treatment cohort (pembrolizumab plus vactosertib). Patients who still have their primary tumor in place (i.e. not surgically removed) would not be eligible for the optional adjuvant treatment.
- If the participant meets all other eligibility criteria to receive pembrolizumab plus vactosertib (e.g., no safety issues), then they will receive adjuvant treatment 6 weeks (±2 weeks) after hepatic metastasectomy. Participants will receive adjuvant pembrolizumab plus vactosertib for up to eight 6-week cycles (approximately 1 year) or until disease progression is radiographically documented, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the patient, administrative reasons requiring cessation of treatment, or withdrawal of consent, whichever occurs first.
- Correlative labs will be performed every 12 weeks during the adjuvant treatment period.
- Participants will be followed for up to 1 year after the last dose of pembrolizumab is administered, or until disease progression, the start of new anticancer treatment, or withdrawal of consent, whichever occurs first.

List of Abbreviations

5-FU	5-fuorouracil
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	Absolute neutrophil count
AST	aspartate aminotransferase
BID	twice a day (bis in die)
CBC	complete blood cell (count)
CD	Cluster of differentiation
CEA	Carcinoembryonic antigen
CNB	core needle biopsy
CR	complete response
CRC	Colorectal cancer
CrCl	creatinine clearance
CRF	case report form
CT	computerized tomography
CTCEA	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CTMS	Clinical Trial Management System
dMMR	Mismatch repair deficient
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECI	events of clinical interest
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ELISA	enzyme-linked immunoassay
EORTC	European Organisation for Research and Treatment of Cancer
EPO	Erythropoietin
ERC	Ethics Review Committee
FDA	United States Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FOLFIRI	Chemotherapy regimen: 5-FU, leucovorin and irinotecan
FOLFOX	Chemotherapy regimen: 5-FU, leucovorin and oxaliplatin
FSH	Follicle stimulating hormone

List of Abbreviations

FT4	Free thyroxine
GCP	Good Clinical Practice
GEP	Gene expression profiling
GFR	glomerular filtration rate
GI	Gastrointestinal
HBeAg	Hepatitis B “e” antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HIPAA	Health Insurance Portability and Accountability Act
HIS PDX	human immune system patient-derived xenografts
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator’s Brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IF	Immunofluorescence
IgG4	immunoglobulin G4
IHC	Immunohistochemistry
IND	investigational new drug application
INR	International Normalized Ratio
IO	Immuno-oncology
irAEs	Immune-related adverse events
IRB	Institutional Review Board
IV	Intravenous(ly)
IVD	*in vitro* diagnostic
JSC	Joint Steering Committee
LD	Longest dimension
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MEK	Mitogen-activated protein kinase
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
MSI-H	Microsatellite instability high

List of Abbreviations

MSS	microsatellite stable
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PBPK	Physiologically-based pharmacokinetics
PD	progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death 1 ligand 1
PD-L2	Programmed cell death 1 ligand 2
PFS	Progression-free survival
PK	Pharmacokinetic
PKCθ	protein kinase C-theta
pMMR	Mismatch repair proficient
PO	by mouth (per os)
PR	partial response
PRMC	Protocol Review & Monitoring Committee (UCSF)
QD	once a day (quaque die)
Q6W	Every 6 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	relapse-free survival
RNAseq	RNA sequencing
SAE	Serious adverse event
SD	Stable disease
SNP	single-nucleotide polymorphism
T3	Triiodothyronine
TIICs	Tumor-infiltrating immune cells
TILs	Tumor-infiltrating lymphocytes
Tregs	regulatory T cells
TSH	Thyroid stimulating hormone
ULN	upper limit of normal

List of Abbreviations

US	United States

Table of Contents

1 Introduction

1.1 Background on Indication

Colorectal cancer (CRC) is a major global public health problem. Approximately 1 in 20 Americans will be diagnosed with CRC in their lifetime. Metastatic CRC is the second leading cause of cancer death in the United States (US), with nearly 50,000 deaths attributed to this disease each year. The 5-year survival rate is only 13% for patients with distant metastases [1]. The liver is the most common site of metastases for CRC, occurring in ~40-50% of patients either at the time of initial diagnosis (synchronous) or at disease progression (metachronous). Due to the closed portal circulation, liver metastases from CRC are potentially resectable with curative intent, with a 5-year survival rate approaching 50% [2]. Factors that influence likelihood of cure with metastasectomy include the presence of extrahepatic disease, node-positive primary tumor, size and number of metastases, disease-free interval between original diagnosis and development of metastases, and preoperative carcinoembryonic antigen (CEA) level [3, 4]. However, progression is common and ultimately occurs in up to 75% of patients. About 30% of patients who undergo liver resection with curative intent are indeed cured, defined by 10-year survival without evidence of CRC.

Perioperative chemotherapy is now an established standard of care for patients with CRC with resectable hepatic metastases. Neoadjuvant chemotherapy can improve clinical risk scores to predict outcomes of patients with CRC liver metastases who undergo metastasectomy [5]. A Phase 3 study, European Organisation for Research and Treatment of Cancer (EORTC) Intergroup trial 40893 [6], randomized 364 patients with CRC and up to 4 liver metastases to receive either 6 cycles of 5-fluorouracil (5-FU), leucovorin, and oxaliplatin (FOLFOX) pre- and post-operatively, or surgery alone. The absolute increase in 3-year progression-free survival (PFS) associated with perioperative FOLFOX was 7.3% (35.4 vs. 28.1%; HR 0.79, p=0.058) in randomized patients, and 9.2% (42.4 vs. 33.1%; HR 0.73, p=0·025) in patients actually undergoing resection. However, the postoperative complication rate was higher in the chemotherapy arm (25 vs 16%; p=0.04); and long-term follow-up data showed no difference in median overall survival (OS) between the 2 groups (61.3 vs 54.3 months) [7].

There remains a significant unmet need for new agents that may increase the survival of patients with CRC undergoing liver metastasectomy. The need is particularly great for the ~95% of patients with mismatch repair proficient (pMMR) metastatic CRC, whose cancers have not responded to pembrolizumab monotherapy [8]. As detailed below, there is evidence of immune-stimulatory effects induced by both 5-FU and oxaliplatin, which we hypothesize will promote tumor response to pembrolizumab.

1.2 Background on the Compounds

1.2.1 Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with PD-1 ligand 1 (PD-L1) and PD-L2. Based on preclinical *in vitro* data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV)

immunotherapy for advanced malignancies. KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications. For more details on specific indications refer to the Investigator's Brochure (IB).

1.2.1.1 Pharmaceutical and Therapeutic Background on Pembrolizumab

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [9]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of cluster of differentiation 8 positive (CD8+) T cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells (Tregs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma (RCC). Tumor-infiltrating lymphocytes can be expanded *ex vivo* and reinfused, inducing durable objective tumor responses in cancers such as melanoma [9] [10].

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 cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [11] [12].

The structure of murine PD-1 has been resolved [13]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. After T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [12, 14-16]. The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [17, 18]. As a consequence, the PD 1/PD-L1 pathway is an attractive target for therapeutic intervention in CRC.

1.2.1.2 Preclinical and Clinical Trial Data

Refer to the pembrolizumab IB for detailed Preclinical and Clinical data.

1.2.1.3 Clinical Trials Testing Pembrolizumab in Colorectal Cancer

Immune checkpoint inhibitors such as pembrolizumab have shown robust single-agent antitumor activity in the ~5% of patients with metastatic CRCs harboring microsatellite instability (MSI-high [MSI-H]) or mismatch repair deficiency (dMMR). Preliminary reporting indicated an (immune-related) objective response rate of 40% (4 of 10 patients). On the other hand, 0% (0 of 18 patients)

with microsatellite stable (MSS) or pMMR metastatic CRCs achieved an objective response (NCT01876511)[8]. As a result, additional studies are underway for patients with metastatic CRC and MSI-H or dMMR to test pembrolizumab monotherapy in the previously-treated with chemotherapy setting [19] or pembrolizumab versus standard chemotherapy in the first-line setting [20].

Pembrolizumab is approved for use in CRC or other tumors that are MSI-H. Specifically, for the treatment of adult and pediatric patients with unresectable or metastatic, MSI-H or dMMR:

- solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or
- colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.2.2 Vactosertib

Transforming growth factor beta (TGF-β) has been shown to be a potent growth inhibitor for normal epithelial, hematopoietic, and immune cells, and has a major role in normal tissue homeostasis. In the early stage of cancer development, TGF-β acts as a tumor suppressor, whereas in late stages, TGF-β can take on tumor promoter roles, favoring invasion and metastasis. In the TGF-β signaling pathway, TGF-β receptor type I (TGFBR1) inhibitors have shown promise blocking TGF-β-mediated tumor progression, metastasis, and suppression of antitumor immunity in nonclinical animal models. TGFBR1 inhibitors specifically inhibit the Smad pathway by occupying the ATP binding site of the TGFBR1 kinase domain, which is essential for the phosphorylation of its substrates, Smad2 and Smad3.

Vactosertib (International non-proprietary name [INN] name; also known as TEW-7197, EW-7197) is a potent, highly selective, oral inhibitor of TGFBR1.

Refer to the IB for detailed background information on vactosertib.

1.2.2.1 Pharmaceutical and Therapeutic Background on Vactosertib

The Enhanced antitumor activity with the combination of TGF-β inhibition with anti-PD-(L)1 was observed in a number of preclinical studies.

In a recent publication, quadruple-mutant mice developed metastatic intestinal tumors that display key hallmarks of human MSS colorectal cancers, including low mutational burden, T-cell exclusion and TGF-β-activated stroma. Inhibition of the PD-1-PD-L1 immune checkpoint provoked a limited response in this model system. By contrast, inhibition of TGF-β unleashed a potent and enduring cytotoxic T cell response against tumor cells that prevented metastasis. In mice with progressive liver metastatic disease, blockade of TGF-β signaling rendered tumors susceptible to anti-PD-1–PD-L1 therapy. These results show that increased TGF-β in the tumor microenvironment represents a primary mechanism of immune evasion that promotes T-cell exclusion and blocks acquisition of the TH1-effector phenotype [21].

In an autochthonous $BRAF^{V600E}PTEN^{-/-}$ melanoma model, vactosertib (25 mg/kg, PO daily) in combination with CTLA4 antibody (100 µg IP every 3 days) induced a suppression of primary melanoma growth, a reduction of pulmonary metastatic lesions, and a significant improvement in the overall survival of tumor-bearing mice [22]. An increased number of CD8+ T cells are observed in primary melanoma lesions as well as draining lymph nodes. Using syngeneic $BRAFV600EPTEN^{-/-}$ melanoma model, addition of vactosertib to anti-PD-1 treatment enhanced antitumor response in this study.

Combination of vactosertib and anti-mouse-PD-1 significantly increased antitumor activity and survival rate compared to control, vactosertib monotherapy and anti-PD-1 monotherapy in a mouse CEA2-MC38 colorectal cancer model (MedPacto data, TED-229, refer to IB). In another syngeneic mouse model using NCC-S1M, a diffuse type gastric cancer cell line, synergistic antitumor effect resulting in decreases in tumor volume and weight were observed with the combined vactosertib and anti-PD-1 treatment comparing to anti-PD-1 monotherapy (MedPacto data, refer to IB).

Enabling immune infiltration using TGF-β inhibitors is sufficient to confer susceptibility to anti-PD-1 checkpoint-based therapies, a strategy that may have broad applications for treatment of cancers that grow in a TGF-β-rich environment.

1.2.2.2 Preclinical and Clinical Trial Data

Preclinical studies showed anti-tumor efficacy and sufficient target gene suppression with vactosertib of human equivalent dose to 125 mg QD. The pharmacokinetics and pharmacodynamics of vactosertib were analyzed in mouse melanoma SC model (B16F10) after single oral administration of vactosertib at a dose of 25 mg/kg (MedPacto data, TED-199). Refer to the vactosertib IB for detailed preclinical and clinical data.

1.2.2.3 Clinical Trials Testing Vactosertib in Colorectal Cancer

The MP-VAC-204 study (NCT03724851) is a phase 1b/2a, open-label, multi-center, dose finding study to assess safety, tolerability, pharmacokinetics and anti-tumor activity of vactosertib in combination with pembrolizumab in previously treated mCRC. The study includes dose escalation (Phase 1b) and dose expansion (Phase 2a).

Seventeen patients were enrolled in the 200 mg BID group and 33 patients enrolled in the 300 mg BID group. Six patients in the 300 mg BID group are currently being treated, describing the preliminary result as of April 1, 2021. Ninety-four percent of the 200 mg group and 48% of the 300 mg group were previously treated with more than third line therapy. Most patients have received fluoropyrimidine, irinotecan and oxaliplatin treatment. Ninety-four percent of patients in both groups were previously treated with bevacizumab while 53% of the 200 mg group and 42% of the 300 mg group received prior anti-EGFR inhibitors (panitumumab/cetuximab). In addition, patients in 53% of the 200 mg group and 18% of the 300 mg group received regorafenib treatment. In the MP-VAC-204 study, 11 of the 50 subjects (22.0%) were found to have treatment-related adverse event (TRAE) of grade 3 or higher with 9 (18.0%) reported to have TRAE of grade 3 or higher related to vactosertib. Two patients (4%) discontinued treatment due to grade 2 pneumonitis and grade 3 rash. Most frequently reported TRAEs were rash followed by pruritus, fatigue, decreased appetite and amylase/lipase increase. Two cases of adrenal insufficiency, asthma, decreased

appetite, diarrhea, vomiting, pneumonia, tuberculosis, and rash have also been reported as grade 3 treatment related serious adverse event (SAE). No cardiac toxicity was observed during the study. Both 200 mg or 300 mg BID vactosertib doses in combination with pembrolizumab were well tolerated in this metastatic mCRC patients who had previously been treated with oxaliplatin and irinotecan based chemotherapy.

Based on the available tolerability data from 11 patients enrolled as of March 5, 2021, a decision was made to decrease the vactosertib dose from 300 mg BID to either 200 mg BID or 200 mg QD. Dose adjustment or withdrawal was required in 4 out of 11 patients and 2 Gr 3 events (acute hepatitis and skin rash) were considered to be related to the enhanced immune response to the study treatment. This reduced tolerability was unexpected as vactosertib 300 mg BID with pembrolizumab had shown acceptable tolerability in metastatic colorectal cancer patients inMP-VAC-204. The differences in tolerability between the two studies may be attributed to differences in the host immune status and prior exposures to cytotoxic chemotherapy. Subjects in MP-VAC-204 study had experienced 4 lines (median) of prior chemotherapy. Vactosertib 200 mg showed effective decrease in TGF-β downstream markers including phospho-SMAD, PAI-1, CTGF and PDGF.

In a mouse model, vactosertib 25 mg/kg, equivalent to human dose of approximately 120 mg QD, exerted antitumor activity when combined with anti-PD-1 treatment.

Arm 1 will evaluate the vactosertib dose escalation strategy. Vactosertib 200 mg QD will be administered with pembrolizumab during the 1st Cycle. If no significant drug-related toxicity is observed, vactosertib 200 mg BID will be administered with pembrolizumab during subsequent cycles. This will allow patients to develop tolerability. Such dose-escalation strategy based on tolerability has been successfully tested in other trials [Bekaii-Saab, T.S., et al., The Lancet Oncology, 2019]. Set dose of vactosertib 200 mg QD with pembrolizumab will be evaluated in Arm 2.

1.3 Rationale for the Proposed Study

Metastatic CRC is the second leading cause of cancer death in the US, accounting for nearly 50,000 deaths each year. Approximately 95% of patients with metastatic CRC have pMMR disease, and are in need of new therapies with manageable side-effects which can produce durable treatment responses, as has been observed with pembrolizumab monotherapy in patients with MSI-H/dMMR CRC[8]. First- and second-line standard of care regimens for metastatic CRC are FOLFOX and 5-FU, leucovorin, and irinotecan (FOLFIRI) with or without a biologic agent (bevacizumab or, if RAS wild-type, an epidermal growth factor receptor [EGFR]-targeted antibody). Recently US Food and Drug Administration (FDA)-approved third-line therapies are regorafenib and TAS-102. Regorafenib was approved based on a median OS of 6.4 months compared to 5 months with placebo and is associated with a median PFS of 2 months and objective response rate (ORR) of 1% [35]. TAS-102 was approved based on a median OS of 7.1 months, versus 5.3 months with placebo; with a median PFS of 2 months and ORR of 1.6% [23].

Patients with resectable liver metastases have a chance for cure with metastasectomy. Perioperative chemotherapy is standard of care in such cases, with a goal to eliminate any extra-hepatic micrometastatic disease [6]. FOLFOX (or CapeOx) is the preferred preoperative

chemotherapy regimen in patients with resectable metastatic disease at diagnosis (synronous metastases), as it is associated with reversible morbidity (sinusoidal injury) without increased mortality. By contrast, the other first-line chemotherapy regimen, FOLFIRI, is associated with increased mortality related to steatohepatitis (especially in high-risk populations or with extended resections)[6, 24]. Moreover, the addition of biologics to chemotherapy in the context of (potentially) resectable metastatic CRC remains uncertain, with agents such as cetuximab not clearly demonstrating benefit in this setting [25]. Bevacizumab is also typically not used in this context, as it should be stopped at least a month prior to surgery to avoid bleeding or wound healing complications. Additionally, there is evidence that once started bevacizumab should be continued even beyond progression [26].

As in the Nordlinger study, we typically give 6 cycles of FOLFOX to patients with synchronous metastases who are candidates for liver resection [6]. Practice patterns vary greatly for patients with metachronous metastatic disease, based on the specific circumstances, hence flexibly was built into this protocol for feasibility. When applicable, it is then standard to wait 4 to 8 weeks from the time of last FOLFOX administration until surgery. This waiting period represents a window of opportunity to intervene.

Additionally, only about 30% of patients with hepatic metastases treated with curative intent actually achieve cure [2, 27]. Most recurrences occur within 2 years of surgery, so 2-year relapse-free survival (RFS) is a common intervention endpoint [28, 29]. Importantly, despite the high recurrence rate, observation is recommended after surgery for resectable metastases in patients who have received prior oxaliplatin-based therapy because no standard chemotherapy has been proven to improve RFS [30]. Introduction of experimental adjuvant therapy after metastasectomy offers another opportunity for intervention, with a goal to clear any remaining micrometastatic disease.

1.3.1 Rationale for Perioperative Pembrolizumab-Based Treatment

Identification of new strategies to augment immune-related responses in the broader population of metastatic CRC patients, without dMMR or MSI-H tumors, is essential[31]. Whereas immune checkpoint inhibitors such as pembrolizumab have shown robust single-agent antitumor activity in the ~5% of patients with metastatic CRCs harboring MSI-H or dMMR, novel strategies are needed for the ~95% of patients with MSS or pMMR metastatic CRC [8]. These strategies may include combining pembrolizumab with cytotoxic, targeted, or other immunotherapy agents.

Potentially resectable metastatic CRC represents an ideal clinical setting to assess both the clinical efficacy and immunologic/pharmacodynamics effects of pembrolizumab-based therapies, as the majority of carefully selected patients are ultimately taken to surgery following preoperative therapy (87.3% in the Nordlinger EORTC study)[6]; therefore, a large quantity of tumor tissue is available for immune cell characterization and immune/molecular profiling.

The Primary Objective of this study is to characterize change in the populations of TILs induced by neoadjuvant pembrolizumab-based therapy in patients with metastatic CRC with potentially resectable hepatic metastases. The Primary Endpoint is specifically defined as the proportion of patients with a ≥2-fold increase in the TILs in post- vs. pre-pembrolizumab-based treatment tumor specimens. A ≥2 fold increase was the threshold used for 2 prior trials of neoadjuvant immunotherapy [28, 29]. Including a prospective study evaluating the direct immune effects of sipuleucel-T on prostate cancer tissue in the peri-operative setting. Sipuleucel-T, which was FDA-

approved for improved OS in prostate cancer, induced a >2 fold increase in TILs per unit area of tissue [28]. We believe that a doubling in immune infiltration would be deemed as biologic meaningful, whereas magnitudes of change less than that can be more arguable for publication. In two published trials of prostate cancer we have shown that neoadjuvant immunotherapies can induce a >3x increase in TILs[36]. This is in excess of the doubling with which we set the threshold in this trial.

This concept is part of a larger collaboration between UCSF and Merck to dissect the changes within the tumor microenvironment induced with pembrolizumab-based combinations in 3 distinct indications (non-small cell lung cancer [NSCLC], RCC, and CRC). The combinations and cohorts that will move forward will be selected by a Joint Steering Committee (JSC) comprised of both UCSF and Merck researchers. We anticipate flexibility in the design to "go where the science takes us." Thus, patient accruals may ultimately shift between the indications.

The Secondary Objectives of this study are to establish the safety/toxicity profile and explore the efficacy of pembrolizumab + vactosertib in patients with CRC with potentially resectable hepatic metastases. The following outcomes will be measured: adverse events (AEs) and perioperative complications, pathologic response, R0 resection rate, and 2-year RFS. Two-year RFS rates will be compared between participants who do and do not receive adjuvant pembrolizumab-based therapy.

While the current protocol focuses on pembrolizumab + vactosertib following chemotherapy, we anticipate exploring other novel pembrolizumab-based combinations during this same post-chemotherapy/preoperative window (e.g., pembrolizumab in combination with other immuno- or molecularly targeted agents following FOLFOX). These novel combinations will be incorporated into the study as protocol amendments, and patients will be enrolled to them in a sequential, non-randomized fashion.

1.3.2 Rationale for Dose Regimen

The planned dose of pembrolizumab for this study is 200 mg (IV) for 1 neoadjuvant cycle and 400 mg (IV) for up to eight 6-week adjuvant cycles (optional). The pembrolizumab doses used in this trial have been demonstrated to be well tolerated in earlier clinical trials.

The planned dose of vactosertib for this study is 200 mg PO QD, 5 days per week for 2 weeks during the neoadjuvant treatment period, and 200 mg PO QD, 5 days per week for 6 weeks (1 cycle) and depending on tolerability, patients will receive 200 mg PO BID, 5 days per week for up to 42 weeks (7 cycles) during the optional adjuvant treatment period. The vactosertib dosing regimen used in this trial has been demonstrated to be well tolerated in the ongoing early phase clinical trials.

1.3.3 Correlative Studies Background

Correlative science to inform optimal use of pembrolizumab + vactosertib with chemotherapy in patients with metastatic CRC and to identify candidate biomarkers of response, resistance or toxicity, is an integral part of this study. As a result, serial blood samples as well as tissues from biopsies and surgical resection will be used to perform deep immunologic and molecular profiling prior to, during and following treatment.

Correlative research will be performed on:

- Baseline liver tumor biopsies (just prior to administration of neoadjuvant treatment).
- Surgical resection specimens (after neoadjuvant pembrolizumab-based treatment). Note that if patients undergo resection of multiple liver metastases, surgical removal of liver metastases plus colon primary, or other cases where surgical specimens are available from multiple sites, collection of multiple specimens is encouraged, with priority given to the liver metastasis corresponding to the pre-treatment biopsy.
- If a patient is unable to undergo surgery but had a pre-treatment biopsy that was confirmed to contain adequate tumor material for analysis and received one cycle of neoadjuvant pembrolizumab-based treatment, a second liver biopsy should be performed after the cycle of neoadjuvant treatment (biopsy of same liver metastasis as sampled in the pre-treatment biopsy preferred).
- Serial blood samples (pre-neoadjuvant treatment, pre-surgery, post-surgery, and at progression or end of study, whichever comes first).
- Stool samples collected at screening (-4 and -2 days of first pembrolizumab dose), at pre-surgical evaluation, and at the safety follow-up visit [optional].

Goals of the correlative research are to determine how immunotherapy perturbs both the circulating and intratumoral immune responses. Assays will be detailed in the Procedure Manual.

Stool will be collected, and a stool questionnaire will be completed at screening (-4 and -2 days of first pembrolizumab dose), at pre-surgical evaluation, and at the safety follow-up visit [optional] to assess the microbiome associated with clinical activity. This research may help identify factors predictive of pembrolizumab-based treatment response and resistance and novel targets for cancer immunotherapy.

Additionally, a dietary and physical activity questionnaire will be administered at screening (-28 to -1 day prior to first pembrolizumab dose).

1.3.4 Correlative Studies Hypotheses

Translational research hypotheses to be investigated are:

a) Pembrolizumab-based treatment will induce increased populations of TILs within metastatic CRC tumor samples.

b) Increase in TILs induced by pembrolizumab-based treatment is correlated with pathological response in patients with metastatic CRC.

c) Pembrolizumab-based treatment will increase PD-L1 expression in TIICs and may be associated with pathological response.

d) Distinct T cell repertoire changes in tumor tissue will be associated with response, resistance, or toxicity to pembrolizumab-based treatment.

e) Pembrolizumab-based treatment will induce characteristic changes in circulating T cell populations.

f) Distinct T cell repertoires in tumor tissue as well as in circulating T cells may be associated with response/resistance or toxicity to pembrolizumab-based treatment, and may in turn serve as biomarkers of response/resistance or toxicity.

g) Molecular characteristics beyond MSI/MMR (candidates include BRAF, BAP1, and SETD2) may be associated with higher levels of TIICs or PD-L1 expression on TIICs in response to pembrolizumab-based treatment, and thus be candidates for further study as predictive biomarkers in patients with metastatic CRC treated with immunotherapy.

h) Genomic mutations and gene copy variants may associate with clinical and/or immunologic response to therapy.

i) Correlate changes in microbiome composition and diversity (by metagenomic sequencing and untargeted metabolomics of stool collected before, during, and after immunotherapy), with diet and lifestyle factors.

1.3.5 Biomarker Research

Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy and other treatments administered, as well as determinants of AEs in the course of our clinical trials. These efforts will identify novel predictive/pharmacodynamic biomarkers and generate information that will better guide single-agent and combination therapy with immuno-oncology (IO) drugs. To identify novel biomarkers, biospecimens (i.e., blood components, tumor material, and microbiome) will be collected to support analyses of cellular components (e.g., protein, DNA, RNA, metabolites) and other circulating molecules. Procedures are detailed in the Lab Manual. Investigations may include but are not limited to:

<u>Tissue proteomic analysis by immunohistochemistry (IHC) and Immunofluorescence (IF)</u>

IHC staining of PD-L1 protein in tumor sections has been shown to correlate with response to pembrolizumab in patients with NSCLC, and an *in vitro* diagnostic (IVD) device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicates that this association may also be true in additional cancer types (i.e., triple negative breast, head and neck, and gastric cancer). Additional proteins expressing in the tumor microenvironment at baseline or following treatment may also correlate with response to pembrolizumab. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include but are not limited to IHC and IF. Multiplex IHC and IF may be performed on tumor core samples and resected tissues utilizing immune marker panels to assess for different cell types, including T cells, antigen presenting cells and stromal cells. Stained sections will be scanned, and the number of stained cells enumerated per area of tissue by computerized image analysis. The staining panels to be utilized will be developed in collaboration and agreement with Merck and the Principal Investigator. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab (MK-3475) therapy.

For the Primary Endpoint, defined as the proportion of patient with a ≥2-fold increase in TILs in post- vs. pre-pembrolizumab-based treatment tumor specimens, TILs will be enumerated per area of tissue (5 high power fields). We have developed this methodology and applied it to other

neoadjuvant immunotherapy trials (28, 29). This automated methodology can be applied to biopsies and resection tissues.

Gene Expression Profile (GEP)

Intratumoral expression levels of select genes will be analyzed using an analytically validated platform, such as the NanoString nCounter Analysis System and RNAseq. Association between the immune-related GEP and response to pembrolizumab has been established using these genes in melanoma and in cancers from clinical studies KN012 (head and neck, bladder, and gastric cancers) and KN028 (ovarian, esophageal, and other cancers). Data from these cohorts has been used to derive a GEP, which combines the expression levels of several key genes into a single scalar score. The GEP includes genes from immune-regulatory pathways and a GEP score will be tested for association with response to pembrolizumab-based treatment in retrospective fashion.

Flow Cytometry

Peripheral blood mononuclear cells (PBMC) and dissociated single cell suspensions of fresh tissue (where available) will be assessed for immune cell composition and functional status using flow cytometry staining. Other cell types (including stroma and tumor cells) may also be assessed by flow cytometry.

Additional biomarker research to identify factors important for pembrolizumab-based treatment therapy may also be pursued. For example, tumor and blood samples (including serum and plasma) from this study may undergo proteomic, genomic, metabolomic, and transcriptional analyses. Additional research may evaluate factors important for predicting responsiveness or resistance to pembrolizumab-based treatment and other immunologic targets.

Germline (blood) genetic analyses (e.g. single-nucleotide polymorphism [SNP] analyses, whole exome sequencing, whole genome sequencing)

This research will also evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to correlate with efficacy or AEs, the data might inform hypotheses regarding optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations. Finally, MSI may be evaluated as this is an important biomarker for some cancers (i.e. CRC).

Other blood-derived biomarkers- Proteomic Analysis

In addition to expression on the tumor tissue, PD-L1 can be shed from tumor and released into the blood. Assays such as enzyme-linked immunoassay (ELISA) can measure PD-L1 in serum. Correlation of expression with response to pembrolizumab (MK-3475) therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

Genetic (DNA) analyses from tumor

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (i.e. mutations, methylation status, MSI). Key molecular changes of interest to immune-oncology drug development include the mutational burden of tumors and the clonality of T cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a ”hyper-mutated” state) may generate neo-antigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. Note that in order to understand tumor-specific mutations; it is necessary to compare the tumor genome with the germline genome.

Tumor and blood RNA analyses

Both genome-wide and targeted messenger RNA (mRNA) expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that correlate to clinical response to pembrolizumab-based treatment or other immunotherapies. Pembrolizumab induces a response in tumors that likely reflects an inflamed/immune phenotype. Specific immune-related gene sets (i.e. those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated (e.g. IL-10). MicroRNA profiling may also be pursued.

Planned Genetic Analysis

Genetic variation may impact a patient’s response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and Institutional Review Boards (IRBs)/Ethics Review Committees (ERCs) allow, a sample will be collected for DNA analysis from consenting patients.

DNA samples will be used for research related to the study treatment(s), the disease under study and related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases and study drug(s). Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome (or analysis of the entire genome, as appropriate).

DNA samples will be analyzed for variation across the entire genome. Analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

Whole Exome Sequencing

Flash freezing of fresh biopsy cores in liquid nitrogen may allow for RNA-sequencing and Whole Exome Sequencing of tumor. This analysis will be performed using fresh frozen tissue specimens from both core needle biopsy (CNB) and resected tumor tissues.

Microbiome analysis of stool

Stool samples from this study will be collected for analyses including, but not limited to, metagenomic sequencing and untargeted metabolomics to reveal changes in gut microbial structure and function during treatment, including overall diversity and relative abundance of gut bacterial species, genes, and metabolites implicated in response to immunotherapy.

1.3.6 Future Biomedical Research Sample Collection

The investigators will conduct Future Biomedical Research on specimens for which consent was provided during this clinical trial. This research may include flow cytometry, genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), microbiome analysis of stool, characterization of circulating cell free DNA, and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. Decisions on Future Biomedical Research will be made by the Joint Steering Committee.

1.3.6.1 Future Biomedical Research Samples

The following specimens could be obtained as part of Future Biomedical Research:

- DNA for future research
- Leftover tumor for future research
- Leftover DNA and RNA from Correlative Studies
- Leftover plasma and serum from Biomarker Studies
- Leftover PBMC from whole blood from Correlative Studies
- Microbiome

2 Objectives of the Study

2.1 Hypothesis

We hypothesize that pembrolizumab plus vactosertib will increase tumor-infiltrating immune cells (TIICs) and promote response without increasing perioperative complications.

2.2 Primary Objective and Endpoint

Primary Objective	Endpoint	Time Frame
To characterize the change in the populations of TILs induced by	The primary endpoint is the proportion of patients with a ≥2-fold increase in the	From pre-treatment to surgery.

Primary Objective	Endpoint	Time Frame
neoadjuvant pembrolizumab plus vactosertib in patients with metastatic CRC.	TILs per unit area (5 high power fields) in post- vs. pre-pembrolizumab-based treatment tumor specimens.	

2.3 Secondary Objectives and Endpoints

Secondary Objectives	Endpoints	Time Frame
1. To establish the safety/toxicity profile of pembrolizumab-based treatment in the perioperative setting for patients with CRC with resectable hepatic metastases.	• Proportion of participants with Adverse Events, as graded by NCI CTCAE version 5.0 • Proportion of participants with events of clinical interest (ECIs) • Rates of perioperative complications	From initiation of study treatment until 1 year post last dose of pembrolizumab.
2. To explore the efficacy of pembrolizumab plus vactosertib in patients with CRC with resectable hepatic metastases.	• R0 resection rate • Pathologic response in resected tumor • Objective response rate • 2-year relapse-free survival (RFS)	From baseline to surgery. From surgery to up to 2 years post-surgery.

2.4 Exploratory Objectives and Endpoints

Exploratory Objectives	Endpoints
1. To determine the impact of pembrolizumab-based treatment on PD L1 expression in tumor cells and TIICs, in patients with mCRC. 2. To determine the change in T cell repertoire within the tumor and blood induced by neoadjuvant pembrolizumab-based treatment in patients with mCRC. 3. To explore molecular profiles to identify potentially predictive biomarkers for patients with metastatic CRC treated with immunotherapy (including but not limited to MSI testing). 4. To correlate change in TIICs, PDL-1 expression, and T cell repertoires as well as molecular profiles with response/resistance and toxicity. 5. To identify immune response mRNA expression analysis to derive signatures associated with tumor response	• Change in T-cell repertoire in pre-neoadjuvant treatment liver biopsies vs. surgical tumor specimens as well as in blood samples from the same time-points • Change in PD-L1 expression and other molecular markers in pre-neoadjuvant treatment liver biopsies vs. surgical tumor specimens • Correlate changes in microbiome composition and diversity (by metagenomic sequencing and untargeted metabolomics of stool collected before, during, and after immunotherapy), with diet and lifestyle factors determined by self-reported questionnaires. • Explore the correlation between change in TILs and T-cell repertoire.

Exploratory Objectives	Endpoints
6. To identify genomic mutations and gene copy aberrations associated with response and resistance to therapy 7. To correlate changes in microbiome composition and diversity with diet and lifestyle factors	

3 Study Design

3.1 Characteristics

This is a single arm, open-label trial evaluating the feasibility, immune effects, safety, and efficacy of pembrolizumab-based treatment in the preoperative setting for patients with CRC undergoing planned liver resection for hepatic metastases. The primary endpoint is the proportion of patients with a ≥2-fold increase in the number of TILs in post- vs. pre-pembrolizumab-based treatment tumor specimens.

Based on the results of this initial cohort, this trial may be subsequently amended to explore other novel pembrolizumab-based combinations (such as pembrolizumab in combination with another IO agent, chemotherapeutic, or a molecularly targeted agent that potentiates the efficacy of pembrolizumab) that will be decided by the Joint Steering Committee (JSC). Each of these new cohorts will be tested and enrolled to in sequential, non-randomized fashion. The trial is not designed to compare arms.

3.2 Number of Patients

In order to accrue 17 patients who are evaluable for the primary endpoint, the plan is to enroll a total of 19 patients. If 2 or more of first 6 patients are unable to undergo planned surgical resection of their liver metastases in timely fashion (i.e., within 4-6 weeks of the final chemotherapy administration [if applicable]) or experience surgical complications attributed to pembrolizumab-based treatment, accrual will be suspended, and our strategy will be revisited.

3.3 Eligibility Criteria

Patients must have baseline evaluations performed prior to dosing of study drug and must meet all of the inclusion and none of the exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent form (ICF) must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

3.3.1 Inclusion Criteria

Patients are eligible for this trial if all of the following inclusion criteria are met:

1. Has histologically or cytologically confirmed CRC with liver metastases. In addition to liver metastases, extrahepatic metastases (e.g. pulmonary metastases) may be permitted if all

other eligibility criteria are met. Patients are permitted to have primary tumor *in situ* (Neoadjuvant Arm only).

2. Has received previous oxaliplatin-based chemotherapy.
   a. FOLFOX or CapeOx does not need to be a direct lead-in to this study.
   b. If chemotherapy is a direct lead-in to this study, concurrent mAb therapy (bevacizumab, cetuximab, or panitumumab) is acceptable, however the antibody must be omitted from the final cycle of chemotherapy prior to pembrolizumab.
3. Is an appropriate candidate to undergo liver biopsy and resection (±ablation) of liver metastases (Neoadjuvant Arm Only)
4. Is willing and able to provide written informed consent/assent for the trial. The patient may also provide consent for Future Biomedical Research. However, the patient may participate in the main trial without participating in Future Biomedical Research.
5. Is ≥18 years of age on day of signing informed consent.
6. Has measurable disease based on RECIST 1.1 as assessed by the investigator. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. (Neoadjuvant Arm Only)
7. Is willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. Newly-obtained is defined as a specimen obtained after last dose of standard of care lead-in chemotherapy [if applicable] and within 28 days prior to first dose of pembrolizumab. (Neoadjuvant Arm Only)
8. Has a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale (Appendix 1).
9. Has adequate organ function as defined in Table 1, within 10 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500/μL
Platelets	≥100,000/μL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or erythropoietin (EPO) dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × upper limit of normal (ULN) **OR** ≥60 mL/min for patient with creatinine levels >1.5 × institutional ULN
Hepatic	
Serum total bilirubin	≤1.5 × ULN **OR**
	Direct bilirubin ≤ULN for patients with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN
Albumin	≥2.5 mg/dL

System	Laboratory Value
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 × ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 × ULN unless patient 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.	

10. Female patients of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication (Day 1). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
11. Female patients of childbearing potential must be willing to use an adequate method of contraception* as outlined in Section 6.6, for the course of the study through 120 days after the last dose of study medication.
12. Male patients of childbearing potential must agree to use an adequate method of contraception* as outlined in Section 6.6, 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 patient.

13. Have locally confirmed MSS or pMMR CRC. MSS is defined as 0-1 allelic shifts among 3-5 tumor microsatellite loci using a PCR-based assay. pMMR is defined as presence of protein expression of 4 MMR enzymes (MLH1, MSH2, MSH6 and PMS2) by immunohistochemistry.
14. Have no radiographic evidence of malignancy as assessed by Investigator (Adjuvant Phase Only)

3.3.2 Exclusion Criteria

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

1. 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.

   Note: Patients who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks since the last dose of the previous investigational agent or device use.
2. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
3. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.

4. Has an active autoimmune disease that has required systemic treatment in 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) is not considered a form of systemic treatment and is allowed.
5. Has active Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or active Hepatitis C virus (defined as HCV RNA [qualitative] [32] is detected) infection.
6. Has received prior anti-cancer mAb, systemic anticancer therapy other than FOLFOX (including investigational agents), targeted small molecule therapy, or radiation therapy within 14 days prior to the first dose of study treatment (Day 1). Note: patients must have recovered from all AEs due to a previous therapies to ≤Grade 1 or baseline. Patients with Grade 2 neuropathy or alopecia are eligible. If a patient received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.
7. Has received FOLFOX less than 7 days prior to the first dose of study treatment (Day 1). Has not recovered (i.e., ≤Grade 1 or at baseline) from AEs due to FOLFOX chemotherapy. Note: Patients with ≤Grade 2 neuropathy or alopecia are exceptions to this criterion and may qualify for the study.
8. Has not recovered adequately from toxicity or complications of a surgery or other procedure, per the assessment of the treating investigator.
9. Has received liver-directed therapy such as radiotherapy or yttrium-90 in the past year involving the lesion to be biopsied. (Neoadjuvant Arm only)
10. Has a known additional malignancy that is progressing or has required active treatment within 5 years prior. Note: Patients with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
11. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are radiologically stable (i.e., without evidence of progression by imaging for at least 4 weeks by repeat imaging [repeat imaging should be performed during the study screening]), clinically stable, and without requirement of steroid treatment for at least 14 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
12. Has a history of (noninfectious) pneumonitis that required steroids or has current pneumonitis.
13. Has an active infection requiring systemic therapy.
14. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion

of the treating investigator. Anticoagulation that cannot be safely held to perform the liver biopsy is an example of a contraindication to participation.

15. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
16. Has received any prior immunotherapy including anti–PD-1, anti–PD-L1, or anti-PD-L2 or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g. CTLA-4, OX-40, CD137) (Neoadjuvant Arm Only).
17. Has severe hypersensitivity (≥Grade 3) to pembrolizumab or vactosertib and/or to any of their excipients.
18. Has received a live or live-attenuated vaccine within 30 days prior to first dose of the trial drug. Administration of killed vaccines are allowed.
19. Has inferior vena cava/cardiac involvement based on imaging.
20. Has had encephalopathy in the last 6 months. Those patients on rifaximin or lactulose to control their encephalopathy are not allowed.
21. Has had a solid organ or hematologic transplant.
22. Has symptomatic ascites or pleural effusion. A patient who is clinically stable following treatment for these conditions (including therapeutic thora- or paracentesis) is eligible.
23. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure (New York Heart Association Class III/IV), uncontrolled hypertension (≥150/90mmHg), unstable angina pectoris or myocardial infarction (≤ 6 months prior to screening), uncontrolled cardiac arrhythmia, clinically significant cardiac valvulopathy requiting treatment, active interstitial lung disease, or serious chronic gastrointestinal conditions associated with diarrhea.

3.4 Duration of Therapy

All participants will receive a single dose of pembrolizumab and 20 doses of vactosertib (QD, 5 days per week for 2 weeks) prior to surgery.

Participants who undergo surgical resection and have adequately receovered from toxicity or complications of a surgery or other procedure, per the assessment of the treating investigator, may receive optional adjuvant treatment of pembrolizumab + vactosertib for up to eight 6-week cycles.

3.5 Duration of Follow Up

Due to the potential for late toxicities from pembrolizumab, patients will be followed for at least 1 year after their last dose of pembrolizumab or up to 2 years post-surgery for RFS whichever occurs last.

3.6 Randomization Procedures

This is a single-arm non-randomized trial. Additionally, this is an open-label trial; therefore, Merck, the investigator, and the patient will know the treatment administered. The trial is not designed to compare arms.

3.7 Study Timeline

3.7.1 Primary Completion

The study will reach primary completion, at the time the last participant has data collected for the primary objective to be measure. We estimate this occurring from the time the study opens to accrual.

3.7.2 Study Completion

The study will reach study completion 72 months from the time the study opens to accrual.

4 Study Drugs

4.1 Description, Supply and Storage of Investigational Drugs

4.1.1 Pembrolizumab

Details on the preparation and administration of pembrolizumab are provided in the Pharmacy Manual and package insert. Refer to the IB for additional information on pembrolizumab.

Classification
PD-L1 inhibitor, immunotherapy

Mechanism of Action
Pembrolizumab (MK-3475) is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical *in vitro* data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. For more details see Section 1.2.1.1 and the IB.

Contraindications
Immunodeficiency, autoimmune diseases requiring treatment with disease modifying agents, corticosteroids or immunosuppressive drugs, active infections.

Availability
Pembrolizumab will be provided to patients enrolled on this study by Merck.

Handling, Storage, and Specific Accountability
The local country Merck personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate.

Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by Merck.

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

Table 2 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 25 mg/mL	Solution for Injection

Clinical Supplies Disclosure
This trial is open-label; therefore, the patient, the trial site personnel, Merck 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.

4.1.2 Vactosertib

Refer to the IB for additional information on vactosertib.

Classification
Serine/threonine kinase inhibitor

Mechanism of Action
For more details see section 1.2.2 and the IB.

Contraindications
Vactosertib is predominately metabolized by CYP3A4. Because grapefruit and grapefruit juice are strong CYP3A4 inhibitors, these should be avoided in this study.

Description
The vactosertib film-coated tablets contain the following inactive ingredients: lactose monohydrate (Fastflo 316), microcrystalline cellulose (Avicel PH 102), crospovidone (Kollidon CL F), povidone Kollidon 30, magnesium stearate, and opadry white. The proposed clinical drug product vactosertib (50 mg, 100 mg and 200 mg film-coated tablets) is compressed from 10%w/w(50 mg), 40%w/w(100 mg, 200 mg) drug loaded common stock wet granulation.

Availability
Vactosertib will be provided to patients enrolled on this study by MedPacto.

Handling, Storage, and Specific Accountability
Clinical Supplies will be provided by MedPacto as summarized in Table 3.

Table 3 Product Descriptions

Product Name & Potency	Dosage Form
Vactosertib 50 mg	Film-coated tablets
Vactosertib 100 mg	Film-coated tablets
Vactosertib 200 mg	Film-coated tablets

Vactosertib tablets are packaged in tightly closed, white, opaque, HDPE bottles with a 1-g silica gel desiccant canister. The bottles are heat-induction sealed with a child-resistant cap. Based on the available laboratory stability data, vactosertib tablets should be stored at 15°C to 25°C (59°F to 77°F) and protected from light. Recent data indicate that 50 mg vactosertib remain stable up to 36 months, 100 mg and 200 mg vactosertib remain stable up to 9 months, respectively, under the same testing conditions as above. Stability test for a longer time period is underway: 50 mg, 100 mg and 200 mg vactosertib up to 60 months.

Clinical Supplies Disclosure
This trial is open-label; therefore, the patient, the trial site personnel, MedPacto 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.

4.2 Drug Accountability

The Investigational Pharmacist will manage drug accountability records.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by Merck.

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 study treatments in accordance with the protocol and any applicable laws and regulations.

4.3 Drug Ordering

UCSF will obtain pembrolizumab directly from Merck as study supply. Commercial drug will be supplied locally. UCSF will obtain Vactosertib directly from MedPacto as study supply.

4.4 Packaging and Labeling of Study Drugs

Drugs will be packaged and affixed with a clinical label per UCSF institutional standards, adhering to applicable local and federal laws.

5 Treatment Plan

5.1 Dosage and Administration

Trial treatment should be administered at the time points specified in the Trial Flow Charts (section 6.2). The treatment to be used in this trial is outlined in Table 4 and Table 5. On Day 1 of each cycle, administer vactosertib after the subject completes their pembrolizumab infusion. Vactosertib may be administered as soon as the pembrolizumab infusion is completed. Vactosertib and pembrolizumab may be administered without regard to meals.

Table 4 Main Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Once	IV infusion	C1D1	Experimental
Vactosertib	200 mg	QD, 5 days per week	PO	C1D1 through C1D14	Experimental
Abbreviation: IV = intravenous, PO = per os, C = cycle, D = day, QD = once a day					

Table 5 Optional Adjuvant Treatment Cohort

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	400 mg	Q6W	IV infusion	Up to 8 cycles	Experimental
Vactosertib	200 mg	Cycle 1: QD, 5 days per week Cycles 2+: BID, 5 days per week	PO	Up to 8 cycles	Experimental
Abbreviation: IV = intravenous, PO = per os, C = cycle, D = day, Q6W = every 6 weeks, QD = once a day, BID = twice a day					

5.1.1 Pembrolizumab

Pembrolizumab will be administered as a 30-minute IV infusion. Every effort will be made to target infusion timing to be as close to 30 minutes as possible. However, 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). All IV infusion treatments will be administered on an outpatient basis.

Note: Treatment with pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons (such as holidays).

5.1.2 Vactosertib

Vactosertib will be administered once daily at 200 mg PO for 5 days followed by a 2-day resting period (5 days on/2 days off) for two weeks during the neoadjuvant treatment phase.

During the optional adjuvant treatment phase, vactosertib will be administered once daily at 200 mg PO (dose level -1) for 5 days followed by a 2-day resting period during Cycle 1. If no significant drug-related toxicities are observed, vactosertib will be administered twice daily at 200 mg PO (dose level 0) for 5 days followed by a 2-day resting period (5 days on/2 days off) for up to 8 cycles.

Please see Section 5.2, Dose Modifications and Dosing Delays for additional details.

5.1.3 Other Modality(ies) or Procedures

Patients are expected to undergo standard of care surgical resection of liver metastases within 4-6 weeks of the final chemotherapy administration (if applicable) and approximately 2 weeks (minimum 1 week) after their neoadjuvant dose of pembrolizumab-base treatment. Standard of care operative plan is at the discretion of the treating surgeon.

5.1.4 Dose Limiting Toxicity

As the toxicities of pembrolizumab are well-established and not necessarily dose-dependent, this study will not use formal dose-limiting toxicity definitions according to NCI CTCAE grading criteria. However, to avoid compromising patient safety in this potentially curative setting, early stopping rules will be followed such that the study will be stopped, and this approach re-evaluated, if 2 or more of the first 6 patients experience any 1 of the following:

- A delay in planned surgery beyond the 8-week window after final chemotherapy treatment due to any grade toxicity attributable to study treatment. Delays in surgery due to other reasons (scheduling, available operating room time, patient preference) will not count.
- Grade IV and V surgical complications according to Clavien-Dindo classification (Appendix 4).

  Note: Surgical complications associated with liver metastastectomy are very common, and we recognize that it may be difficult to attribute any such complications to preoperative administration of pembrolizumab-based treatment. Therefore, the occurrence of such events may not necessarily require stopping the study early, but will be discussed amongst members of the JSC, and Merck with particular attention paid to specific complications such as liver failure, severe colitis, etc.

Moreover, enrollment will be paused for 4 weeks after the sixth patient undergoes surgery (or receives their dose of pembrolizumab-based treatment if unable to undergo surgery). During this interval the study investigators will meet with the participating surgeons and Merck to review the first 6 cases. A recommendation will be made regarding whether or not to enroll additional patients and if any changes are needed to optimize safety or feasibility.

5.2 Dose Modifications and Dosing Delays

Dose modification guidelines for pembrolizumab-related AEs during the adjuvant period are provided in Table 7. Dose modification guidelines for pembrolizumab-related AEs during the neoadjuvant period do not apply as only a single dose of pembrolizumab will be administered.

Vactosertib dose reduction based on treatment-related adverse events observed is permitted.

According to the dose levels in Table 6, participants who receive vactosertib below the initially assigned treatment level (200 mg QD or BID) due to vactosertib-related AEs, will have the option to re-escalate to the assigned vactosertib dose if AE(s) resolves to baseline and does not recur for at least 3 consecutive weeks (one treatment cycle).

For the optional adjuvant treatment phase, participants who experience the following drug-related toxicities may escalate to dose level 0 based on the judgement of the investigator:

- Grade 1 or 2 Hematologic Toxicity
- Grade 1 non-hematologic toxicity and/or other drug related toxicities.
- Grade 1 ALT or AST elevation possibly related with total bilirubin <2x ULN

If a Grade 2 or lower vactosertib treatment-related toxicity is experienced but not specified, above dose escalation could be considered after discussions with MedPacto.

If a participant experiences several adverse events and there are conflicting recommendations, the investigator should use the recommended dose adjustment that reduces the dose to the lowest level or if warranted, discontinues therapy.

Table 6 Vactosertib Dose Modification

Neoadjuvant Treatment Phase			Optional Adjuvant Treatment Phase	
Treatment Level	**Vactosertib Dose**		**Treatment Level**	**Vactosertib Dose**
0	200 mg QD		0	200 mg BID
-1	100 mg QD		-1	200 mg QD
-2	100 mg QD		-2	100 mg QD

Vactosertib dose can be reduced to manage a treatment related AE as indicated in Table 9.

5.3 Monitoring and Toxicity Management

Each patient receiving pembrolizumab-based treatment will be evaluable for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical findings, and spontaneous reports of AEs reported to the investigator by patients.

Each patient will be assessed periodically for the development of any toxicity as outlined in 5.3.5. Toxicity will be assessed according to NCI CTCAE v5.0 (Appendix 3).

5.3.1 Toxicity Management for Immune-Related AEs Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab 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, 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 monotherapy, coformulations, or IO combinations are provided in Table 7.

Table 7 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations and IO Combinations

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab monotherapy, coformulations, or IO combinations 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 ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab monotherapy, coformulations or IO combinations has been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	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		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent)	• Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea,

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	Recurrent Grade 3 or Grade 4	Permanently discontinue	followed by taper	abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus) • Participants with ≥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
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)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
T1DM or Hyperglycemia	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 or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (e.g., propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (e.g., 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		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (which was previously myocarditis Grade 1 using CTCAE v4.0)	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		
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		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
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 × ULN if baseline normal; >3.0 to 5.0 × baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 × ULN if baseline normal; >1.5 to 3.0 × baseline if baseline abnormal [b] AST/ALT: >5.0 to 20.0 × ULN, if baseline normal; >5.0 to 20.0 × baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 × ULN if baseline normal; >3.0 to 10.0 × baseline if baseline abnormal [c] AST/ALT: >20.0 × ULN, if baseline normal; >20.0 × baseline, if baseline abnormal; bilirubin: >10.0 × ULN if baseline normal; >10.0 × baseline if baseline abnormal [d] The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab monotherapy, coformulations, or IO combinations 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).				

5.3.2 Toxicity Management of Infusion-Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab-associated infusion reaction are provided in Table 8.

Table 8 Pembrolizumab Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately.

NCI CTCAE Grade	Treatment
	Patient is permanently discontinued from further study drug treatment.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; NSAIDs = non-steroidal anti-inflammatory drugs; PO = by mouth.

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the CTCAE v5.0 at http://ctep.cancer.gov

5.3.3 Other Allowed Dose Interruption for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. For patients who receive optional adjuvant therapy with pembrolizumab and vactosertib, pembrolizumab is to be restarted within 42 days (6 weeks) of the originally scheduled dose for Q6W dosing and within 84 days of the previously administered dose, unless otherwise discussed with Merck. The reason for study treatment interruption is to be documented in the patient's study record.

5.3.4 Rescue Medication and Supportive Care for AEs Associated with Pembrolizumab

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined with the dose modification guidelines in Section 5.3.1.

5.3.5 Monitoring and Management for AEs Associated with Vactosertib

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested monitoring and dose modifications are for the management of a treatment related AE are outlined in Table 9. Refer to Table 6 in section 5.2 for vactosertib treatment levels.

Table 9 Vactosertib Dose Modifications for Treatment-Related Toxicity

Toxicity	Severity Grade	Vactosertib Dose Modification
Hematologic toxicity	1/2	Continue at the same Treatment Level
	3	Withhold until toxicity is Grade ≤2, or has returned to baseline, then resume treatment at the same Treatment Level or reduce the dose by 1 Treatment Level after discussion with the Sponsor a
	4	Withhold until toxicity is Grade ≤2, or has returned to baseline, then reduce by 1 Treatment Level
Non-hematologic toxicity and/or other drug related toxicities b	1	Continue at the same Treatment Level
	2	For persistent (>1-2 week) Grade 2 events, consider holding study drug until resolution to Grade ≤1 or baseline. If the study drug is withheld and the toxicity resolved to Grade ≤1 or baseline, resume treatment at the same Treatment Level or reduce by 1 Treatment Level
	3	Withhold until toxicity is Grade ≤1, or has returned to baseline, then resume treatment at the same Treatment Level or reduce the dose by 1 Treatment Level after discussion with the Sponsor
	4	Discontinue vactosertib

ALT or AST elevation possibly related with total bilirubin <2x ULN	1	Continue at the same Treatment Level
	2	Continue at the same Treatment Level Repeat ALT or AST and total bilirubin within 7 days when subject is symptomatic; If not symptomatic, monitor weekly. For persistent (>1-2 week) Grade 2 events, consider holding study drug until resolution to Grade ≤1 or baseline. If the study drug is withheld and the toxicity resolved to Grade ≤1 or baseline, resume treatment at the same Treatment Level or reduce by 1 Treatment Level
	3/4	Withhold dose until toxicity is Grade ≤ 1, or has returned to baseline, then resume treatment by reducing by one Treatment Level. Repeat within 48~72 hours until resolution to Grade ≤1. If Grade 3 ALT or AST elevation recurs at dose level -2, then discuss with Sponsor whether to discontinue permanently.
ALT or AST elevation and total bilirubin ≥ 2x ULN (in the absence of cholestasis or haemolysis)	1	Continue at the same Treatment Level Repeat ALT or AST and total bilirubin within 48 hours and monitor every 48 hours until Grade<1.
	2	Withhold until resolution to baseline then resume treatment by reducing by one Treatment Level. Repeat ALT or AST and total bilirubin within 48~72 hours until resolution to Grade ≤1 or baseline. Discontinue if not resolved to Grade≤1 or baseline within 3 weeks
	3/4	Discontinue vactosertib. Repeat ALT or AST and total bilirubin within 48 hours and monitor every 48 hours until Grade ≤1.
Left ventricular systolic dysfunction c	G3/4	Permanently discontinue vactosertib

a. Subjects who develop Grade 3 or 4 lymphopenia without other dose-limiting events (e.g., opportunistic infection) may continue study treatment without interruption
b. Subjects with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study medication for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose
c. According to CTCAE v5.0, development of LV systolic dysfunction is considered AE of grade ≥ 3. Therefore, subjects who develop left ventricular (LV) systolic dysfunction will permanently discontinue both of study drugs
d. If vactosertib dose modification is required due to treatment-related toxicity, changing a dose level of vactosertib, or temporarily holding IP(s) not specified in the table could be considered in discussion with sponsor

6 Study Procedures and Observations

6.1 Schedule of Procedures and Observations

The study-specific assessments are detailed in this section and outlined in Table 10. Screening assessments must be performed within 28 days prior to the first dose of investigational product. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. All on-study visit procedures are allowed **a window of ±3 days** unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

A signed informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization will be obtained prior to performing screening procedures (see section 9.3 for details).

6.1.1 Screening Assessments

The screening procedures and assessments must be completed within 28 days prior to the dose of pembrolizumab, unless specified otherwise. Note that the cycle of pembrolizumab-based treatment should begin ≥7 days after the final chemotherapy administration.

Note: A screening CT chest/abdomen/pelvis with IV contrast must be performed and reviewed to re-confirm candidacy for hepatic resection prior to liver tumor biopsy.

Screening procedures and assessments:

- Review of eligibility
- Complete physical examination
- Vital sign measurements and weight
- Complete medical history (including MMR/MSI status) and demographics
- Documentation of disease status assessment/measurable disease
- ECOG performance status performed within 7 days prior to treatment administration
- History of prior treatments and any residual toxicity relating to prior treatment. Include number of cycles of FOLFOX/CapeOx received prior to pembrolizumab; interval between last FOLFOX/CapeOx treatment and pembrolizumab; addition of monoclonal antibodies to chemotherapy; growth factor support.
- Baseline medications taken within 28 days of Day 1
- Tumor marker assessments (CEA): also record CEA at diagnosis, prior to and after lead-in FOLFOX/CapeOx (if applicable).
- Complete blood count (CBC) with differential and platelet count
- Hematology labs (other than CBC w/ Diff)
- Blood chemistry assessment, including:
    - Alkaline phosphatase (ALP), aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, direct bilirubin *(If total bilirubin is elevated above the upper limit of normal)*, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, total protein, albumin, fasting glucose, potassium,

sodium, magnesium, chloride, bicarbonate, uric acid, lactate dehydrogenase (LDH)

- Thyroid function tests: thyroid-stimulating hormone (TSH), free thyroxine (FT4); free and total triiodothyronine (T3)
- Coagulation assessment (prothrombin time [PT], partial thromboplastin time [PTT], international normalized ratio [33])
- Serum Hepatitis assessment, including Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (HBsAb), Hepatitis B core antibody (HBcAb), HCV RNA
- Urinalysis
- Serum or urine pregnancy test within 72 hours prior to the start of study drug
- Echocardiogram (ECHO)
- Imaging (CT chest/abdomen/pelvis with IV contrast) for tumor/lesion assessment and to confirm candidacy for liver resection surgery.
- Archival specimen collection for banking (formalin-fixed paraffin-embedded [FFPE] tumor specimen, if available)Biopsy of liver metastasis. Criteria for selecting the lesion for biopsy are that it is safely accessible and is expected to contain viable tumor (rather than necrotic material) based on radiographic appearance. If there are several such liver metastases to choose from, select the largest one
- Stool collection and stool questionnaire (-4 and -2 days of first pembrolizumab dose)
- Dietary and physical activity questionnaire

6.1.2 Neoadjuvant Pembrolizumab + Vactosertib Dosing Day 1

One cycle of pembrolizumab + vactosertib will be administered approximately 2 weeks (minimum 1 week) after the last dose of chemotherapy (if applicable).

Study procedures and assessments:

- Directed physical examination
- Vital sign measurements and weight
- ECOG Performance status
- Evaluation of AEs
- Concomitant medications
- Hematology (other than CBC with diff), CBC with Differential and platelet count
- Comprehensive Serum Chemistry (see Table 12)
- ECG* (within 7 days of Cycle 1)
- Urinalysis
- T3 (free and total), FT4 and TSH
- Tumor Marker: CEA
- Correlative studies blood collection
- Pembrolizumab administration (see section 5.1)
- Vactosertib administration (see section 5.1)

- Dispense vactosertib supply

6.1.3 Pre-surgical Evaluation

A pre-surgical visit will be scheduled 1-2 weeks after pembrolizumab dosing, prior to surgery.

Study procedures and assessments:

- Disease status assessment/measurable disease
- Directed physical examination
- Vital sign measurements and weight
- ECOG Performance status
- Evaluation of AEs
- Concomitant medications
- Hematology (other than CBC with diff), CBC with Differential and platelet count
- Comprehensive Serum Chemistry (see Table 12)
- PT/INR and aPTT
- Urinalysis
- T3 (free and total), FT4 and TSH
- Tumor Marker: CEA
- Correlative studies blood collection
- Stool collection and stool questionnaire

6.1.4 Liver Resection Surgery

Liver resection for hepatic metastases will be performed per standard of care. Patients are expected to undergo surgical resection of liver metastases within 4-6 weeks of the final chemotherapy administration (if applicable) and approximately 2 weeks (minimum 1 week) after their neoadjuvant dose of experimental therapy. If vactosertib must be held for toxicity, and full course of treatment cannot be completed, the surgery will still proceed as planned unless there are safety concerns regarding the surgery. Standard of care operative plan is at the discretion of the treating surgeon.

In the event that the surgery is canceled, and the first liver biopsy yielded adequate tumor material, a second liver biopsy will be requested (same lesion as the first biopsy preferred). Do not perform second liver biopsy if the first liver biopsy yielded inadequate tumor cells for analysis or excessively high procedural risk due to location or other factors.

6.1.5 Post-surgical Safety Follow-up Visit

A post-surgical safety follow-up visit should be conducted approximately 14 days (±7 days) after surgery.

Study procedures and assessments:

- Directed Physical examination

- Vital sign measurements and weight
- ECOG Performance Status
- Evaluation of AEs
- Concomitant medications
- Hematology (other than CBC with diff), CBC with Differential and platelet count
- Comprehensive Serum Chemistry Panel (see Table 12)
- Urinalysis
- T3 (free and total), FT4 and TSH
- Tumor Marker: CEA
- Correlative studies blood collection
- Optional stool collection and stool questionnaire
- Obtain standard of care MSI/MMR and expanded RAS/BRAF mutation testing from liver resection specimen if not tested previously. Review pathology report.
- Optional adjuvant treatment (pembrolizumab + vactosertib) recruitment.
    - Interested participants will complete the adjuvant pre-treatment procedures outlined in Table 11 and section 6.1.6.1.
    - Participants who are not interested or are ineligible for the adjuvant treatment cohort will be followed every 90 days (±14d) for up to 2 years post-surgery as outlined in Table 10 and section 6.1.7.

6.1.6 Optional Adjuvant Treatment

6.1.6.1 Pre-treatment

Participants interested in participating in the optional adjuvant treatment cohort (pembrolizumab + vactosertib) will complete the pre-treatment procedures 2 weeks (±7 days) after surgery.

Study procedures and assessments:

- Informed consent for adjuvant treatment
- Review of eligibility (per the investigator's discretion). The rationale for enrolling (or not enrolling) participants in adjuvant therapy will be recorded, along with any supporting test results (e.g., circulating tumor DNA analysis).
- Concomitant medications
- Evaluation of AEs
- Directed physical examination
- Vital sign measurements and weight
- ECOG Performance status
- Serum or urine pregnancy test within 72 hours prior to the start of adjuvant treatment
- PT/INR and aPTT
- Hematology (other than CDC with diff), CBC with differential and platelet count

- Comprehensive serum chemistry (see Table 12)
- Urinalysis
- T3 (free and total), FT4 and TSH

Participants who are ineligible for the adjuvant treatment cohort will be followed every 90 days (Q90D; ±14 days) for up to 2 years post-surgery per Table 10 and section 6.1.7.

6.1.6.2 Cycle 1 through Cycle 8

Eligible participants will receive adjuvant treatment 6 weeks (±2 weeks) after hepatic metastasectomy. Participants will receive adjuvant pembrolizumab + vactosertib for up to eight, 6-week cycles (approximately 1 year) or until disease recurrence is radiographically documented, unacceptable AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the patient, administrative reasons requiring cessation of treatment, or withdrawal of consent, whichever occurs first.

Perform the following procedures and assessments on day 1 of each cycle unless specified otherwise:

- Concomitant medications
- Evaluation of AEs
- Directed physical examination
- Vital sign measurements and weight
- ECOG Performance status
- Hematology (other than CBC with diff), CBC with differential and platelet count*
- Comprehensive serum chemistry (see Table 12)*
- Urinalysis*
- T3 (free and total), FT4 and TSH*
- ECHO - perform at cycle 2 only
- Tumor Marker: CEA
- Tumor imaging with IV contrast to monitor disease status - perform every 12 weeks (i.e., day 1 of every other cycle)
- Correlative studies blood collection - perform every 12 weeks (i.e., day 1 of every other cycle)
- Pembrolizumab administration (see section 5.1)
- Vactosertib administration (see section 5.1)
- Dispense vactosertib supply as needed

*Tests do not need to be repeated at adjuvant C1D1 treatment visit if they were performed within 7 days prior to C1D1.

6.1.6.3 End of Treatment Visit

An *End of Treatment Visit* should be conducted at treatment discontinuation (+7 days).

Procedures and assessments:

- Concomitant medications
- Evaluation of AEs
- Directed Physical examination
- Vital sign measurements and weight
- ECOG Performance Status
- Hematology (other than CBC with diff), CBC with Differential and platelet count
- Comprehensive Serum Chemistry Panel (see Table 12)
- Urinalysis
- T3 (free and total), FT4 and TSH
- ECHO – only if echocardiography is not performed within the past 12 weeks.
- Tumor Marker: CEA
- Tumor imaging with IV contrast

6.1.6.4 Safety Follow-up Visit

For patients receiving adjuvant treatment with pembrolizumab and vactosertib, the mandatory *Safety Follow-Up Visit* should be conducted approximately 30 days (+7 days) after the last dose of study treatment or before the initiation of a new anticancer treatment, whichever comes first.

Procedures and assessments:

- Concomitant medications
- Evaluation of AEs

6.1.7 Follow-up Phase

All participants will be followed for up to 1 year after the last dose of pembrolizumab and vactosertib is administered or up to 2 years after surgery, whichever occurs last. Follow-up may end sooner if disease progression, withdrawal of consent, or death occur.

Additional post-operative chemotherapy, subsequent anti-neoplastic therapy, and follow-up assessments will be at the discretion of the treating physician. Information regarding post-study anti-neoplastic treatment will be collected if such treatment is initiated.

The following study procedures and assessments will be done Q90D (±14 days) for up to one year after last dose of pembrolizumab and vactosertib or up to two years after surgery, whichever occurred last:

- Disease status assessment/measurable disease
- Concomitant medications
- Post-study anticancer therapy status
- Survival Status

- Evaluation of AEs for the timeframe defined in Section 7.5
- Radiologic CT imaging with IV contrast to monitor disease status.
- Correlative studies blood collection

Note: Safety labs and correlative labs will be collected up to 1 year post-pembrolizumab.

6.2 Trial Flow Chart

Table 10 Main Trial Flow Chart

Trial Period:	**Screening**	**Preoperative Treatment**	**Pre-Surgery**	**Surgery**	**Post-Surgery Safety F/U**	**Follow Up Phase[a,m]**
Treatment Cycle/Visit:		**C1D1**				
Scheduling Window:	-28d to -1d	≥7d post-last chemotherapy	+7-14d post-C1D1	+7-14d post-C1D1, 28-42d post-last chemo	14d ±7d post-op	Q90D ±14d post-op for up to 2y
Directed Medical History	X					
Main Trial Study Informed Consent	X[b]					
Future Biomedical Research consent (optional)	X[b]					
Inclusion/ Exclusion Criteria	X					
Demographics and Full Medical History, including MMR/MSI status	X				X[c]	
Prior and Concomitant Medication Review	X[d]	X	X		X	X[k]
History of Prior Treatments and residual toxicity to prior treatment	X					
Trial Treatment Administration[j]		X				
Dispense vactoserib supply		X				

Trial Period:	**Screening**	**Preoperative Treatment**	**Pre-Surgery**	**Surgery**	**Post-Surgery Safety F/U**	**Follow Up Phase[a,m]**
Treatment Cycle/Visit:		**C1D1**				
Scheduling Window:	-28d to -1d	≥7d post-last chemotherapy	+7-14d post-C1D1	+7-14d post-C1D1, 28-42d post-last chemo	14d ±7d post-op	Q90D ±14d post-op for up to 2y
Post-study anticancer therapy status						X[k]
Survival Status						X
Review Adverse Events		X	X		X	X[k]
Complete Physical Examination	X					
Directed Physical Examination		X	X		X	
Vital Signs and Weight	X	X	X		X	
ECOG Performance Status	X[i]	X	X		X	
Pregnancy Test – Urine or Serum	X					
PT/INR and aPTT	X[n]		X			
Hematology, CBC with Differential and platelet count	X[n]	X	X		X	X[a.]
Comprehensive Serum Chemistry Panel (see Table 12)	X[n]	X	X		X	X[a.]
Urinalysis	X	X	X		X	X[a.]

Trial Period:	**Screening**	**Preoperative Treatment**	**Pre-Surgery**	**Surgery**	**Post-Surgery Safety F/U**	**Follow Up Phase[a,m]**
Treatment Cycle/Visit:		**C1D1**				
Scheduling Window:	-28d to -1d	≥7d post-last chemotherapy	+7-14d post-C1D1	+7-14d post-C1D1, 28-42d post-last chemo	14d ±7d post-op	Q90D ±14d post-op for up to 2y
T3 (free and total), FT4 and TSH	X	X	X		X	X[a.]
Tumor Marker: CEA [p.]	X	X	X		X	
Hep B surf Ag, Hep B sur Ab, Hep B core Ab, Hep C RNA	X					
Echocardiogram (ECHO)	X					
Electrocardiogram (ECG)		X[i]				
Disease Status Assessment/ Measurable disease	X		X			X
Tumor Imaging[h]	X[g]					X
Archival Tissue Collection	X[o]					
Biopsy of Liver Metastasis	X			X[e]		
Hepatic metastasectomy				X		
Correlative Studies: Blood Collection		X	X		X	X[k]
Correlative Studies: Stool	X		X		(X)	

Trial Period:	**Screening**	**Preoperative Treatment**	**Pre-Surgery**	**Surgery**	**Post-Surgery Safety F/U**	**Follow Up Phase[a,m]**
Treatment Cycle/Visit:		**C1D1**				
Scheduling Window:	-28d to -1d	≥7d post-last chemotherapy	+7-14d post-C1D1	+7-14d post-C1D1, 28-42d post-last chemo	14d ±7d post-op	Q90D ±14d post-op for up to 2y
Collection and Questionnaire[f]						
Dietary and physical activity questionnaire	X					
Optional Adjuvant TX Recruitment[l,m]					X	

Abbreviations: aPTT – activated partial thromboplastin time; CBC = complete blood count; CEA = carcinoembryonic antigen; ECOG = Easter Cooperative Oncology Group; FT4 = free thyroxine; GI = gastrointestinal; INR = international normalized ratio; LDH = lactate dehydrogenase; MMR = mismatch repair; MSI = microsatellite instability; post-op = post-operation; PT = prothrombin time; T3 = triiodothyronine; TSH = thyroid stimulating hormone; DC = discontinuation; F/U = follow-up; TX = treatment; d = day(s); w = week(s); y = year(s); c = cycle.

a. Follow-up: every effort should be made to collect information regarding disease status for 1 year after pembrolizumab dosing, progressive disease or death, whichever comes first. Follow-up assessments and subsequent anti-neoplastic therapy are at the discretion of the treating investigator. It is advised that patients should be assessed every 90 days (±14 days) for 1 year after liver resection surgery by radiologic CT imaging with IV contrast to monitor disease status. Additional post-operative chemotherapy will be at the discretion of the treating physician. Information regarding post-study anti-neoplastic treatment will be collected if such treatment is initiated. Safety labs and correlative labs will be collected up to 1 year post-pembrolizumab.

b. Screening procedures and assessments must be completed within 28 days prior to C1D1. C1D1 should occur approximately 2 weeks (minimum 1 week) after the final chemotherapy administration (if applicable). Screening CT chest/abdomen/pelvis with IV contrast must be performed and reviewed to confirm candidacy for hepatic resection prior to liver tumor biopsy. Every effort shall be made to collect future biomedical research samples, but failure to collect this sample due to patient refusal or logistical constraints shall not constitute a protocol deviation or violation and does not prevent the patient from enrolling on-study.

c. Obtain standard of care MSI/MMR and expanded RAS/BRAF mutation testing from liver resection specimen if not tested previously. Review pathology report.

d. Baseline medications taken within 28 days of C1D1.

e. Repeat liver biopsy if patient unable to undergo liver resection surgery.

f. Stool collection at following time points ±2 day window: mandatory collection post-chemo/ pre-C1D1 on day minus 4 and day minus 2, mandatory collection post-C1D1/ pre-surgery; optional at post-surgical follow-up.

g. Review of baseline imaging to establish anticipated candidacy for liver resection.

h. Baseline imaging should include a CT chest and IV contrast-enhanced CT or magnetic resonance imaging (MRI) abdomen/pelvis.

i. Can be performed within 7 days prior to C1D1.

j. Pembrolizumab will be administered at a fixed dose of 200 mg (IV) and vactosertib will be taken QD, PO 5 days per week C1D1 through C1D14 . See section 5.1.

k. All participants will be followed for up to 1 year after the last dose of pembrolizumab is administered or up to 2 years after surgery whichever occurs last.

l. Interested participants will complete the pre-treatment procedures outlined in Table 11 below and section 6.1.6.1.

m. Participants who are not interested or are ineligible for the adjuvant treatment cohort will be followed Q90D ±14d post-surgery for up to 2 years as outlined in Table 10 and section 6.1.7.

n. Can be performed within 10 days of C1D1

o. Not needed for eligibility. Every effort should be made to collect archival tissue samples but if sample is not collected or unavailable it should not constitute a protocol deviation.

p. For tumor marker assessments (CEA): record CEA at diagnosis, prior to and after lead-in FOLFOX/CapeOx

Table 11 Flow Chart for Adjuvant Treatment Cohort

Trial Period:	**Pre-Treatment**	**Adjuvant Treatment**				**Post-Treatment**		
Treatment Cycle/Visit:		**C1 D1**	**C2 D1**	**C3 D1**	**C4-8 D1**	**End of TX**	**Safety F/U**	**Follow Up Phase[g]**
Scheduling Window:	2w ±14d post-op	6w ±14d post-op	12w ±3d post-op	18w ±3d post-op	24w-48w ±3d post-op	At DC +7d	30d after DC +7d	D90D ±14d post-last pembro dose for 1y or post-surgery for 2y (whichever occurs last)
Adjuvant TX Informed Consent	X							
Review of Eligibility[a]	X							
Disease Status Assessment/Measurable disease	X[e]							X
Tumor Imaging		X[e]		X[e]	X[e]	X		X
Concomitant Medication Review	X	X	X	X	X	X	X	X
Trial Treatment Administration[f]		X	X	X	X			
Dispense vactosertib		X	X	X	X			
Post-study anticancer therapy status								X
Survival Status								X
Review Adverse Events	X	X	X	X	X	X	X	X
Directed Physical Examination	X	X	X	X	X	X		
Vital Signs and Weight	X	X	X	X	X	X		
ECOG Performance Status	X	X	X	X	X	X		

Trial Period:	**Pre-Treatment**	**Adjuvant Treatment**				**Post-Treatment**		
Treatment Cycle/Visit:		**C1 D1**	**C2 D1**	**C3 D1**	**C4-8 D1**	**End of TX**	**Safety F/U**	**Follow Up Phase[g]**
Scheduling Window:	2w ±14d post-op	6w ±14d post-op	12w ±3d post-op	18w ±3d post-op	24w-48w ±3d post-op	At DC +7d	30d after DC +7d	D90D ±14d post-last pembro dose for 1y or post-surgery for 2y (whichever occurs last)
Pregnancy Test – Urine or Serum	X							
PT/INR and aPTT	X							
Hematology, CBC with Differential and Platelet Count	X	X[c]	X	X	X	X		X
Comprehensive Serum Chemistry Panel (see Table 12)	X	X[c]	X	X	X	X		X
Urinalysis	X	X[c]	X	X	X	X		X
T3, FT4 and TSH	X	X[c]	X	X	X	X		X
Tumor Marker: CEA		X		X	X	X		
ECHO			X			X[d]		
Correlative studies: Blood collection		X[e]		X[e]	X[e]			X

Abbreviations: aPTT – activated partial thromboplastin time; CBC = complete blood count; CEA = carcinoembryonic antigen; ECOG = Easter Cooperative Oncology Group; FT4 = free thyroxine; GI = gastrointestinal; INR = international normalized ratio; LDH = lactate dehydrogenase; pembro = pembrolizumab; post-op = post-operation; PT = prothrombin time; T3 = triiodothyronine; TSH = thyroid stimulating hormone; DC = discontinuation; F/U = follow-up; TX = treatment; d = day(s); w = week(s); y = year(s).

a. Enrollment of eligible patients in the optional adjuvant therapy arm will be based on criteria listed in Section 3.3 and per the investigator's discretion. The rationale for enrolling (or not enrolling) participants in adjuvant therapy will be recorded, along with any supporting test results (e.g., circulating tumor DNA analysis). Ineligible participants will be followed q90d ±14d post-surgery for up to 2y as outlined in Table 10 and section 6.1.7.

b. Test within 72 hours prior to the start of adjuvant treatment

c. Tests do not need to be repeated at adjuvant C1D1 treatment visit if they were performed within 14 days prior to C1D1.

d. ECHO does not need to be repeated at the End of Treatment visit if it was performed within the past 12 weeks.

e. Perform every 12 weeks (i.e., day 1 of every other cycle) during the adjuvant treatment period. For imaging, it will be reviewed to note no evidence of radiographic progression or malignancy as determined by the PI.

f. Pembrolizumab will be administered at a fixed dose of 400 mg (IV) Q6W and vactosertib will be taken PO 5 days per week. See section 5.1.

g. Follow-up: every effort should be made to collect information regarding disease status for 1 year after last pembrolizumab dosing, progressive disease or death, whichever comes first. Follow-up assessments and subsequent anti-neoplastic therapy are at the discretion of the treating investigator. It is advised that patients should be assessed every 90 days (±14 days) for 1 year after liver resection surgery by radiologic CT imaging with IV contrast to monitor disease status. Additional post-operative chemotherapy will be at the discretion of the treating physician. Information regarding post-study anti-neoplastic treatment will be collected if such treatment is initiated Safety labs and correlative labs will be collected up to 1 year post-pembrolizumab.

6.3 Duration of Follow-up

Follow-up visit procedures are listed in Section 6.1.5 and Section 6.1.7. All participants will be followed for up to 1 year after the last dose of pembrolizumab and vactosertib is administered or 2 years after surgery, whichever occurs last. Follow-up assessments will occur according to Section 6.1.5, if discontinuation occurs post-surgery, or according to Section 6.1.7 if discontinuation occurs during and/or after post-adjuvant treatment. Follow-up assessments will occur until PD, death, withdrawing consent or becoming lost to follow-up, whichever occurs first.

6.4 Withdrawal Criteria

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to be monitored in this study and participate in the study visits and procedures as specified in Section 6.1.5, if discontinuation occurs during post-surgery, and as specified in Section 6.1.6.3 and Section 6.1.6.4, if discontinuation occurs during and/or after post-adjuvant treatment.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study intervention, but continue to be monitored in the study for any of the following reasons, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a patient's request to end participation, or a patient's non-compliance.

6.4.1 Withdrawal from the Study

A patient must be withdrawn from the study if the patient or patient's legally acceptable representative withdraws consent from the study.

If a patient withdraws from the study, they will no longer receive study treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study are outlined in Section 6.2 (post-surgery visit). The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 6.3.2.

6.4.2 Lost to Follow-up

If a patient fails to return to the clinic for a required study visit and/or if the site is unable to contact the patient, the following procedures are to be performed:

- The site must attempt to contact the patient and reschedule the missed visit. If the patient is contacted, the patient should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the patient at each missed visit (e.g., phone calls and/or a certified letter to the patient's last known mailing address or locally equivalent methods). These contact attempts should be documented in the patient's medical record.
- Note: A patient is not considered lost to follow-up until the last scheduled visit for the individual patient. The amount of missing data for the patient will be managed via the pre-specified data handling and analysis guidelines.

6.5 Usage of Concurrent/Concomitant Medications/Vaccinations

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the treatment period. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from trial therapy may be required. The investigator should discuss prohibited medications/vaccinations with the Merck Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary physician. However, the decision to continue the patient on study treatment requires the mutual agreement of the investigator, Merck, and the patient.

6.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a patient's welfare may be administered at the discretion of the investigator in keeping with the 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, 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 90 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.5.

6.5.2 Prohibited Medications

If during the course of the trial, a patient requires treatment with following medicines for a limited period of time, it should not be given concurrently with the study treatment and its use should be reviewed with the Sponsor-Investigator who will provide guidance based on the half-life of the medication as well as other clinical considerations. The Investigator is also advised to consider

alternative medicines. Listed below are specific restrictions for concomitant therapy or vaccination during the study:

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab and vactosertib
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live or live attenuated vaccines within 30 days prior to the first dose of triaQl treatment and while participating in the trial. Note: killed vaccines are allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with Merck.
- Liver directed therapy such as radiotherapy or yttrium-90
- Rifaximin or lactulose to control encephalopathy
- Strong CYP3A inhibitors including but not limited to clarithromycin, itraconazole, ketoconazole, nefazodone, nelfinavir, saquinavir, voriconazole - *Grapefruit juice is not allowed in the study. The topical use of medications, such as 2% ketoconazole cream, may be allowed when discussed with the Sponsor-Investigator.*
- Potent CYP3A inducers, including but not limited to carbamazepine, phenytoin, rifampin - *St. John's Wort is not allowed*
- Drugs that prolong QT Interval and have a risk of Torsades de Pointes

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial.

All concomitant medications received within 28 days prior to the first dose of study treatment and up to 30 days after the last dose of study treatment should be recorded. Concomitant medications administered 90 days after the last dose of study treatment should be recorded for SAEs and ECIs as defined in Section 7.5.

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

6.6 Dietary Restrictions

There are no dietary restrictions on this study. Patients should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

6.7 Pregnancy/Contraception

6.7.1 Contraception

Pembrolizumab and vactosertib 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.

Patients 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, patients of childbearing potential must adhere to the contraception requirement from the time of screening throughout the total duration of the drug treatment and the drug washout period. If there is any question that a patient of childbearing potential will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

For this trial, male patients will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

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

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

OR

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

OR

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

Those who, in the opinion of the investigator, are sexually active and at risk for pregnancy, must agree to use highly effective contraception throughout the study and continue for at least 90 days after the last dose of vactosertib or 120 days after the last dose of pembrolizumab, whichever is later. Female and male patients of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, by complying with one of the following effective contraception methods:

(1) Practice abstinence† from heterosexual activity;

OR

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

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- intrauterine device (IUD)

- vasectomy of a female patient's male partner
- contraceptive rod implanted into the skin

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

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

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the patient's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and IRBs/ERCs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for patients participating at sites in this country/region.

Patients 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, patients of childbearing potential must adhere to the contraception requirements from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of study medication. If there is any question that a patient of childbearing potential will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

6.7.2 Use in Pregnancy

If a patient inadvertently becomes pregnant while on pembrolizumab-based treatment, the patient will be immediately discontinued from study treatment. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck without delay and within 24 hours if the outcome is a SAE (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The 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 Merck. If a male patient impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to Merck and followed as described in Section 7.5.

6.7.3 Use in Nursing Women

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

6.7.4 Pregnancy Tests

All women who are being considered for participation in the trial, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours of each cycle of trial treatment and 30 days post treatment. If a urine test is positive or not evaluable a serum test will be required. Patients must be excluded/discontinued from the study in the event of a positive or borderline-positive test result.

6.8 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 patients
4. Plans to modify or discontinue the development of the study drug

In the event of Merck's decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to patient treatment can be made.

6.9 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per patient can be found in the laboratory manual.

Refer to the Trial Flow Chart (Table 10) for the schedule of laboratory assessments.

6.9.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 12.

Table 12 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	

Hematology	Chemistry	Urinalysis	Other
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total triiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡ *(CO_2 or bicarbonate)*	results are noted	Free thyroxine (T4)
Absolute Lymphocyte Count	Creatinine	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		CEA
	Calcium		Hepatitis B surface antigen (HBsAg)
	Chloride		Hepatitis B surface antibody (HBsAb)
	Fasting glucose		Hepatitis B core antibody (HBcAb)
	Phosphorus		Hepatitis C virus RNA
	Potassium		Blood for correlative science
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

Abbreviations: aPTT = activated partial thromboplastin time; INR = international normalized ratio; PT = prothrombin time; WBC = white blood cell.

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required within 72 hours prior to Day 1 of cycle 1.

‡ If considered standard of care in your region.

Screening hematology, chemistry and urinalysis laboratory tests should be performed within 10 days prior to treatment. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to dose of trial treatment. Unresolved abnormal laboratory values that are drug-related AEs should be followed until resolution. Laboratory tests do not need to be repeated after the end of treatment if laboratory results are within normal range.

7 Reporting and Documentation of Results

7.1 Evaluation of Efficacy (or Activity)

The 2-year RFS rate is defined as the proportion of patients without radiographic PD within 2 years of liver resection surgery with curative intent.

Pathologic response rate is defined as the proportion of patients with no residual cancer cells (complete response) or 1% to 49% residual cancer cells remaining (major response) in the liver resection specimen.

7.2 Evaluation of Safety

7.2.1 Sponsor Responsibility for Reporting Adverse Events

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

Analyses will be performed for all patients having received at least 1 dose of study drug. The study will use the NCI CTCAE v5.0 for reporting of non-hematologic AEs and modified criteria for hematologic AEs, see Section 7.3.1.1.

7.3 Definitions of Adverse Events

7.3.1 Adverse Event

An AE 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 AE 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 AE.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered AEs. 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's 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 as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an AE.

7.3.1.1 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI CTCAE, version 5.0 (Table 13). Any AE which changes NCI CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

All AEs regardless of NCI CTCAE grade must also be evaluated for seriousness.

Table 13 Evaluating Adverse Events

V5.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid 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; unplanned 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 Pembrolizumab that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the patient, 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 unplanned hospitalization 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 for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of pembrolizumab and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of patient taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. 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 to the Sponsor and to Merck within 2 working days..	
	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 patient 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 pembrolizumab to be discontinued?	
Relationship to pembrolizumab	Did pembrolizumab cause the adverse event? The determination of the likelihood that pembrolizumab 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 pembrolizumab and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely pembrolizumab caused the adverse event (AE):	
	Exposure	Is there evidence that the patient was actually exposed to pembrolizumab 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 pembrolizumab? 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

7.3.2 Adverse reaction

An adverse reaction is defined as any AE caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

7.3.2.1 Suspected

A suspected adverse reaction is defined as any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of Investigational New Drug Application (IND) safety reporting, "reasonable possibility" indicates that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

7.3.2.2 Unexpected

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the IB or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

"Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the IB. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the IB.

Some AEs are listed in the IB as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the ACE inhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes.

7.3.3 Serious Adverse Event

An AE or suspected adverse reaction is considered *serious* if, in the view of either the investigator or Merck, it results in any of the following outcomes:

- In death
- Is life-threatening adverse event (Section 7.3.3.1)
- In persistent or significant disability/incapacity;
- An unplanned inpatient hospitalization or prolongation of an existing inpatient hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Is a congenital anomaly/birth defect
- Is another important medical event

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or unplanned surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Note: In addition to the above criteria, AEs meeting either of the below criteria, although not serious per International Council for Harmonisation (ICH) definition, are reportable to Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.

- Is a new cancer (that is not a condition of the study);

- Is associated with an overdose.

Additionally, any SAE, considered by an Investigator who is a qualified physician to be related to Merck's product that is brought to the attention of the Investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Merck clinical team.

All patients with SAEs must be followed up for outcome.

7.3.3.1 Life-threatening

An AE or suspected adverse reaction is considered *life-threatening* if, in the view of either the investigator or Merck, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.3.4 Definition of an Overdose Definition

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Vactosertib overdose is defined as any daily dose more than 900 mg or more than 1.5 times of weekly indicated dose. The effects of an overdose with vactosertib are unknown.

7.3.5 Events of Clinical Interest

Selected non-serious and SAE are also known as ECIs.

Events of clinical interest that must be reported to Merck include:

1. An overdose of Merck's product, as defined in Section 7.3.4, that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT lab value that is greater than 5 × ULN and an elevated total bilirubin lab value that is greater than or equal to 2 × ULN and, at the same time, an ALP lab value that is less than 2 × ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   Note: Liver function test abnormalities are expected after hepatic metastatectomy. Therefore, AST, ALT or total bilirubin elevations occurring after hepatic metastatectomy and considered by an investigator who is a qualified physician to be related to surgery (unlikely related to pembrolizumab), must be reported to the Sponsor and to Merck at the time of the first post-surgical safety follow-up visit or within 30 days of hepatic metastatectomy surgery, whichever comes first.

   *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.

Events of clinical interest that must be reported to MedPacto include:

1. Any abnormal changes in cardiac valves detected by ECHO which will be conducted at the screening, cycle 2 during adjuvant treatment, and EOT.

7.3.6 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section 7.5, unless there is evidence suggesting a causal relationship between the drug and the event.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study. Hospitalization related to convenience (e.g. transportation issues etc.) or planned surgery will not be considered a SAE.

The Investigator will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the patients in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Merck as a SAE within 2 working days of determination that the event is not progression of the cancer under study.

7.4 Recording of an Adverse Event

All Grade 3 and above AEs will be entered into OnCore®, whether or not the event is believed to be associated with use of the study drug. Data about these events and their severity will be recorded using the NCI CTCAE v5.0.

The Investigator will assign attribution of the possible association of the event with use of the investigational drug, and this information will be entered into OnCore® using the classification system listed in Table 14.

Table 14 Classification System for Assigning Attribute to Adverse Events

Relationship	Attribution	Description
Unrelated to investigational drug/intervention	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely	The AE *is doubtfully related* to the intervention
Related to investigational drug/intervention	Possible	The AE *may be related* to the intervention
	Probable	The AE *is likely related* to the intervention
	Definite	The AE *is clearly related* to the intervention

Signs or symptoms reported as AEs will be graded and recorded by the Investigator according to the NCI CTCAE v5.0. When specific AEs are not listed in the NCI CTCAE they will be graded by

the Investigator as *none*, *mild*, *moderate* or *severe* according to the following grades and definitions:

Grade 0	No AE (or within normal limits)
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (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

7.5 Reporting Adverse Events to Merck

All AEs, SAEs and other reportable safety events that occur after the ICF is signed but before treatment allocation must be reported by the investigator if the patient is receiving placebo run-in or other run-in treatment, if the event cause the patient to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of treatment allocation through 30 days following cessation of study treatment must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Merck clinical team if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Merck clinical team.

All initial and follow-up AEs, SAEs and other reportable safety events will be recorded and reported to the Merck clinical team or designee within the timeframes as indicated in Table 15.

Table 15 Reporting Time Periods and Timeframes for Adverse Events and Other Reportable Safety Events to Merck

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization / Allocation through Protocol-Specified Follow-up Period	Reporting Time Period: After the Protocol Specified Follow-up Period	Timeframe to Report Event and Follow-up Information to Merck[a]:
Serious Adverse Event (SAE)	Report if: - due to protocol-specified intervention - causes exclusion - patient is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome.)	Within 24 hours of learning of event*
Non-Serious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - patient is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 days of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential DILI - Require regulatory reporting	Not required	Within 24 hours of learning of event*

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization / Allocation through Protocol-Specified Follow-up Period	Reporting Time Period: After the Protocol Specified Follow-up Period	Timeframe to Report Event and Follow-up Information to Merck[a]:
Event of Clinical Interest (Do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 days of learning of event*
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 days of learning of event
Pregnancy/ Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event

a. **SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety [redacted].**

* Note: Serious AEs and ECIs occurring after hepatic metastatectomy, considered by an investigator who is a qualified physician to be related to surgery (unlikely related to pembrolizumab), must be reported to the Sponsor and to Merck Global Safety at the time of the first post-surgical safety follow-up visit or within 30 days of hepatic metastatectomy surgery, whichever comes first.

7.5.1 Reporting of Pregnancy and Lactation

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a patient (spontaneously reported to the investigator or their designee) that occurs during the trial are reportable to the Merck clinical team.

All reported pregnancies 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 Merck clinical team by either electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.6 Reporting Adverse Events to MedPacto

All SAEs and AESIs that occur from the time of the patient signing the informed consent form until 90 days after the last dose of IP, whether or not considered causally related to vactosertib, will be reported to the MedPacto via e-mail or fax within one calendar day (i.e., immediately but no later than 24 hours) of the investigator's knowledge of the event. For fatal or life-threatening AEs where important or relevant information is missing, active follow-up should be undertaken immediately. The Investigator or designee will submit any updated SAE or AESI data to the MedPacto via e-mail or fax within one calendar day (i.e., immediately but no later than 24 hours) of the investigator's knowledge of the information.

If an SAE or AESI starts/occurs after the defined safety follow-up period noted above and is considered to be due to a late onset toxicity to vactosertib, it should be recorded in the eCRFs and reported to the MedPacto.

Investigators are not obligated to actively seek AEs in former study patients. However, if the Investigator learns of any SAE, including a death, or AESI at any time after a patient's last visit and he/she considers the event to be reasonably related to vactosertib, it should be reported to the MedPacto.

A copy of all SAEs should be submitted to MedPacto at the contact information below.

MedPacto contact:

[redacted]

7.7 Follow-up of Adverse Events

All AEs will be followed with appropriate medical management until resolved. All AEs that occur prior to the post-surgery follow-up visit should be recorded. Patients with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0 to 1 or until the beginning of a new anticancer therapy, whichever occurs first. Serious AEs that occur within 90 days of the end of treatment or before initiation of a new anticancer treatment should also be followed and recorded.

Patients removed from study for unacceptable AEs will be followed until resolution or stabilization of the AE. For selected AEs for which administration of the investigational drug was stopped, a re-challenge of the patient with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

7.8 Adverse Events Monitoring

All AEs, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, as noted above.

The Investigator will assess all AEs and determine reportability requirements to the UCSF Data and Safety Monitoring Committee (DSMC) and UCSF's Institutional Review Board, the IRB; and, when the study is conducted under an IND, to the FDA if it meets the FDA reporting criteria.

All AEs entered into OnCore® will be reviewed by the Helen Diller Family Comprehensive Cancer Center Site Committee on a weekly basis. The Site Committee will review and discuss at each weekly meeting the selected toxicity, the toxicity grade, and the attribution of relationship of the AE to the administration of the study drug(s).

All grade(s) 3-5 AEs 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 the attribution of relationship of the AE to the administration of the study drug(s).

In addition, all suspected adverse reactions considered "serious" entered into OnCore®, will be reviewed and monitored by the DSMC on an ongoing basis and discussed at DSMC meetings, which take place every six weeks.

Reporting to the Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Reporting to UCSF Institutional Review Board

The Principal Investigator must report events meeting the UCSF IRB definition of "Unanticipated Problem" (UP) within 10 business days of his/her awareness of the event.

Expedited Reporting to the Food and Drug Administration

If the study is being conducted under an IND, the Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction (as defined in Section 7.3.2.1)
- Unexpected (as defined in Section 7.3.2.2)
- Serious (as defined in Section 7.3.3)

If the AE does not meet all 3 of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

8 Statistical Considerations and Evaluation of Results

8.1 Study Endpoints

Primary endpoint: the proportion of patients with a >2 fold increase in the number of tumor infiltrating TILs cells per unit area (5 high power fields) post- vs. pre-pembrolizumab-based neoadjuvant treatment tumor specimens.

Secondary endpoints:

- Safety: An important secondary objective of this study is to characterize the safety and tolerability of pembrolizumab-based treatment in patients with resectable liver metastases. The safety analysis will be based on patients who experience toxicities as defined by NCI CTCAE 5.0 criteria (Appendix 3). Safety will be assessed by quantifying the toxicities and grades experienced by patients who have received pembrolizumab-based treatment, including all AEs and ECIs.

  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, and fatal AEs. Furthermore, specific immune-related AEs (irAEs) will be collected and designated as immune-related ECIs as described in Section 7.3.5.

  Surgical complications will be characterized using Clavien-Dindo criteria (Appendix 4). Early stopping rules have been defined to mitigate risk of perioperative complications (see section 8.3).

- Efficacy: Endpoints for preliminary estimation of the clinical efficacy of pembrolizumab-based treatment in the perioperative setting for patients with CRC with resectable hepatic metastases are as follows:

  - Pathologic response rate [34]
  - R0 resection rate
  - 2-year RFS with and without adjuvant pembrolizumab-based therapy
  - Objective Response Rate

Exploratory endpoints:

- Change in T-cell repertoire in pre-neoadjuvant treatment liver biopsies vs. surgical tumor specimens as well as in blood samples from the same time-points
- Change in PD-L1 expression and other molecular markers in pre-neoadjuvant treatment liver biopsies vs. surgical tumor specimens
- Correlate changes in microbiome composition and diversity (by metagenomic sequencing and untargeted metabolomics of stool collected before, during, and after immunotherapy), with diet and lifestyle factors determined by self-reported questionnaires.
- Explore the correlation between change in tumor infiltrating TILs and T-cell repertoire.

8.1.1 Study Design

This is a single-site, single-arm, open-label Phase 2 clinical trial of pembrolizumab + vactosertib in patients with CRC with resectable hepatic metastases.

8.1.2 Randomization

This is a non-randomized study.

8.1.3 Stratification Factors

None. There are no planned patient stratification factors.

8.2 Determination of Sample Size and Accrual Rate

8.2.1 Sample Size and Power Estimate

For the primary objective, there will be a binary classification (28). A patient will be considered to have a “positive response” if there is a ≥2-fold increase (from pre- to post-treatment) in the number of TILs, and a “negative response” if there is <2-fold increase. Obtaining paired specimens from 17 patients will be sufficient to determine whether 40% or more achieve a “positive response,” compared to a null hypothesis of 10% or less. This comparison has a power of 0.91 at a significance level of 0.05 for a directional binomial test.

8.2.2 Replacement Policy

We plan to enroll 19 patients to achieve our goal of 17 patients evaluable for the primary study outcome. If more than 2 patients turn out not to be evaluable for the primary study outcome (i.e., do not have available post-pembrolizumab-based neoadjuvant treatment tumor tissue available for analysis), they may be replaced upon discussion with the study Principal Investigator and JSC.

8.2.3 Accrual estimates

Based on current estimates of the number of eligible patients seen at UCSF annually, as well as strong interest among patients in receiving immunotherapy, we anticipate completing accrual within 1 year.

8.3 Interim Analyses and Stopping Rules

The trial will be stopped early if 2 of the first 6 patients fail to undergo liver resection surgery within 6 weeks of their final chemotherapy treatment (if applicable) due to AEs attributed to pembrolizumab-based treatment, or experience Grade IV-V surgical complications according to Clavien-Dindo classification attributed to pembrolizumab -base treatment (Appendix 4).

Of particular significance to this study, enrolling patients being treated with curative intent, are perioperative complications attributed to pembrolizumab-based treatment. These may include delaying surgery due to pre-operative AEs and complications during or after surgery attributed to pembrolizumab-based treatment. Early stopping rules have been defined to mitigate risk of perioperative complications. The study will be stopped and the approach will be re-evaluated if 2 or more of the first 6 patients experience any one of the following:

- A delay in planned surgery beyond the 6-week window from final chemotherapy (if applicable), due to any grade toxicity attributable to study treatment. Delays in surgery due to other reasons (scheduling, available O.R time, patient preference) will not count.
- Grade IV and V surgical complications according to Clavien-Dindo classification (Appendix 4). *Note*: Surgical complications associated with liver metastastectomy are very common, and we recognize that it may be difficult to attribute any such complications to preoperative administration of pembrolizumab. Therefore, the occurrence of such events may not necessarily require stopping the study early, but will be discussed amongst members of the JSC, with particular attention paid to specific complications such as liver failure, severe colitis, etc.

Enrollment will be paused for 4 weeks after the sixth patient undergoes surgery (or receives their last dose of pembrolizumab if unable to undergo surgery). During this interval the study investigators will meet with the participating surgeons to review the first 6 cases. A recommendation will be made regarding whether or not to enroll additional patients and if any changes are needed to optimize safety or feasibility.

8.4 Analyses Plans

8.4.1 Analysis Population

The analysis population for the primary outcome will be all patients with pre- and post-pembrolizumab-based neoadjuvant treatment tumor specimens that are evaluable for TILs.

The All Patients as Treated (APaT) population will be used for the analysis of the secondary safety/toxicity outcomes and the clinical efficacy endpoint, ORR. The APaT population consists of all patients who received at least one dose of pembrolizumab and/or vactosertib and at least one laboratory or vital sign measurement. To assess change from baseline, a baseline measurement is also required.

Patients who undergo surgical resection of liver metastases will be evaluable for the secondary clinical efficacy endpoints: pathologic response rate, R0 resection rate and RFS at 2-years.

Safety analyses will be performed for all patients having received at least one dose of pembrolizumab and/or vactosertib. The study will use the NCI CTCAE v5.0.

8.4.2 Primary Analysis (or Analysis of Primary Endpoints)

TILs will be analyzed in pre- and post-pembrolizumab-based neoadjuvant treatment tumor specimens. Testing for evidence of an increase in CD3+ T-cells will be conducted using a paired t-test and the Wilcoxon signed-rank test and results compared for consistency. Testing for a difference in the central tendency of the change in CD3+ T-cells for responders vs. non-responders under either the objective radiographic or pathological response definitions of will use a two-sample t-test and a Wilcoxon rank-sum test and results compared for consistency. All tests will be conducted at a nominal significance level of 0.05 with no adjustment for multiplicity.

8.4.3 Secondary Analysis (or Analysis of Secondary Endpoints)

The study will use descriptive statistics to report on the safety/toxicity and efficacy of pre-operative pembrolizumab-based treatment, including adverse events by NCI CTCAE (v 5.0) criteria and perioperative complications; pathologic response; R0 resection rate; and 2-year RFS. The sample size of each cohort will be too small to compare these results to historic data (i.e. from the Nordlinger EORTC study). However, we would consider the approach feasible if (1) ≥14 of 17 patients (≥83%) are able to successfully undergo R0 resection within 6 weeks of last chemotherapy administration (if applicable); and (2) the rate of serious postoperative complications attributable to pembrolizumab-based treatment does not exceed 33% (6 of 17 patients).

The study will also use descriptive statistics to compare 2-year RFS rates in patients who do or do not receive adjuvant pembrolizumab-based therapy.

8.4.4 Exploratory Analysis (or Analysis of Exploratory Endpoints)

Wilcoxon rank-sum test will be used to assess whether there is a relationship between any of the immune cell subsets and objective radiographic response as well as pathologic response. Cox-proportional hazard models will be applied to assess if there is relationship between any of the immune cell subsets and RFS. Parallel analysis will be performed for PD-L1 expression. Wilcoxon rank-sum test will also be used to assess whether the T cell receptor clonality diversity index is different between responders vs. non-responders (defined by objective radiographic response or pathologic response), and between patients who have progression within 1-year vs. those whose disease has not progressed. Additional analyses of immunocorrelative data are detailed in the Lab Manual.

9 Study Management

9.1 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 IRB for the protocol, written ICF, patient recruitment materials, and any other written information to be provided to patients before any protocol related procedures are performed on any patients.

The clinical investigation will not begin until either FDA has determined that the study under the 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.

9.2 Institutional Review Board Approval

The protocol, the proposed ICF, 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 IRB. 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.

9.3 Informed Consent

A signed informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. The investigator or qualified designee will explain the study to the patient and answer all of his/her questions.

All patients 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 ICF 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.

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.

9.4 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 5 working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

9.5 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.

9.6 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 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 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 Principal Investigator 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.

9.7 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 2 Data and Safety Monitoring Plan for a Phase 2 or 3 Institutional Study, for additional information.

9.8 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 patients, 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.

9.9 Coordinating Center Documentation of Distribution

It is the responsibility of the Study Chair to maintain adequate files documenting the distribution of study documents as well as their receipt (when possible). The HDFCCC recommends that the Study Chair maintain a correspondence file and log for each segment of distribution (e.g., FDA, drug manufacturer, participating sites, etc.).

Correspondence file: should contain copies (paper or electronic) of all protocol versions, cover letters, amendment outlines (summary of changes), etc., along with distribution documentation and (when available) documentation of receipt.

Correspondence log: should be a brief list of all documents distributed including the date sent, recipient(s), and (if available) a tracking number and date received.

At a minimum, the Study Chair must keep documentation of when and to whom the protocol, its updates and safety information are distributed.

10 Protection of Human Patients

10.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all patients 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 patient'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.

10.2 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.

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Appendices

Appendix 1: Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
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)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active 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	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

Appendix 2: UCSF Data and Safety Monitoring Plan for a Phase 2 or 3 Institutional Study

2. 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 studies. A summary of DSMC activities for this study includes:

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

3. 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 2 and 3 studies are designated with a moderate risk assessment. The data is audited semiannually with a random selection of twenty percent of the participants audited (or at least three participants if the calculated value is less than three). The DSMC Monitor/Auditor will audit a maximum of 5 cycles of treatment in the participants selected for the review, or until the selected participants discontinue study participation or the trial is closed with the IRB. Additionally, 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. Additionally, a regulatory audit will occur on a biennial basis to review all regulatory documents for the trial.

4. Review and Oversight Requirements

1.1 Adverse Event Review and 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.

1.2 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.

1.3 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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[DSMP language updated 08/21/2020]

Appendix 3: Common Terminology Criteria for Adverse Events V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting.(http://ctep.cancer.gov/reporting/ctc.html)

Appendix 4: The Clavien-Dindo Classification of Surgical Complications

Full Scale			Contracted Form	
Grades	**Definition**		**Grades**	**Definition**
Grade I:	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.		**Grade I:**	Same as for Full Scale
Grade II:	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.		**Grade II:**	Same as for Full Scale
Grade III:	Requiring surgical, endoscopic or radiological intervention		**Grade III:**	Grades IIIa & IIIb
Grade III-a:	intervention not under general anesthesia			
Grade III-b:	intervention under general anesthesia			
Grade IV:	Life-threatening complication (including CNS complications)‡ requiring IC/ICU-management		**Grade IV:**	Grades IVa & IVb
Grade IV-a:	single organ dysfunction (including dialysis)			
Grade IV-b:	multi organ dysfunction			

Full Scale			Contracted Form	
Grades	**Definition**		**Grades**	**Definition**
Grade V:	Death of a patient		**Grade V:**	Same as for Full Scale
Suffix 'd':	If the patients suffers from a complication at the time of discharge, the suffix “d” (for ‘disability’) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.			
‡ brain hemorrhage, ischemic stroke, subarachnoid bleeding, but excluding transient ischemic attacks (TIA);IC: Intermediate care; ICU: Intensive care unit. Dindo D., Demartines N., Clavien P.A.; Ann Surg. 2004; 244: 931-937				