TITLE: A Phase Ib\II Study of Cetuximab and Pembrolizumab in Metastatic Colorectal Cancer.

Roswell Park Cancer Institute

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Sponsor: **Roswell Park Cancer Institute**

Industry/Other Supporter: **Merck & Co., Inc.**

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SYNOPSIS

Title / Phase	A Phase Ib\II Study of Cetuximab and Pembrolizumab in Metastatic Colorectal Cancer
Roswell Park Cancer Institute Study Number	I 274515
Roswell Park Cancer Institute Investigator	Christos Fountzilas, MD
Sponsor	Roswell Park Cancer Institute
Industry/ Other Supporter	Merck & Co., Inc.
Study Drugs	Pembrolizumab Cetuximab
Objectives	**Primary:** • To estimate the objective response rate of patients with metastatic colorectal cancer treated with pembrolizumab and cetuximab. • To estimate the 6-month progression-free survival (PFS) rate of patients with metastatic colorectal cancer treated with pembrolizumab and cetuximab. • To examine the adverse event profile of combining pembrolizumab and cetuximab. **Secondary:** • To examine the PFS of patients with metastatic colorectal cancer treated with pembrolizumab and cetuximab. • To determine the objective response rate by immune-related response criteria (irRECIST) of patients with metastatic colorectal cancer treated with pembrolizumab and cetuximab • To examine the overall survival of patients with metastatic colorectal cancer treated with pembrolizumab and cetuximab. **Exploratory:** • To identify tumor and peripheral blood biomarkers of response and/or resistance to the study treatment.
Study Design	Phase Ib\II study, single arm, multi-institutional study.
Target Accrual and Study Duration	We will target 42 eligible and treated patients, but will require at least 38 eligible and treated patients. An initial 9 patient phase Ib study is planned to ensure safety of the combination. This will be followed by further enrollment of 33 patients on the phase II study. It is expected that this study will enroll 1-2 patients per month. With this accrual rate, this study is anticipated to finish accrual in 4 years. Assuming a minimum of 6 months of follow-up in all patients, the study will take 4 years to complete in total.
Study Procedures	**Disease Evaluation:** CT chest/abd/pelvis (or acceptable alternative) every 9 weeks (+/- 7 days) **Physical Examination (including vital signs, and body weight):** Baseline, Day 1 of all Cycles, End of Treatment, Safety Follow-Up

	Medical History: Baseline **Hematology:** Baseline, Day 1 of all Cycles, End of Treatment, Safety Follow-Up **CMP:** Baseline, Day 1 of all Cycles, End of Treatment, Safety Follow-Up, Safety Follow-up #2 **BMP:** Days 8 and 15 of all cycles **TSH, Total T3, Free T4:** Baseline, Day 1 of every other cycle (Beginning with Cycle 2, i.e. 2, 4, 6, 8…etc), Safety Follow-Up **Urinalysis:** Baseline **CEA:** Day 1 of all Cycles **Tumor biopsy:** Within 30 days of Cycle 1, Day 1, Cycle 4 day 1 (+/- 7 days) **Biomarker Sampling;** Cycle 1Day 1, Cycle 2 Day 1, Cycle 4 Day 1 **Pregnancy Test (serum):** Baseline **ECOG Performance Status:** Baseline, End of Treatment **CT Scan (chest, abdomen, pelvis):** Baseline (within 30 days of day 1), every 9 weeks after cycle 1-day 1 (± 7 days) **Concomitant Medications:** Baseline, Day 1 of all Cycles, End of Treatment, Safety Follow-up **Adverse Events:** Baseline, Day 1 of all Cycles, End of Treatment, Safety Follow-up **Tumor Molecular Assessment:** MSI/MMR status documented or testing requested: baseline
Statistical Analysis	**Sample Size Determination:** We utilize two primary endpoints for this study: the proportion of patients achieving complete or partial RECIST objective response rate and the proportion surviving progression-free for at least six months. While the addition of pembrolizumab to cetuximab may have cytotoxic effect, it may act primarily in a cytostatic fashion; therefore, it is important to consider both endpoints, and thus declare the agent worthy of further investigation if it shows activity on either endpoint. We utilize a single-stage version of the bivariate design of Sill, et al (2012). Based on historical data, the response rate for cetuximab alone in this patient population is approximately 20%, and the proportion of patients surviving progression-free for at least six months is approximately 30%. We will target 42 eligible and treated patients, but will require at least 38 eligible and treated patients in order to have ≥80% power to detect activity based on response alone, ≥80% power to detect activity based on 6-month PFS alone, and ≥97% power if the regimen is active on both endpoints. This assumes independence of the two endpoints; slight losses of power occur for moderate dependence between the two endpoints. Type I error is controlled at <0.10. **Randomization:** The study is not randomized. **Efficacy Analysis:** The primary endpoints of objective tumor response and 6-month PFS will be tested using an exact binomial test. **Safety Analysis:** The frequency of AEs will be tabulated by grade across all dose levels and cycles. All patients who receive any study treatment will be considered evaluable for toxicity.

INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM

Participant Name: (Network sites use participant initials): _____

Medical Record No.: (Network sites use participant ID): _____

Title: A Phase II Study of Cetuximab and Pembrolizumab in Metastatic Colorectal Cancer.

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Have a pathologically confirmed diagnosis of colorectal cancer, which is metastatic or otherwise unresectable	
☐	☐	☐	2. Have received at least 1 prior systemic therapy in the metastatic or unresectable disease setting. Patients who have recurred within six months of adjuvant chemotherapy are not required to have received an additional line of chemotherapy	
☐	☐	☐	3. RAS wild-type. Both KRAS and NRAS testing are necessary. The presence of pathogenic mutations in KRAS or NRAS is exclusionary. Primary tumor or metastatic tumor may be tested.	
☐	☐	☐	1. Appropriate for anti-EGFR therapy: Naive to anti-EGFR therapy (cetuximab or panitumumab) or a candidate for rechallenge by virtue of the following: 2. the investigator deems anti-EGFR retreatment with cetuximab to be a reasonable standard of care option AND 3. outcome of prior anti-EGFR therapy was not rapid progression (i.e. <= 3 months on therapy) AND 4. prior anti-EGFR therapy was administered > 6 months prior to the start of protocol therapy	
☐	☐	☐	4. Age ≥ 18 years of age.	
☐	☐	☐	5. Have an ECOG Performance Status ≤ 2. Refer to **Appendix B**	
☐	☐	☐	6. Have measurable disease per RECIST 1.1 criteria present	
☐	☐	☐	7. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. Newly-obtained is defined as a specimen obtained up to 30 days prior to initiation of treatment on Day 1.	
☐	☐	☐	8. Have the following clinical laboratory values (all screening labs must be performed within 14 days of treatment initiation): • Hemoglobin ≥ 8 g/ dL • Absolute neutrophil count ≥ 1000/ mm^3 • Platelet count ≥ 100,000/ mm^3 • Serum creatinine clearance ≥ 15 mL/min (refer to **Appendix C**: Cockroft-Gault Equation). • Serum total bilirubin ≤ 1.5 ULN ***or***, direct bilirubin ≤ ULN for participants with total bilirubin levels > 1.5 ULN. • AST (SGOT) and ALT (SGPT) ≤ 2.5 ULN ***or***, ≤ 5 ULN for	

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
			participants with liver metastases	
☐	☐	☐	9. Female participants of childbearing potential are to have a negative serum pregnancy test.	
☐	☐	☐	10. Female participants of child-bearing potential must agree to use an acceptable method of birth control, be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of pembrolizumab and 180 days after the last dose of cetuximab. Participants of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately	
☐	☐	☐	11. Male participants must agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of pembrolizumab and 180 days after the last dose of cetuximab	
☐	☐	☐	12. Participant or legal representative must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.	

Investigator Signature: _____ Date: _____

Printed Name of Investigator: _____

INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM

Participant Name: (Network sites use participant initials): _____

Medical Record No.: (Network sites use participant ID): _____

Title: A Phase II Study of Cetuximab and Pembrolizumab in Metastatic Colorectal Cancer.

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Participants who have had chemotherapy, targeted therapies, radiotherapy, or used an investigational device within 2 weeks prior to the first dose of treatment or those who have not recovered from adverse events (i.e., ≤ Grade 1 or at baseline) due to agents administered more than 2 weeks earlier. Note: Participants with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study	
☐	☐	☐	2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.	
☐	☐	☐	3. Has a known history of active TB (Bacillus Tuberculosis)	
☐	☐	☐	4. Hypersensitivity to pembrolizumab or any of its excipients	
☐	☐	☐	5. Prior severe infusion reaction to cetuximab	
☐	☐	☐	6. Has a known additional malignancy that requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer	
☐	☐	☐	7. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability	
☐	☐	☐	8. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment	
☐	☐	☐	9. Has known history of, or any evidence of active, non-infectious pneumonitis.	
☐	☐	☐	10. Uncontrolled clinically significant intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, unstable cardiac arrhythmia, or psychiatric illness, substance abuse disorders or social situations that	

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
			would limit compliance with study requirements	
☐	☐	☐	11. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment	
☐	☐	☐	12. Has a known history of Human Immunodeficiency Virus (HIV or HIV 1/2 antibodies). Testing is not required	
☐	☐	☐	13. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected). Testing is not required	
☐	☐	☐	14. Has received a live vaccine within 30 days of planned start of study therapy (Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and shingles are not allowed)	
☐	☐	☐	15. Received an investigational agent within 30 days prior to starting study treatment	
☐	☐	☐	16. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator	
☐	☐	☐	17. Unwilling or unable to follow protocol requirements	

Participant meets all entry criteria: ☐ **Yes** ☐ **No**
If "NO", do not enroll participant in study.

Investigator Signature: _____ **Date:** _____

Printed Name of Investigator: _____

TABLE OF CONTENTS

IN-TEXT TABLES

APPENDICES

1 BACKGROUND

1.1 Metastatic Colorectal Cancer

Metastatic colorectal cancer remains a major problem worldwide. In the United States, it is estimated that there will be approximately 50,000 deaths secondary to colorectal cancer in the year 2015(1). The median survival of patients with metastatic disease stands near 30 months in recent trials (2, 3). Multiple agents are currently in use, including the cytotoxic drugs: 5-FU, oxaliplatin, irinotecan which are typically used in combinations denoted as FOLFOX and FOLFIRI. Multiple targeted therapies have also been approved, including the anti-angiogenic agents bevacizumab, aflibercept and ramucirumab, as well as the anti-EGFR targeting drugs cetuximab and panitumumab. There is no clearly superior strategy for order of administration, with progression free survival and response rates grossly similar regardless of the chemotherapy back-bone or monoclonal antibody utilized in therapy(3). The largest study to date demonstrated equivalent outcomes, including survival whether an initial anti-EGFR strategy or initial anti-VEGF strategy was utilized(4).

1.2 EGFR Inhibitors and Colorectal Cancer

Cetuximab is an IgG1 monoclonal antibody targeting EGFR and approved for metastatic colorectal cancer. It possesses a high degree of activity as a single agent or in combination with chemotherapy, regardless of line of therapy in which it is utilized. Most commonly cetuximab is utilized as second or third line therapy in patients with metastatic colorectal cancer. The single agent response rate in molecularly selected patients (RAS wt) stands at approximately 20% with a median progression free survival of 4 months. This is identical for both cetuximab and the humanized monoclonal anti-EGFR antibody, panitumumab (5). Increasingly data has shown that patients who previously derived benefit from anti-EGFR therapy and then discontinued for reasons other than progression, frequently benefit (with up to 30-50% response rates and 4-6 month median PFS) through re-treatment after a holiday (6, 7). Clinically, the efficacy of anti-EGFR therapy can be predicted in part based upon the absence of activating KRAS mutations (8). More recently, a preponderance of data has emerged to suggest that beyond the initially evaluated KRAS exons 2 and 3, additional mutations in KRAS exon 4 or NRAS may also predict for lack of benefit from EGFR inhibition(9).

The side effect profile of anti-EGFR therapies is well established. The most commonly witnessed adverse events in include rash (frequently acneiform), dry skin, diarrhea, and hypomagnesemia. Rash is by far the most common side effect, seen in almost 50% of patients, but typically grade I. Grade III rash is uncommon, occurring in ≤ 5% of patients(5). The STEPP study established that a strategy of pre-emptive skin treatment minimizes the risk of ≥ grade 2 rash to a substantial degree. In this study, in the intervention arm, beginning the day prior to therapy, moisturizers were applied to the face, feet, hands, neck, back and chest every morning, with topical steroids (1% hydrocortisone cream) applied to the same areas at bedtime. Sunscreen (PABA free, SPF ≥ 15, UVA and UVB) was applied to sun exposed areas prior to going outdoors and doxycycline was taken twice daily (10). This treatment was continued for at least 6 weeks, reducing the incidence of ≥ grade 2 rash from 62% to 29%.

Pre-clinically, the success of anti-EGFR inhibition has been additionally linked to immune mechanisms (11-13). The down-regulation of MHC Class I expression, which is associated with reduced antigen processing, is linked to poor survival and loss of inflammatory response in colorectal cancer (14). Decreased MHC Class I expression is also associated with EGFR over-expression and activation of RAS signaling; the EGFR-RAS-MAPK pathway is known to be a driving pathway in colorectal cancer pathogenesis. Research for some time has suggested a link between effective cancer control through EGFR inhibition and an intact host immune system, though clinically this has been more difficult to establish. Interestingly, in preclinical models, EGFR inhibitors upregulate MHC Class I and II gene expression (15). Further, in various pre-clinical models, EGFR inhibitors are capable of inducing a tumoral lymphocytic infiltrate. This is seen in colon cancer tumor spheroids, as well as murine models using the 7A7 murine anti-EGFR antibody. In these same situations, depletion of CD4+ and CD8+ cells abrogates the efficacy of anti-EGFR therapy (11). In recently data presented by Dr. Galon's group, the hepatic resection specimen of colorectal cancer patients who were treated with anti-EGFR therapy demonstrated the most robust CD3+, CD8+ and CD45RO+ lymphocytic infiltrates (as compared to chemotherapy alone)(16). In summary, the anti-EGFR anti-tumor effect is mediated in part through immune mechanisms and is capable of increasing tumor infiltrating lymphocytes. As such, there is reason to think that an anti-EGFR targeting antibody may increase tumor infiltrating lymphocytes, which might prove synergistic when combined with additional therapies which may limit intrinsic tumor immune suppression.

1.3 PD-1 and PD-L1: Pharmaceutical and Therapeutic Background

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

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

regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

1.3.1 PD-1 and PD-1 Blockade in Colorectal Cancer

Immunotherapy has seen limited success to date in colorectal cancer, including with new drugs targeting PD-1. At present, the predictors of checkpoint inhibition efficacy remain incompletely understood, though there is some suggestion of a correlation between benefit and a dense tumor infiltrating lymphocyte population and/or pronounced PD-L1 expression. In a small subset of colorectal cancer patients, those with MSI-H tumors, there is frequently a dense lymphocytic infiltrate, presumably secondary to increased mutational rates and the resultant immunogenic neo-antigens produced. Early data has suggested efficacy of PD-1 inhibition in this population, and ongoing studies are testing this hypothesis (17). However, MSI-H metastatic colorectal cancers are distinctly uncommon, comprising approximately 3% of all patients (18). A subset of non-MSI-H (MSS) colorectal cancers also display dense lymphocytic infiltrates, though most do not; recent TCGA data suggests a marked decrease in the expression of tumor neo-antigens as compared to that which would be expected based upon mutation frequency in colorectal cancers(19). This is consistent with pronounced depletion of neo-antigens via immunoediting in these tumors. Therapies which may increase the expression of tumor neo-antigens may allow for PD-1 inhibition to experience success in colorectal cancers

1.4 Pembrolizumab (MK-3475)

Pembrolizumab (MK-3475) is a is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Upon administration, pembrolizumab binds to PD-1, an inhibitory signaling receptor expressed on the surface of activated T cells, and blocks the binding to and activation of PD-1 by its ligands, which results in the activation of T-cell-mediated immune responses against tumor cells. The ligands for PD-1 include PD-L1, which is expressed on

antigen presenting cells (APCs) and overexpressed on certain cancer cells, and PD-L2, which is primarily expressed on APCs. Activated PD-1 negatively regulates T-cell activation through the suppression of the PI3K/Akt pathway. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

1.4.1 Preclinical Studies with Pembrolizumab

A detailed discussion of the preclinical pharmacology, pharmacokinetics, and toxicology of pembrolizumab can be found in the Investigator's Brochure.

1.4.1.1 Mechanism of Action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

1.4.1.2 Pharmacokinetics

The pharmacokinetics of pembrolizumab was studied in 479 patients who received doses of 1 to 10 mg/kg every 2 weeks or 2 to 10 mg/kg every 3 weeks. Based on a population pharmacokinetic analysis, the mean [% coefficient of variation (CV %)] clearance (CL) is 0.22 L/day (28%) and the mean (CV%) elimination half-life ($t_{1/2}$) is 26 days (24%). Steady-state concentrations of pembrolizumab were reached by 18 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.1-fold. The peak concentration (C_{max}), trough concentration (C_{min}), and area under the plasma concentration versus time curve at steady state (AUC_{ss}) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

1.4.2 Clinical Studies with Pembrolizumab

The efficacy of pembrolizumab (MK-3475) was investigated in a multicenter, open-label, randomized (1:1), dose comparative, activity-estimating cohort of Trial 1(20). Key eligibility criteria were unresectable or metastatic melanoma with progression of disease; refractory to two or more doses of ipilimumab (3 mg/kg or higher) and, if BRAF V600 mutation-positive, a BRAF or MEK inhibitor; and disease progression within 24 weeks following the last dose of ipilimumab. The trial excluded patients with autoimmune disease; a medical condition that required immunosuppression; and a history of severe immune-mediated adverse reactions with ipilimumab, defined as any Grade 4 toxicity requiring treatment with corticosteroids or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks. Patients were randomized to receive 2 mg/kg (n=89) or 10 mg/kg (n=84) of (MK-3475) every 3 weeks until unacceptable toxicity or disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a

decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging. Assessment of tumor status was performed every 12 weeks. The major efficacy outcome measures were confirmed overall response rate (ORR) according to RECIST 1.1 as assessed by blinded independent central review and duration of response.

Among the 173 patients enrolled, the median age was 61 years (36% age 65 or older); 60% male; 97% White; and 66% and 34% with an ECOG performance status 0 and 1, respectively. Disease characteristics were BRAF V600 mutation (17%), elevated lactate dehydrogenase (39%), M1c (82%), brain metastases (9%), and two or more prior therapies for advanced or metastatic disease (73%).

The ORR was 24% (95% confidence interval: 15, 34) in the 2 mg/kg arm, consisting of 1 complete response and 20 partial responses. Among the 21 patients with an objective response, 3 (14%) had progression of disease 2.8, 2.9, and 8.2 months after initial response. The remaining 18 patients (86%) had ongoing responses with durations ranging from 1.4+ to 8.5+ months, which included 8 patients with ongoing responses of 6 months or longer. One additional patient developed two new asymptomatic lesions at the first tumor assessment concurrent with a 75% decrease in overall tumor burden; (MK-3475) was continued and this reduction in tumor burden was durable for 5+ months.

There were objective responses in patients with and without BRAF V600 mutation-positive melanoma. Similar ORR results were observed in the 10 mg/kg arm.

1.5 Risks and/or Benefits

The most common adverse effects of cetuximab include rash, hypomagnesemia, infusion reactions and diarrhea. Grade III/IV dermatologic reactions occur in up to 5% of patients with infusion reactions in up to 4.5%.

Pembrolizumab has been well tolerated thus far, with the most common adverse effects (reported in $\geq$ 20% of patients) being fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, and diarrhea.

Currently, there is no published data on the combination of EGFR antibodies and anti PD-1 therapy for treatment of metastatic colorectal cancer. At least two studies have combined anti-EGFR TKIs and anti-PD-1 or anti-PD-L1 antibodies. Nivolumab (anti-PD-1) and erlotinib (EGFR TKI) have been combined in chemotherapy-naive advanced NSCLC (21). In the 21 patients reported to date, this was well tolerated. While there was a 71% incidence of rash, there was no grade 3/4 rash. A 10% incidence of grade 3/4 diarrhea as well as grade 3/4 transaminitis was observed. Though all but 1 patient had previous erlotinib resistance, 15% of patients were seen to have responses with a 24 week PFS of 51%. Similarly, safety and tolerability data have recently been reported on a phase I study of MEDI-4736 (anti-PD-L1) and gefitinib (EGFR TKI)(22) . Generally, the treatment was well tolerated. Unexpected AEs did not emerge. There was an increase in grade 3 transaminitis, though only 2/15 (15%) of patients in the expansion cohort ultimately discontinued therapy due to AEs. Thus, there is reason to believe anti-EGFR inhibition can be safely combined with PD-1 inhibition and may have clinical efficacy in advanced cancer.

2 RATIONALE

Anti-EGFR therapy has the potential to increase a localized anti-tumor immune response and increase the expression of antigen presenting MHC molecules. Recently, in a syngeneic mouse model utilizing the CT-26 colon cancer cell line, combined MEK and PD-1 inhibition was shown to be of benefit, where PD-1 provided little benefit on its own (23). Thus, therapeutic strategies which jointly target the EGFR-RAS-MAPK pathway as well as block critical immune checkpoints may be of benefit for patients with advanced colorectal cancer. With this in mind, we propose a phase II study of cetuximab and pembrolizumab in metastatic colorectal cancer

2.1 Rationale for Dose Selection/Regimen/Modification

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

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

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3)

will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

3 OBJECTIVES

3.1 Primary Objectives

- To estimate the objective response rate of patients with metastatic colorectal cancer treated with pembrolizumab and cetuximab.
- To estimate the 6-month PFS rate of patients with metastatic colorectal cancer treated with pembrolizumab and cetuximab.
- To examine the adverse event profile of combining pembrolizumab and cetuximab.

3.2 Secondary/ Exploratory Objectives

- To examine the PFS of patients with metastatic colorectal cancer treated with pembrolizumab and cetuximab.
- To determine the objective response rate by immune-related response criteria (irRECIST) of patients with metastatic colorectal cancer.
- To examine the overall survival of patients with metastatic colorectal cancer treated with pembrolizumab and cetuximab.

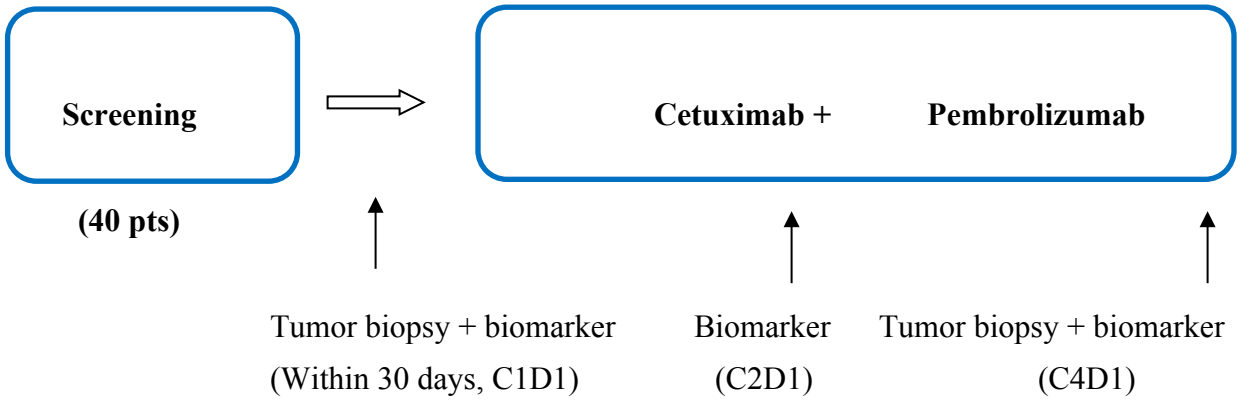
3.3 Exploratory Objectives

- Identify tumor and peripheral blood biomarkers of response and/or resistance to the study treatment.

4 METHODOLOGY

4.1 Study Design

This is an open-label, non-randomized, multi-institutional Phase Ib\II study of the anti-PD-1 antibody pembrolizumab in combination with cetuximab in patients with metastatic colorectal cancer. The study will include an initial phase Ib lead-in cohort, consisting of 9 patients. The Study schema is depicted below (**Figure 1**).Figure 1Study Schema



4.1.1 Phase Ib\II

There will be an initial phase Ib cohort to examine the safety and tolerability of the combination. Study progress will be monitored regularly by the RPCI Phase I Committee. After up to 9 patients are enrolled, and a minimum of 6 have completed at least two cycles of chemotherapy, the study will be suspended, and the safety/tolerability of the combination will be examined. At that time, the study team will decide what action to take, e.g., continue the study as is, make changes to the study with regard to treatment or dose modifications, or discontinue the study. Once analysis is complete and a safe treatment plan has been established, the phase II study will commence.

The Phase II study will enroll patients with metastatic colorectal cancer who are eligible for anti-EGFR therapy (i.e. RAS wt, no known expanded KRAS or NRAS mutations, anti-EGFR therapy naïve or appropriate for anti-EGFR rechallenge). For the purposes of the study, a cycle will be defined as three weeks. Patients will be treated with cetuximab, administered weekly and pembrolizumab, administrated every 3 weeks as described in **Section 6.** A regimen of pre-emptive skin care is recommended, as described in **Section 6.4**. Disease assessments will occur every 9 weeks to assess response, using RECIST v 1.1. As described in **Section 6.1**, after initial progressive disease, if fulfilling certain criteria, patients may continue on therapy with further response assessments in line with irRECIST criteria (**Appendix D**). Per local policy, a consent addendum should be obtained to continue on treatment past progression. Progression free survival and objective response rate will be observed. Additional blood based biomarker tests will be performed prior to treatment, at 4 weeks (cycle 2, day 1) and 10 weeks (cycle 4, day 1). A mandatory biopsy will be performed prior to treatment; a secondary biopsy at approximately 10 weeks (cycle 4, day 1) will be optional, but strongly encouraged. However, in order to obtain sufficient samples for informative analysis, for the final 10 patients of the study, both biopsies will be mandatory.

Primary Endpoints

- Six-month progression free survival and objective tumor response rate will be evaluated according to RECIST 1.1 guidelines after every 3 cycles (9 weeks) of treatment.

- Adverse events will be categorized and graded according to NCI CTCAE v4.0.

Secondary Endpoints

- Progression-free survival
- Overall survival
- Objective tumor response using irRECIST (**Appendix D**)
-

Exploratory Endpoints

- Tumor and immune cell biomarkers (using IHC):
    - PD-1, PD-L1
    - Tumor infiltrating and stromal lymphocytes
    - Additional biomarkers to evaluate mechanisms of EGFR and PD-1 resistance will be evaluated in exploratory analysis
- Tumor immune cell populations (via flow cytometry)
    - Regulatory T cell populations.
    - Tumor infiltrating lymphocyte, monocyte and NK cell populations.
    - Myeloid derived suppressor cell populations.
- Peripheral blood biomarkers (flow cytometry and ELISA):
    - Cytokines (including IFNγ and IL-10) and additional circulating factors (including sPD-L1)
    - Regulatory T cell populations.
    - Tumor infiltrating lymphocyte, monocyte and NK cell populations.
    - Myeloid derived suppressor cell populations.

All participants will sign an informed consent prior to study related tests. All participants will meet the inclusion and exclusion criteria summarized in **Section 5.1** and **Section 5.2**.

4.2 Target Accrual and Study Duration

A maximum of 42 participants at 3 sites, including RPCI will be enrolled. Accrual is expected to take up to 4 years, with an expected minimum six months of follow-up for all patients; for study duration of approximately 4 years.

5 PARTICIPANT SELECTION

5.1 Inclusion Criteria

To be included in this study, participants must meet the following criteria:

1. Have a pathologically confirmed diagnosis of colorectal cancer, which is metastatic or otherwise unresectable.
2. Have received at least 1 prior systemic therapy in the metastatic or unresectable disease setting. Patients who have recurred within six months of adjuvant chemotherapy are not required to have received an additional line of chemotherapy.

3. RAS wild-type. Both KRAS and NRAS testing are necessary. The presence of pathogenic mutations in KRAS or NRAS is exclusionary. Primary tumor or metastatic tumor may be tested.
4. Appropriate for anti-EGFR therapy: Naive to anti-EGFR therapy (cetuximab or panitumumab) or a candidate for rechallenge by virtue of the following:
    a. the investigator deems anti-EGFR retreatment with cetuximab to be a reasonable standard of care option AND
    b. outcome of prior anti-EGFR therapy was not rapid progression (i.e. <= 3 months on therapy) AND
    c. prior anti-EGFR therapy was administered > 6 months prior to the start of protocol therapy
5. Age ≥ 18 years of age.
6. Have an ECOG Performance Status ≤ 2. Refer to Appendix B.
7. Have measurable disease per RECIST 1.1 criteria present.
8. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. Newly-obtained is defined as a specimen obtained up to 30 days prior to initiation of treatment on Day 1.
9. Have the following clinical laboratory values (all screening labs must be performed within 14 days of treatment initiation):

    - Hemoglobin ≥ 8 g/ dL
    - Absolute neutrophil count ≥ 1000/ mm3
    - Platelet count ≥ 100,000/ mm3
    - Serum creatinine clearance ≥ 15 mL/min (refer to Appendix C: Cockroft-Gault Equation).
    - Serum total bilirubin ≤ 1.5 ULN or, direct bilirubin ≤ ULN for participants with total bilirubin levels > 1.5 ULN.
    - AST (SGOT) and ALT (SGPT) ≤ 2.5 ULN or, ≤ 5 ULN for participants with liver metastases.

10. Female participants of childbearing potential are to have a negative serum pregnancy test.
11. Female participants of child-bearing potential must agree to use an acceptable method of birth control, be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of pembrolizumab and 180 days after the last dose of cetuximab. Participants of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.
12. Male participants must agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose pembrolizumab and 180 days after the last dose of cetuximab.
13. Participant or legal representative must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.

5.2 Exclusion Criteria

Participants will be excluded from this study for the following:

1. Participants who have had chemotherapy, targeted therapies, radiotherapy, or used an investigational device within 2 weeks prior to the first dose of treatment or those who have not recovered from adverse events

(i.e., ≤ Grade 1 or at baseline) due to agents administered more than 2 weeks earlier. Note: Participants with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
3. Has a known history of active TB (Bacillus Tuberculosis).
4. Hypersensitivity to pembrolizumab or any of its excipients.
5. Prior severe infusion reaction to cetuximab
6. Has a known additional malignancy that requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
7. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability
8. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
9. Has known history of, or any evidence of active, non-infectious pneumonitis.
10. Uncontrolled clinically significant intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, unstable cardiac arrhythmia, or psychiatric illness, substance abuse disorders or social situations that would limit compliance with study requirements.
11. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
12. Has a known history of Human Immunodeficiency Virus (HIV or HIV 1/2 antibodies). Testing not required.
13. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected). Testing not required.
14. Has received a live vaccine within 30 days of planned start of study therapy (Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and shingles are not allowed).
15. Received an investigational agent within 30 days prior to starting study treatment.
16. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
17. Unwilling or unable to follow protocol requirements.

5.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this study.

6 TREATMENT PLAN

6.1 Dosing and Administration

The treatment regimen to be used in this trial is outlined below:

Cetuximab 400 mg/m^2 loading dose on day 1 cycle 1, followed by 250 mg/m^2 intravenously weekly. Pembrolizumab 200 mg fixed dose intravenously every 3 weeks.

Reported adverse events (AEs) and potential risks are described in **Section 1.5**. Appropriate dose modifications are described in **Section 6.1**

A cycle is defined as 3 weeks of treatment, with cetuximab administered weekly and pembrolizumab administered every 3 weeks, on day 1 of each cycle. Absent relevant limiting toxicities, pembrolizumab may be administered even if cetuximab is to be held on day 1 for cetuximab related AEs. Likewise, in the instance of pembrolizumab related AEs which require dose holding or discontinuation, cetuximab administration should continue as appropriate. Cetuximab will be administered prior to pembrolizumab on day 1, due to concern for infusion reactions. Pembrolizumab may be administered on Day 2 of any cycle in the event of a Cetuximab related infusion reaction; or any other adverse event at the discretion of the PI.

If cetuximab is held for greater than 2 weeks for reasons other than cetuximab related adverse events, the 400 mg/m^2 loading dose may be readministered upon resumption, at the discretion of the investigator.

6.1.1 Pembrolizumab

Dose Selection

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

The package insert contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

Timing of Dose Administration

Trial treatment will be administered on Day 1 of each cycle after all procedures/assessments have been completed (as detailed in **Table 4** Schedule of Procedures and Observations). Of note, the results of laboratory tests which are send-out tests (including TFTs) are not necessary prior to treatment. Pembrolizumab is to be administered after cetuximab infusion is complete. Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab Dose Modification and Treatment Delay Guidelines

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per **Table 1**. See **Section 6.3** and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids

The following dose modification rules will be used with respect to potential toxicity. Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0).

Table 1 Dose Modification Guidelines for Drug-Related Adverse Events: Pembrolizumab

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Diarrhea/Colitis	2[1]	Toxicity resolves to Grade ≤ 1[1]	Resume once improved to Grade ≤ 1
	3	Toxicity resolves to Grade ≤ 1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade ≤ 1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[2]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients are clinically and metabolically stable
Hypophysitis	2-3	Toxicity resolves to Grade ≤ 1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hyperthyroidism	3	Toxicity resolves to Grade ≤ 1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade ≤ 1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
			corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade ≤ 1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	
Rash[3]	3 or Severe[4, 5]	Toxicity improves to Grade ≤ 2	Toxicity does not improve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent within 12 weeks
All Other Drug-Related Toxicity, [3]	3 or Severe[4]	Toxicity resolves to Grade ≤ 1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

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

[1] For grade 2 diarrhea which is attributed to cetuximab and sub-optimally managed with anti-diarrheal agents, Pembrolizumab may be continued. Patients should be seen in clinical follow-up within 1 week with additional phone follow-up within 72 hours. If optimally managed with anti-diarrheal agents and it is not felt that the toxicity is clearly cetuximab related, Pembrolizumab should be held until toxicity resolves to Grade ≤ 1.

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

[3] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug 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.

4 For these purposes, a severe toxicity is a toxicity which does not otherwise meet the criteria for grade 3 or 4, but which the investigator deems as being substantial enough to merit the holding of therapy.

5 For an acneiform or maculopapular rash which is deemed to be clearly related to cetuximab, at the investigator's discretion, pembrolizumab may be administered even for grade 3 rash, as long as the rash is showing signs of improvement and cetuximab is held as per protocol.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

6.1.2 Cetuximab

Dose Selection

Cetuximab will be administered as per the package insert. The initial loading dose (400 mg/m2) will be administered over 120 minutes. Subsequent doses will be delivered over 60 minutes

provided there are no significant infusion reactions. The package insert contains specific instructions for the preparation of the cetuximab infusion fluid and administration of infusion solution. As appropriate, dose modifications are to be pursued as per **Table 1**.

Table 1.

Dose Level (DL)	Pembrolizumab (mg)	Cetuximab** (mg)
Regimen I: Pembrolizumab + Cetuximab		
-2	200 mg every 3 weeks	150 mg/m^2 weekly
-1	200 mg every 3 weeks	200 mg/m^2 weekly
*1	200 mg every 3 weeks	250 mg/m^2 weekly

**Cetuximab is administered with a loading dose of 400 mg/m^2 to be administered on cycle 1 day 1, at all dose levels.

Timing of Dose Administration

Trial treatment will be administered on Days 1, 8 and 15 of each cycle after all procedures/assessments have been completed (as detailed in **Table 4** Schedule of Procedures and Observations). Of note, the results of laboratory tests which are send-out tests (including TFTs) are not necessary prior to treatment. Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Cetuximab Dose Modification and Treatment Delay Guidelines

Table 2 Dose Modification Guidelines for Drug-Related Adverse Events: Cetuximab

Worst toxicity observed (NCI CTCAE version 4.0)	Subsequent administration
Skin Toxicity (e.g. Acneiform rash, deemed attributable to cetuximab)	
Grade 1 or 2	• Continue at same dose level
Grade 3 or 4: 1st occurrence[1]	• Delay infusion one to two weeks • Once symptoms improve, continue dosing at same dose level. • If there is no improvement in symptoms for ≥ 4 weeks, discontinue cetuximab.
Grade 3 or 4: 2nd occurrence	• Delay infusion one to two weeks • Once symptoms improve, continue dosing and reduce by one dose level • If there is no improvement in symptoms for ≥ 4 weeks, discontinue cetuximab.

Worst toxicity observed (NCI CTCAE version 4.0)	Subsequent administration
Grade 3 or 4: 3rd occurrence	• Delay infusion one to two weeks • Once symptoms improve, continue dosing and reduce by one further dose level • If there is no improvement in symptoms for ≥ 4 weeks, discontinue cetuximab.
Grade 3 or 4: 4th occurrence	• Discontinue cetuximab
Diarrhea	
Grade 1	• Continue at same dose level
Grade 2[2]	• If anti-motility agents not maximized, maximize supportive care.[1] • If anti-motility agents maximized, hold cetuximab When symptoms improve to ≤ grade 1, resume with dose reduced by one dose level
Grade 3 or 4	• Hold cetuximab until adequate resolution • If symptoms improve to grade 1, resume with dose reduced by one dose level • If symptoms do not improve within 2 weeks, permanently discontinue
Respiratory toxicity	
Acute onset or worsening pulmonary symptoms	• Interrupt cetuximab dosing
Confirmed ILD	• Permanently discontinue cetuximab
Infusion reaction	• Reduce the infusion rate by 50% for NCI CTC Grade 1 or 2 and non-serious NCI CTC Grade 3 infusion reactions. Immediately and permanently discontinue cetuximab for serious infusion reactions, requiring medical intervention and/or hospitalization.

18. For patients who find the rash to be intolerable, the dose may be reduced at the investigator's discretion.
19. Additionally refer to 6.3.2. Patients who are receiving additional supportive care measures require close follow-up, minimally within 72 hours by phone and 7 days in clinic.

6.2 General Concomitant Medications

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

Participants may be pretreated for nausea and vomiting with appropriate anti-emetics.

6.2.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant'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 1 week prior to the first dose of trial treatment and 30 days after the last dose of trial treatment or a new treatment is started, whichever comes first, will be recorded"**.** Concomitant medications administered after 30 days after the last dose of trial treatment will be recorded for SAEs and ECIs as defined in **Section 10).**

Participants may be pretreated for nausea and vomiting with appropriate anti-emetics.

6.2.2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and shingles.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology (and as described for grade 3 cetuximab AEs). The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor. NOTE: Brief courses of steroids to prevent allergic reactions (IV contrast dye) or for similar purposes are permitted, but should first be reviewed with the sponsor.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria (**Section 5.2**) describe other medications which are prohibited in this trial.

6.3 Supportive Care Guidelines for Pembrolizumab

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below and in greater detail in the

ECI Guidance Document. Where appropriate, these guidelines include the use of oral or intravenous corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation the event is determined not to be related to the study drug, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI Guidance Document). Refer to **Section 6.1.1**for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI Guidance Document.

Note: All adverse events, regardless of grade, that are considered Events of Clinical Interest should be reported regardless of etiology.

6.3.1 Pneumonitis

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

6.3.2 Diarrhea/Colitis

Participants should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). Diarrhea from Pembrolizumab most commonly presents at 6 weeks or later during therapy. If cetuximab is suspected as the etiology, particularly if early onset within the first 6 weeks, anti-motility agents and close f/u along with appropriate cetuximab management should be instituted.

- All participants who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. Anti-motility agents (e.g. loperamide, diphenoxylate/atropine) may be utilized initially.
- For Grade 2 diarrhea/colitis, first initiate above supportive measures and initiate or intensify anti-motility agents. Close clinical f/u is necessary (i.e. follow-up via phone within 72 hours and in clinic within 7 days). If cetuximab is held and symptoms are still not improving promptly, or there is suspicion for Pembrolizumab toxicity, consider GI

consultation and endoscopy to rule out or confirm colitis. If suspicion for pebrolizumab related colitis is high and/or endoscopy cannot be performed promptly, administer oral corticosteroids. For Grade 3 or 4 diarrhea/ colitis that persist for > 1 week, treat with intravenous steroids followed by high dose oral steroids.

- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

6.3.3 Type 1 Diabetes Mellitus or ≥ Grade 3 Hyperglycemia

- Type 1 diabetes mellitus (TIDM), if new onset, including diabetic ketoacidosis (DKA)
- Grade 3 or higher hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)
- For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
- Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

6.3.4 Hypophysitis

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

6.3.5 Hyperthyroidism or Hypothyroidism

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

- **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
- In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
- In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
- **Grade 3-4** hyperthyroidism:
- Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over

no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

6.3.6 Hematologic

- For **Grade 2** events, treat with oral corticosteroids, if indicated.
- For **Grade 3-4** events, treat with systemic or oral corticosteroids, as appropriate.

6.3.7 Hepatic

- For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
- For **Grade 3-4** events, treat with intravenous glucocorticosteroids for 24 to 48 hours.

When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

In addition, the event must be reported as a Drug Induced Liver Injury (DILI) ECI, if the patient meets the laboratory criteria for potential DILI defined as:

- An elevated alanine transaminase (ALT) or aspartate transaminase (AST) lab value that is greater than or equal to three times (3X) the upper limit of normal (ULN) and
- An elevated total bilirubin lab value that is greater than or equal to two times (2X) ULN and at the same time, an alkaline phosphatase (ALP) lab value that is less than 2X ULN,
- As a result of within-protocol-specific testing or unscheduled testing.

6.3.8 Neurologic

- For **Grade 2** events, consider treatment with corticosteroids, as appropriate.
- For **Grade 3-4** events, treat with systemic corticosteroids. If condition worsens, consider IVIG or other immunosuppressive therapies, as per local guidelines.

When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

6.3.9 Ocular

- For **Grade 2** events, treat with topical steroids, such as 1% prednisolone acetate suspension and iridocyclitics.
- For **Grade 3-4** events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

6.3.10 Renal Failure or Nephritis

- For **Grade 2** events, treat with corticosteroids.

- For **Grade 3-4** events, treat with systemic corticosteroids.

When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

6.3.11 Skin***

- For **Grade 2** events, symptomatic treatment with topical glucocorticosteroids or urea-containing creams, in combination with oral anti-pruritics.
- For **Grade 3-4** events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

***Both pembrolizumab and cetuximab can cause a significant incidence of grade 2 / 3 rash. For a ≥ grade 3 maculopapular rash (grading predominantly determined by degree of BSA involvement), which is strongly felt to be related to cetuximab and which is tolerable to the patient, additional supportive measures may be instituted with weekly clinical follow-up, without the initial addition of systemic corticosteroids. Pembrolizumab must be held, however, as noted above. This course of action should be discussed with the PI.

NOTE: Refer to the ECI Guidance Document (Section 3.9.1: Immediate Evaluation for Potential Skin ECIs) for detailed evaluation and reporting requirements.

6.3.12 Other ECIs

The following AEs, regardless of grade, are considered ECIs and should be reported to the Sponsor (see Section **10.4.1**)

- Myocarditis
- Pericarditis
- Pancreatitis
- Any additional Grade 3 or higher event which the investigator considers to be immune-related.
    - For **Grade 2** events, or **Grade 1** events that do not improve with symptomatic treatment: Systemic corticosteroids may be indicated.
    - For **Grade 3-4** events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

6.3.13 Infusion Reactions

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. **Table 3** shows treatment guidelines for participants who experience an infusion reaction associated with administration of pembrolizumab.

Table 3 Infusion Reaction Treatment Guidelines

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

***Note*:** Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.

6.3.14 Diet/Activity/Other Considerations

Diet

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

Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be: two barrier methods or, a barrier method plus a hormonal method, to prevent pregnancy. Participants should start using birth control from study Visit 1 (prescreening visit) throughout the study period up to 120 days after the last dose of pembrolizumab and 180 days after the last dose of cetuximab.

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

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in **Section 8**. If there is any question that a participant will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

Use in Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours to the Sponsor and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). Refer to **Section 10.4.1**

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 10.4.1.

Use in Nursing Women

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

6.4 Supportive Care Guidelines for Cetuximab

6.4.1 Dermatologic Management and AEs

A regimen of pre-emptive skin care is recommended for all patients on the study, as this has been demonstrated to decrease incidence of dermatologic AEs. They should be advised to continue this plan of care for the initial six weeks, with further continuation at the discretion of the investigator. The following components are to be included:

- Twice daily moisturizers – thick, alcohol free emollients of the patients' choice
- Low potency topical corticosteroid twice daily to face, neck, back, chest – e.g. hydrocortisone 2.5%
- Prophylactic oral antibiotics – e.g. doxycycline 100 mg po bid, minocycline 100 mg daily or acceptable alternative such as cephalexin 500 mg po bid, cefadroxil 500 mg po bid, or trimethoprim-sulfamethoxazole 160-800 mg po bid.
- Broad spectrum sunscreen (UVA/UVB) with SPF $\geq$ 15 applied to sun-exposed areas regularly

Additional recommendations for skin care include:

- Limit excessive sun exposure
- Avoiding lotions, detergents with perfumes
- Reduce the frequency and duration of hot showers, and consider using lukewarm water

For **grade 1 rash**, reinforce skin care measures and consider adding topical antibiotics to skin care: Clindamycin 1% gel, Erythromycin 3% gel or cream, metronidazole 1% cream or equivalent products are recommended.

For **grade 2 rash, consider** the addition of a medium to high potency topical corticosteroid to chest/back/extremities: e.g. Fluocinonide 0.05%, hydrocortisone valerate 0.2%.

For **grade 3 rash,** hold cetuximab. If intolerable, consider a short course of oral corticosteroids, prednisone 0.5 mg/kg, to a maximum of 40 mg daily x 7 days.

6.4.2 Hypomagnesemia

Anti-EGFR therapies such as cetuximab have an established link to hypomagnesemia. Magnesium levels are to be monitored and levels replaced on therapy and up to 8 weeks after completion of therapy, as per practice standard.

6.5 Duration of Treatment

Participants may remain on study and continue to receive treatment in the absence of disease progression, unacceptable toxicity and withdrawal from study, intercurrent illness that prevents further administration of treatment, participant demonstrates an inability/refusal to comply with oral medication regime or, participant withdraws from study.

If radiologic imaging by the site identifies PD by RECIST 1.1, subject management and tumor assessment will shift to irRECIST. Consent addendum should be obtained to continue on treatment past progression. Imaging should be repeated ≤ 6 weeks later in order to confirm PD with the option of continuing treatment per below while awaiting radiologic confirmation of progression.

If repeat imaging shows < 20% tumor burden compared to nadir, stable or improved previous new lesion (if identified as cause for initial PD), and stable/improved non-target disease (if identified as cause for initial PD), PD is not confirmed. Treatment may continue and subsequently follow regular imaging schedule.

If repeat imaging confirms PD (irPD) due to any of the scenarios listed below, subjects will be discontinued from study therapy (exception noted in Section 6.6).

In determining whether or not the tumor burden has increased or decreased, site study team should consider all target lesions as well as non-target lesions.

Scenarios where PD is confirmed at repeat imaging:

- Tumor burden remains ≥ 20% and at least 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial PD is worse (qualitative)
- New lesion resulting in initial PD is worse (qualitative)
- Additional new lesion(s) since last evaluation
- Additional new non-target progression since last evaluation

In subjects who have initial evidence of radiological PD by the site, it is at the discretion of the PI whether to continue a subject on study treatment until repeat imaging is obtained (irRECIST subject management). This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of symptoms and signs indicating clinically significant progression of disease, including worsening of laboratory values
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

When feasible, subjects should not be discontinued until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation of PD.

6.6 Treatment Discontinuation

Upon treatment discontinuation all end of treatment evaluations and tests will be conducted. All participants who discontinue due to an AE must be followed until the event resolves or stabilizes. Appropriate medical care should be provided until signs and symptoms have abated, stabilized, or until abnormal laboratory findings have returned to acceptable or pre-study limits. The final status of the AE will be reported in the participant's medical records and the appropriate eCRF.

Reasons for treatment discontinuation should be classified as follows:

- Death
- Progressive disease
- Toxicity; treatment related or unrelated
- Investigator judgment
- The Investigator may discontinue a participant if, in his/her judgment, it is in the best interest of the participant to do so.
- Noncompliance
- Participant voluntary withdrawal
- A participant may withdraw from the study at any time, for any reason. If a participant discontinues treatment, an attempt should be made to obtain information regarding the reason for withdrawal.
- Sponsor decision.
- Intercurrent illness that prevents further administration of treatment.
- The participant has a confirmed positive serum pregnancy test.
- The participant is lost to follow-up.
- Confirmed radiographic disease progression.
    - *Note*: For unconfirmed radiographic disease progression, please see Section 6.5.
    - *Note*: A participant may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 6.5. Consent addendum should be obtained to continue on treatment past progression.

- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.
    - *Note*: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in **Section 8.10**.

The End of Treatment and Follow-up visit procedures are listed in **Section 8**. After the end of treatment, each participant will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in **Section 10.2**). Participants who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each participant will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.6.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for participants who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Participants who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the participant meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Participants will resume therapy at the same dose and schedule at the time of initial discontinuation.

7 INVESTIGATIONAL PRODUCT

7.1 Pembrolizumab (KEYTRUDA®)

Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.

7.1.1 Active Substance and Source

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

KEYTRUDA for injection is a sterile, preservative-free, white to off-white lyophilized powder in single-use vials. Each vial is reconstituted and diluted for intravenous infusion. Each 2 mL of reconstituted solution contains 50 mg of pembrolizumab and is formulated in L-histidine (3.1

mg), polysorbate 80 (0.4 mg), and sucrose (140 mg). May contain hydrochloric acid/sodium hydroxide-adjust pH to 5.5.

KEYTRUDA injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

7.1.2 Drug Shipment

Pembrolizumab will be provided by Merck & Co., Inc. and shipped to the participating site. The investigational drug will be labeled in accordance with regulatory requirements (Drug identity, i.e., name, strength) is included in the label.

The date of receipt and the amount of drug received will be documented. Drug shipment records will be retained by the investigational pharmacist or designee.

7.2 Preparation

Refer to the package insert.

7.3 Storage and Stability

The Investigator or designate will be responsible for ensuring that the investigational product is securely maintained in a locked, limited-access facility, as specified by the Sponsor and in accordance with the applicable regulatory requirements.

Drug storage temperature will be maintained and recorded, as applicable.

KEYTRUDA for injection (lyophilized powder): Store vials under refrigeration at 2°C to 8°C (36°F to 46°F).

KEYTRUDA injection (solution): Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

Refer to Investigator's Brochure/ package insert for storage and stability requirements.

7.3.1 Handling and Disposal

The Investigator or designee will be responsible for dispensing and accounting for all investigational drug provided by Merck & Co., Inc., exercising accepted medical and pharmaceutical practices. Study drugs must be handled as cytotoxic agents and appropriate precautions taken per the institution's environmentally safe handling procedures. All investigational drugs will be dispensed in accordance with the Investigator's prescription or written order.

All products dispensed will be recorded on a product accountability record. Records of product lot numbers and dates received will be entered on a product accountability form. This record will be reviewed by the Sponsor's staff or representative during periodic monitoring visits. It is the

Investigator's responsibility to ensure that an accurate record of investigational drug issued and returned is maintained.

All unused and/or partially used investigational drug will be destroyed according to standard practices after properly accounting for the dispensing. Partially used vials of study drug will not be re-used for other participants.

Under no circumstances will the Investigator supply investigational drug to a third party or allow the investigational drug to be used in a manner other than as directed by this protocol.

7.3.2 Overdose

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab.

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

7.4 Cetuximab

Please refer to package insert. This will be commercially supplied. As per the package insert, an intravenous anti-histamine (H_1 antagonist), namely Benadryl 50 mg intravenously, will be administered unless otherwise specified.

8 STUDY PROCEDURES

The study-specific assessments are detailed in this section and outlined in **Table 4** (Schedule of Procedures and Observations). Baseline and/or Screening assessments must be performed within **14** 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.

Informed consent ***MUST*** be completed prior to receiving any study related procedures.

8.1 Participant Registration

8.2 Baseline Evaluations

The following will be performed within 2 weeks prior to first dose of study drug:

- Medical history (including all prior anti-tumoral therapy related to cancer)
- Physical examination (standard of care)
- Vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, body weight, and height)
- ECOG Performance Status (**Appendix B**)
- Urinalysis

- Hematology (complete blood count (CBC) with automated differentials)
- CMP (complete metabolic panel) + Mg: chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap), magnesium.
- Thyroid function tests: TSH, Total T3, Free T4
- Baseline imaging with 30 days of the first dose of study drug: Preferred CT imaging (chest/abdomen/pelvis with contrast). A non-contrast CT chest and MRI abd/pelvis is an acceptable alternative if a contrast enhanced CT cannot be performed.
- Pregnancy test (serum) in females of childbearing potential (at baseline and then every 6 months, see Tables 4 and 5)
- Concomitant Medications: List any medications that are ongoing, or that will be discontinued, within 1 week prior to first dose of study drug.
- Adverse Events
- Tumor biopsy (within 30 days of Cycle 1 day 1)
- Tumor molecular status: Document prior tumor mismatch repair (MMR) testing and/or microsatellite instability (MSI) testing. Either test is acceptable. If neither has been performed, these should be performed, per local protocol.

8.3 Evaluations Performed on Treatment, Every Cycle, Day 1 (± "3" days)

- Physical examination (standard of care)
- Vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, body weight)
- Hematology (complete blood count (CBC) with automated differentials)
- CMP (complete metabolic panel) + Mg: chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap), magnesium.
- Thyroid function tests: TSH, Total T3, Free T4 (beginning with Cycle 2, every other cycle, i.e. cycles 2, 4, 6, 8, etc…)
- CEA
- Restaging imaging, to occur every 9 weeks from cycle 1, day 1 (+/- 7 days): Preferred CT imaging (chest/abdomen/pelvis with contrast). A non-contrast CT chest and MRI abd/pelvis is an acceptable alternative if a contrast enhanced CT cannot be performed.
- Blood biomarker (Cycle 1 day 1, Cycle 2 day 1, and Cycle 4 day 1 only)
- Concomitant Medications: List any medications that are ongoing, or that will be discontinued, within 1 week prior to first dose of study drug.
- Adverse events

- Tumor biopsy (Cycle 4 day 1, ± 7" days)

8.4 Evaluations Performed on Treatment Day 15, cycle 1 only.

- Vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, body weight)
- BMP (basic metabolic panel) + Mg: chloride, CO2, potassium, sodium, BUN, glucose, calcium, creatinine, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap, magnesium.
- Directed physical exam
- Concomitant Medications
- Adverse Events

8.5 Evaluations Performed on Treatment, Every Cycle, Days 8, 15 (± "3" days)

- Vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, body weight)
- BMP (basic metabolic panel) + Mg: chloride, CO2, potassium, sodium, BUN, glucose, calcium, creatinine, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap, magnesium.

8.6 Evaluations Performed at End of Treatment (Off Treatment Visit)

The following evaluations will be performed at the end of treatment or at time of treatment discontinuation:

- Physical examination, including vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, body weight)
- Hematology [(i.e., complete blood count (CBC) with automated differentials)]: WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, % neutrophils, absolute neutrophils, , % monocytes, absolute monocytes, % eosinophils, absolute eosinophils, % basophils, absolute basophils, % lymphocyte, absolute lymphocyte, platelet confirmation (as clinically indicated), and differential confirmation (as clinically indicated).
- CMP +Mg (i.e., complete metabolic panel: chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap), Magnesium
- Thyroid function tests: TSH, Total T3, Free T4
- ECOG Performance Status (**Appendix B**)
- Concomitant medication: List any ongoing medications with dose changes, as applicable.
- Adverse events

8.7 Safety Follow-Up Evaluations

Follow-up safety evaluations will occur 30 days (± 7 days) after last dose of study drug or until resolution of any drug-related toxicity.

- Physical examination, including vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, body weight)
- Hematology [(i.e., complete blood count (CBC) with automated differentials)]: WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, % neutrophils, absolute neutrophils, , % monocytes, absolute monocytes, % eosinophils, absolute eosinophils, % basophils, absolute basophils, % lymphocyte, absolute lymphocyte, platelet confirmation (as clinically indicated), and differential confirmation (as clinically indicated).
- CMP (i.e., complete metabolic panel: chloride, CO2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap) + Magnesium
- Thyroid function tests: TSH, Total T3, Free T4
- Concomitant medications: List any ongoing medications with dose changes, as applicable.

8.8 Adverse events Safety Follow-up #2

A second follow-up safety evaluation will occur 60 days (± 7 days) after last dose of study drug, with blood work only being required (to follow-up on electrolytes).

- CMP (i.e., complete metabolic panel: chloride, CO2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap) + Magnesium

8.9 Long Term Follow-Up Evaluations (± 2weeks)

Participants will be monitored every 3 months for up to 4 years (telephone contact is acceptable). Monitoring will be performed to assess further therapies administered and survival.

Participants who are unavailable for follow-up evaluations should be classified as lost to follow-up for 1 of the following reasons:

- Lost to follow-up: For a participant to be considered lost to follow-up, the investigator must make two separate attempts to re-establish contact with the participant. The attempts to re-establish participant contact must be documented (e.g., certified letter).
- Death: Date and cause of death will be recorded for those participants who die within 30 days after last dose of study drug (telephone verification is acceptable).

8.10 Second Course Phase (Retreatment Period)

Participants who stop cetuximab and pembrolizumab with SD or better may be eligible for up to one year of additional therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- **Either**
    - Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1, and
        - Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy
        - Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

        OR
    - Had SD, PR or CR and stopped pembrolizumab treatment after 24 months of study therapy for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Has a performance status of 0 to 2 on the ECOG Performance Scale (**Appendix B**)
- Meets the safety parameters as detailed in **Section 5.1**
- Female participants of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female participants of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of pembrolizumab and 180 days after the last dose of cetuximab. (Reference **Section 5.1**). Participants of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the participant's participation for the full duration of the trial or is not in the best interest of the participant to participate, in the opinion of the treating investigator.

Participants who restart treatment will be retreated at the same dose and dose interval as when they last received cetuximab and pembrolizumab. Treatment will be administered for up to one additional year.

Visit requirements are outlined in **5**: Schedule of Procedures and Observations for Second Treatment Course. Both cetuximab and pembrolizumab would restart simultaneously.

8.11 Schedule of Procedures and Observations

The schedule of procedures and observations for this study is summarized in **Table 4 below.**

The Second Course Phase Treatment Schedule of procedure and observations for this study is summarized in table 5 below.

Table 4 Schedule of Procedures and Observations

Evaluation	Baseline[1]	Cycle 1 Day 1 (± 3 days)	Cycle 1 Day 8 (± 3 days)	Cycle 1 Day 15 (± 3 days)	Further Cycles Day 1 (± 3 days)	Further Cycles Days 8, 15 (± 3.days)	Cycle 4 Day 1 (± 3 days)	Off Treatment Visit	Safety[2] Follow-Up	Safety[19] Follow-up #2	Long Term Follow-Up[3]
Medical History	X										
Physical Examination[4]	X	X			X		X	X	X		
Vital signs[5]	X	X	X	X	X	X	X	X	X		
Directed Physical Exam				X							
ECOG PS	X							X			
Hematology[6]	X	X			X		X	X	X		
BMP (with Mg)[7]			X	X		X					
CMP (with Mg)[8]	X	X			X		X	X	X	X[19]	
CEA		X			X		X				
Urinalysis[9]	X										
Pregnancy Test (Serum)[10]	X						X[20]				
TSH, total T3, Free T4	X				X[14]		X	X	X		
Tumor Imaging (CT/MRI)[11]	X						X[21]				
Biomarker Analysis Blood Draw[12]		X			X[12]		X				
Tumor Biopsy	X[16]						X[15]				
MMR Documentation/ Testing[17]	X										
Blood draw for MSI[18]	X										
Pembrolizumab		X			X		X				
Cetuximab		X	X	X	X	X	X				

Evaluation	Baseline[1]	Cycle 1 Day 1 (± 3 days)	Cycle 1 Day 8 (± 3 days)	Cycle 1 Day 15 (± 3 days)	Further Cycles Day 1 (± 3 days)	Further Cycles Days 8, 15 (± 3.days)	Cycle 4 Day 1 (± 3 days)	Off Treatment Visit	Safety[2] Follow-Up	Safety[19] Follow-up #2	Long Term Follow-Up[3]
Concomitant Medications	X[13]	X		X	X		X	X	X		
Adverse Events	X	X		X	X		X	X	X		
Post anti-Cancer Therapy Status											X

1 Performed within 2 weeks prior to treatment start.

2 Follow-up safety evaluations will occur 30 days (± 7 days) after last dose of study drug. SAEs to be reported for up until 90 days after last study treatment.

3 Participants will be monitored for survival, further treatments every 3 months for up to 2 years (telephone contact is acceptable). (± 2 weeks)

4 Standard of care physical exam may be used if performed within 2 weeks prior to signed consent.

5 Vital signs: temperature, heart rate, respiratory rate, blood pressure, and body weight. Height collected at baseline only.

6 Hematology (CBC with automated differentials): WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, % neutrophils, absolute neutrophils, % monocytes, absolute monocytes, % eosinophils, absolute eosinophils, % basophils, absolute basophils,), % lymphocyte total, absolute lymphocyte total, platelet confirmation (as clinically indicated), and differential confirmation (as clinically indicated).

7 Basic Metabolic Panel (BMP) with magnesium: chloride, CO2, potassium, sodium, BUN, glucose, calcium, creatinine, magnesium

8 Complete Metabolic Panel (CMP): chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap), direct bilirubin (if total bilirubin is elevated above the upper limit of normal), magnesium.

9 Microscopic exam if results are abnormal.

10 Perform on women of childbearing potential only.

11 Baseline imaging with 30 days prior to the first dose of study drug is acceptable. CT preferred, though Non-contrast CT chest and MRI abd/pelvis is an acceptable alternative if a contrast enhanced CT cannot be performed. Restaging will be performed every 9 weeks (+/- 7 days from Cycle 1 day 1)

12 Blood draws for biomarker analysis will be collected according to Section 8.12. To be performed Cycle 1 day 1, Cycle 2 day 1, Cycle 4 day 1. All are drawn pre-dose.

13 Medications ongoing, or discontinued, within 1 week prior to first dose of study drug.

14 TFTs (TSH, Total T3, Free T4 to be drawn on day 1 every other cycle beginning with cycle 2, i.e. cycle 2, 4, 6, 8, etc…)

15 Tumor Biopsy – cycle 4 Day 1, +/- 7 days

16 Please refer to Section 8.12.1 and Section 8.12.2

17 Mismatch repair protein (MMR) testing (for proteins: MLH1, MSH2, MSH6, PMS2) and/or microsatellite instability(MSI) testing results must be documented. Either is sufficient. If neither is available, testing is to be requested for at least one of these, as per the institution standard.

Evaluation	Baseline[1]	Cycle 1 Day 1 (± 3 days)	Cycle 1 Day 8 (± 3 days)	Cycle 1 Day 15 (± 3 days)	Further Cycles Day 1 (± 3 days)	Further Cycles Days 8, 15 (± 3.days)	Cycle 4 Day 1 (± 3 days)	Off Treatment Visit	Safety[2] Follow-Up	Safety[19] Follow-up #2	Long Term Follow-Up[3]
18 For completion of MSI testing, when necessary, peripheral blood may need to be drawn, depending upon the sample which is able to be tested. Any time point within the 1st 4 weeks on treatment is acceptable, though request at baseline is preferred.											
19 Second follow-up safety eval, labs only, to occur 60 days(± 7 days) after last dose of study drug.											
20 Serum pregnancy test to be performed once every 6 months on women of childbearing potential only – cycle 9, 17, 25, etc…											
21 Consent addendum should be obtained to continue on treatment past progression. See section 6.5											

Table 5 Second Course Phase Treatment Schedule

Evaluation	Cycle 1 Day 1	Cycle 1 Day 8, 15 (± 3 days)	Further Cycles Day 1 (± 3 days)	Further Cycles Days 8, 15 (± 3.days)	Off Treatment Visit	Safety[2] Follow-Up	Safety Follow-up #2[13]	Long Term Follow-Up[3]
Eligibility criteria[1]	X							
Physical Examination	X		X		X	X		
Vital signs[4]	X	X	X	X	X	X		
ECOG PS					X			
Hematology[5]	X		X		X	X		
BMP (with Mg)[6]		X		X				
CMP (with Mg)[7]	X		X		X	X	X	
CEA	X		X					
Pregnancy Test (Serum)[8]	X		X[14]					
TSH, total T3, Free T4	X[12]		X[12]		X	X		
Tumor Imaging (CT/MRI)[9]	X[10]							
Pembrolizumab	X		X					
Cetuximab	X	X	X	X				
Concomitant Medications[11]	X		X		X	X		
Adverse Events	X		X		X	X		
Post Therapy Status								X

1 Performed within 2 weeks prior to treatment start.

2 Follow-up safety evaluations will occur 30 days (± 7 days) after last dose of study drug. SAEs to be reported for up until 90 days after last study treatment.

3 Participants will be monitored for survival, further treatments every 3 months for up to 4 years (telephone contact is acceptable).

Evaluation	Cycle 1 Day 1	Cycle 1 Day 8, 15 (± 3 days)	Further Cycles Day 1 (± 3 days)	Further Cycles Days 8, 15 (± 3.days)	Off Treatment Visit	Safety[2] Follow-Up	Safety Follow-up #2[13]	Long Term Follow-Up[3]

4 Vital signs: temperature, heart rate, respiratory rate, blood pressure, and body weight. Height collected at baseline only.

5 Hematology (CBC with automated differentials): WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, % neutrophils, absolute neutrophils, % monocytes, absolute monocytes, % eosinophils, absolute eosinophils, % basophils, absolute basophils,), % lymphocyte total, absolute lymphocyte total, platelet confirmation (as clinically indicated), and differential confirmation (as clinically indicated).

6 Basic Metabolic Panel (BMP) with magnesium: chloride, CO2, potassium, sodium, BUN, glucose, calcium, creatinine, magnesium

7 Complete Metabolic Panel (CMP): chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap), direct bilirubin (if total bilirubin is elevated above the upper limit of normal), magnesium.

8 Perform on women of childbearing potential only. within 2 weeks prior to start of treatment.

9 CT preferred, though Non-contrast CT chest and MRI abd/pelvis is an acceptable alternative if a contrast enhanced CT cannot be performed. Restaging will be performed every 9 weeks (+/- 7 days from Cycle 1 day 1).

10 Imaging for cycle 1 day 1 of retreatment can be performed up to 28 days prior to cycle 1 day 1/

11 Medications ongoing, or discontinued, within 1 week prior to first dose of study drug.

12 TFTs (TSH, Total T3, Free T4 to be drawn on day 1 every other cycle beginning with cycle 1, i.e. cycle 1, 3, 5, 7, etc…)

13 Second follow-up safety eval, labs only, to occur 60 days(± 7 days) after last dose of study drug.

14 Serum pregnancy test to be performed once every 6 months on women of childbearing potential only – cycle 9, 17, 25, etc…

8.12 Biomarker Blood Sample Collection and Processing

Four 10 mL green-top heparinized tubes of blood will be collected pre-dose via venipuncture for biomarker analysis at multiple time points. These will be collected on Day 1 of Cycles 1, 2 and 4. All tubes will be sent to the Hematologic Procurement Laboratory, one tube (for flow cytometry) will be forwarded at ambient temperature to Dr. Minderman's Laboratory in the Department of Flow and Image Cytometry at RPCI. Plasma and PBMCs will be separated within 2 hours following extraction. These samples will be stored and analyzed by Dr. Minderman's Laboratory.

The other three tubes will be processed in the Hematologic Procurement Laboratory. Plasma samples are to be processed at 4°C using a refrigerated centrifuge at approximately 3000 rpm for about 10 minutes with the plasma being aliquoted into 2 cryovials per time-point. The samples will immediately be frozen at - 70ºC or below until analyzed. PBMC's will then be obtained by ficoll gradient as per the lab's standard procedure. Two of the tubes will be pooled and the PBMC's will be frozen in Gibco Cell culture freezing media and will be stored in LN2 until time of analysis. The remaining tube of PBMC's will be frozen in RNA later and will be stored in -70 degrees or below until analyzed. The screw cap polypropylene cryogenic tubes will be labeled with the clinical study number, participant's MR number, participant's study number, protocol time point, protocol day, date and time of draw. Samples will be analyzed in RPCI's Department of Flow and Image Cytometry:

Roswell Park Cancer Institute
Department of Flow and Image Cytometry Cancer Cell Center, C317
Attn: Orla Maguire, PhD
Refer to Study Number– I 274515
Tel: 716-845-3470
orla.maguire@RoswellPark.org
Kieran.O'Loughlin@RoswellPark.org
Hans.Minderman@RoswellPark.org

Note: All investigator or analyzing research laboratories housing research samples need to maintain current Temperature Logs and study-specific Sample Tracking and Shipping Logs. The Principal Investigator/Laboratory Manager must ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens. This is required for both observational and interventional clinical studies collecting clinical samples.

NETWORK SITES: Four 10 mL green-top heparinized tubes of blood will be collected pre dose via venipuncture for biomarker analysis at multiple time points. These will be collected on Day 1 of Cycles 1, 2 and 4. The samples will be labeled with the Subject ID # (unique to Network patients), initials, clinical study number, protocol time point, dose, protocol day, date and time of draw. As above, the whole blood samples will be kept on ice until shipping and shipped on cold packs.

Whole blood samples will be shipped via Fed Express Overnight on cold packs with delivery on Tuesday-Friday. **NO SATURDAY DELIVERY**. Do not ship on a Friday or the day before a holiday.

Samples should be shipped to:
Roswell Park Cancer Institute
Hematologic Procurement Laboratory
Basic Science Bldg., S524
Attn: Linda Lutgen-Dunckley / Brandon Martens
Refer to Study Number– I 274515
Elm & Carlton Streets
Buffalo, New York 14263
Tel: 716-845-8098

Prior to shipment, please email the following individuals:
linda.lutgendunckley@roswellpark.org,
brandon.martens@roswellpark.org,
orla.maguire@RoswellPark.org, Kieran.O'Loughlin@RoswellPark.org and
Hans.Minderman@RoswellPark.org.
Email should include FedEx number and inventory of what is in the shipment.

8.13 Pathology

Fresh tumor biopsies will be obtained on study, one within 30 days prior to Cycle 1 Day 1 and one within 7 days of Cycle 4 Day 1; biopsy prior to C4D1 is preferred, but may be after C4D1, if necessary. Biopsies can be obtained from any tumor site, though a metastatic site is preferred, e.g. via US guided liver biopsy. Four tumor cores, preferably 16-18 gauge and 1 cm long, will be obtained at each time point, with one core being formalin fixed and paraffin-embedded for later IHC staining, and the remainder kept fresh at 4°C for further processing in Dr. Minderman's laboratory.

8.13.1 Archived Formalin-Fixed Paraffin Embedded (FFPE) Biopsy Samples

Note: Participants for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the Principal Investigator). This does not apply for the last 10 patients enrolled on the study, where a fresh biopsy will be mandatory.

The following sections of tissue from the most recent neoplastic tissue that exists in the Paraffin Archive in the Department of Pathology (or outside institution) will be collected:

1. Ten unstained sections cut at 4 microns on plus glass slides.
2. One H&E stained section

The study coordinator or designee will be responsible for entering the order into the EMR using the standard format for all clinical trial pathology requirements.

For **Network Sites**, de-identified tissue samples using study-specific subject ID number and tissue accession# (GCP requires at least 2 identifiers) are to be sent to RPCI Correlative Science Pathology Office (Attn: Protocol Lab Team). The **shipping label** should read as follows:

Roswell Park Cancer Institute
Elm & Carlton Streets
Correlative Science Pathology Office, GBSB S-636
Attn: Protocol Lab Team (I 274515 Samples)
Buffalo, NY 14263
(716) 845-1678

Please email: CRSLabPathTeam@RoswellPark.org when samples are being shipped. Email should include FedEx number and inventory of what is in the shipment.

8.13.2 Pre-and On-Treatment Biopsies

Formalin-Fixed Paraffin-Embedded (FFPE) Biopsy Samples

Immediately fix one core in 10% neutral buffered formalin then paraffin-embed as per institutional standard. If the entire FFPE core biopsy block cannot be submitted, then submit a minimum of eight unstained sections cut at 4 microns on plus glass slides plus one H&E stained section.

Label the block or slides with the study-specific subject ID number and a second identifier, such as the tissue accession number.

The FFPE specimen should be sent to RPCI Correlative Science Pathology Office (Attn: Protocol Lab Team), where the specimens will be batched until later analysis in RPCI's Core Pathology Laboratory. For **Network Sites**, ship block or slides to:

Roswell Park Cancer Institute
Correlative Science Pathology Office, GBSB S-636
Attn: Protocol Lab Team (I 274515 Samples)
Elm & Carlton Streets
Buffalo, NY 14263
(716) 845-1678

Please email: CRSLabPathTeam@RoswellPark.org when samples are being shipped. Email should include FedEx number and inventory of what is in the shipment.

Viable Fresh Biopsy Samples

The **additional core biopsy samples** will be placed in 10-mL cold sterile RPMI 1640 supplemented with 10% human serum and with final concentrations of penicillin G (100 units/mL) and streptomycin (100 µg/mL) and kept at 4°C. Label the samples with study-specific subject ID number, clinical study number, protocol time point and, protocol day. Samples will be analyzed by Dr. Minderman's Laboratory, CCC 317, in the Department of Flow and Image Cytometry.

Network Sites should ship the cold samples overnight with an ice pack to:

Roswell Park Cancer Institute
Department of Flow and Image Cytometry
Cancer Cell Center, C317
Attn: Orla Maguire, PhD
Refer to Study Number– I 274515
Elm & Carlton Streets
Buffalo, New York 14263
Tel: 716-845-3470
Please email: orla.maguire@RoswellPark.org, Kieran.O'Loughlin@RoswellPark.org and Hans.Minderman@RoswellPark.org when samples are being shipped

Email should include FedEx number and inventory of what is in the shipment.

Note: All investigator or analyzing research laboratories housing research samples need to maintain current **Temperature Logs** and study-specific **Sample Tracking and Shipping Logs**. The Principal Investigator/Laboratory Manager **must** ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens. This is required for both observational and interventional clinical studies collecting clinical samples (ship Monday to Thursday only).

9 EFFICACY EVALUATIONS

9.1 Objective Tumor Response

All protocol-defined imaging studies must be performed at the investigative site or sponsor-approved facility using protocol-defined parameters. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Primary objective tumor response will be assessed according to irRECIST (Appendix D).

9.2 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, will be identified as target lesions and recorded and measured at baseline. Target lesions will be selected on the basis of their size. Lesions with the longest diameter (short axis for lymph nodes) and are ≥ 10 mm (CT and MRI), ≥ 15 mm lymph nodes, > 20 mm CXR and are for accurate repetitive measurements (either by imaging techniques or clinically) will be chosen. A sum of the longest diameter (short axis for lymph nodes) of all target lesions will be calculated and reported as the baseline sum diameters. This will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

- **Complete Response (CR):** Disappearance of all target lesions. Any lymph nodes must have a reduction in short axis to < 10 mm. Changes in tumor measurements must be confirmed by repeat studies performed no less than 6 weeks after the criteria for response are first met.

- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Changes in tumor measurements must be confirmed by repeat studies performed no less than 6 weeks after the criteria for response are first met.
- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as references the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
- **Stable Disease (SD):** Neither a sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameter while on study. Participants having a documented response with no confirmation of the response will be listed with stable disease.

9.3 Non-Target Lesions

All other small lesions (longest diameter < 10 mm or lymph nodes ≥ 10 mm to < 15 mm short axis) and non-measurable lesions (i.e., leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, blastic bone lesions, or abdominal masses / abdominal organomegaly identified by physical exam that is not measurable by imaging) should be identified as non-target lesions and indicated as present in the source documents at baseline. The general location will also be documented on the images drawing a regularly-shaped Region of Interest. Measurements of the non-target lesions will not be performed, but the presence or absence of each should be noted throughout follow-up and evaluation.

- **Complete Response:** Disappearance of all non-target lesions and normalization of tumor marker level, if applicable. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- **Non-Complete Response/Non-Progressive Disease:** Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the upper limits of normal.
- **Progressive Disease:** Appearance of 1 or more new lesions or the unequivocal progression of existing non-target lesions. Although a clear progression of non-target lesions is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed at a later time.

9.4 Evaluation of Response

Time point response assessments will be performed every **9** weeks. To determine time point response, refer to **Table 6** and **Table 7** below.

Table 6 Time Point Response Criteria: target (+/- non-target disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 7 Time Point Response Criteria: non-target disease only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[1]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

1 Non-CR/non-PD is preferred over SD for non-target disease since SD is used as endpoint for assessment of efficacy in trials so to assign this category when no lesions can be measured is not advised.

The best overall response is the best response recorded from the start of study treatment until disease progression/recurrence or study discontinuation, taking into account any requirement for confirmation. In general, the participant's best response assignment will depend on the achievement of both measurement and confirmation criteria and will be determined by combining the participant's status of target lesions, non-target lesions, and new lesions.

- Symptomatic Deterioration: Participants with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not related to study treatment or other medical conditions should be reported as progressive disease due to "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment due to symptomatic deterioration. Symptomatic deterioration that may lead to discontinuation of treatment include, but is not limited to, symptoms such as:
    - Weight loss > 10% of body weight.
    - Worsening of disease-related symptoms (e.g., worsening dyspnea, increasing pain/increasing requirement for narcotic analgesics).
    - Decline in performance status of > 1 level on ECOG scale.

9.5 Confirmation Measurement

A confirmatory assessment is required no less than 6 weeks after a PR or CR is deemed.

9.6 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- **Clinical Lesions:** Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- **Chest x-ray:** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Conventional CT and MRI:** This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

- **PET-CT:** At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

- **Ultrasound:** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- **Endoscopy, Laparoscopy:** The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.
- **Tumor Markers:** Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response.
- **Cytology, Histology:** These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

- **FDG-PET:** While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG PET imaging can be identified according to the following algorithm:
- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

10 SAFETY EVALUATION

10.1 Adverse Events

10.1.1 Definition

An adverse event or adverse experience (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of 'unrelated', 'unlikely', 'possible', 'probable', or 'definite').

An AE is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan in other study-related documents.

10.1.1.1 Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be clinically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

10.1.1.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the CRF.

However, clinically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

10.1.1.3 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF, unless their severity, seriousness, or etiology changes.

10.1.1.4 Preexisting Medical Conditions (Baseline Conditions)

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

10.1.1.5 Overdose

Refer to **Section 7.3.2** for a definition of pembrolizumab overdose.

- If an adverse event(s) is associated with ("results from") the overdose of pembrolizumab, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.
- If a dose of pembrolizumab meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

10.1.2 Grading and Relationship to Drug

The descriptions and grading scales found in the CTEP Version 4 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. CTEP Version 4 of the CTCAE is identified and located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

AEs not covered by specific terminology listed should be reported with common medical terminology, and documented according to the grading scales provided in the CTCAE Version 4.

The relationship of event to study drug will be documented by the Investigator as follows:

- **Unrelated:** The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs administered to the participant.

- **Unlikely:** The event is doubtfully related to investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible:** The event follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs.
- **Probable:** The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions or concomitant drugs.
- **Definite:** The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions or concomitant drugs; AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

10.1.3 Reporting Adverse Events

Table 8 Guidelines for Routine Adverse Event Reporting for Phase 1 Studies (Regardless of Expectedness)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4
Unrelated	X	X	X	X
Unlikely	X	X	X	X
Possible	X	X	X	X
Probable	X	X	X	X
Definite	X	X	X	X

Table 9 Guidelines for Routine Adverse Event Reporting for Pilot, Phase 2, and Phase 3 Studies (Regardless of Expectedness)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4
Unrelated			X	X
Unlikely			X	X
Possible	X	X	X	X
Probable	X	X	X	X
Definite	X	X	X	X

Routine AEs occurring between the start date of intervention until 30 days after the last intervention, or until the event has resolved, the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible, will be reported. New information will be reported after it is received.

10.2 Serious Adverse Events

10.2.1 Definition

A serious adverse event (SAE) is any adverse event (experience) that in the opinion of either the investigator or sponsor results in **ANY** of the following:

- Death.
- A life-threatening adverse event (experience). Any AE that places a participant or participants, in the view of the Investigator or sponsor, at immediate risk of death from the reaction as it occurred. It does **NOT** include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.
- Important Medical Event (IME) that, based upon medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.
- Is associated with an overdose
- Is a new cancer (that is not a condition of the study)

10.2.2 Reporting Serious Adverse Events

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any participant must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

SAEs identified as an Unanticipated Problem by the Investigator must be reported. Please refer to **Section 10.7.2** for details on reporting Unanticipated Problems.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the investigational drug, that is brought to the attention of the

investigator at any time outside of the time period specified in the previous paragraph, also must be reported immediately to the Sponsor and to Merck.

10.3 Events of Clinical Interest (ECIs)

Refer to the separate guidance document entitled "Event of Clinical Interest Guidance Document" for detailed instruction regarding identification, evaluation and management of ECIs and irAEs.

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

Any Grade 3 or higher event that the investigator considers to be immune-related should be reported as an ECI regardless of whether the specific event term is in **Table 10 and reported to Merck within 24 hours** from the time the Investigator/physician is aware of such an occurrence. Adverse events that are both an SAE and an ECI should be reported one time as an SAE only, however the event must be appropriately identified as an ECI as well in in the database.

Table 10 Events of Clinical Interest

Pneumonitis (reported as ECI if ≥ Grade 2)		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis (reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis	Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA)	
Endocrine (reported as ECI)		
Type 1 diabetes mellitus (if new onset)		
Hematologic (reported as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic Thrombocytopenic Purpura (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Hemolytic Uremic Syndrome (HUS)
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic (reported as ECI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Hepatitis	Autoimmune hepatitis	Transaminase elevations (ALT and/or AST)
Infusion Reactions (reported as ECI for any grade)		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic (reported as ECI for any grade)		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular (report as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Uveitis	Iritis	
Renal (reported as ECI if ≥ Grade 2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as ECI if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin (reported as ECI for any grade)		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		
Skin (reported as ECI if ≥ Grade 3)		
Pruritus	Rash	Rash generalized
Rash maculopapular		
Any rash considered clinically significant in the physician's judgment		

Other (reported as ECI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

Events of clinical interest for this study include:

- An overdose of pembrolizumab (see **Section 7.3.2**) that is not associated with clinical symptoms or abnormal laboratory results.
- An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing (see **Section 6.3.7**).

Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs (see **Section10.2.2**).

10.4 Investigator Reporting: Notifying the Study Sponsor

Investigators MUST report within 24 hours upon becoming aware, to the sponsor ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220.

10.4.1 Reporting Events of Clinical Interest (ECIs)

ECIs (both non-serious and serious adverse events) identified in the Event of Clinical Interest Guidance Document from the date of first dose of pembrolizumab through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, need to be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety, regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

Attn: Worldwide Product Safety

FAX 215 993-1220

Reporting of Overdose

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

Reporting of Pregnancy and Lactation

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a participant (spontaneously reported to them), including the pregnancy of a male participant's female partner

that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier. All participants and female partners of male participants who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

10.5 Follow-Up for Serious Adverse Events

All related SAEs should be followed to their resolution, until the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible. New information will be reported when it is received.

10.6 Follow-Up for Events of Clinical Interest

All related ECIs should be followed to resolution. The Adverse Experience eCRF should be updated with information regarding duration and clinical course of the event. Information obtained from the consulting specialist, including diagnosis, should be recorded in the appropriate AE fields. Free-text fields should be used to record narrative information:

- Clinical course of the event
- Course of treatment
- Evidence supporting recovery
- Follow-up to the clinical course

Any treatments administered for the event should also be entered in the Concomitant Medication eCRF.

10.7 Unanticipated Problems

10.7.1 Definition

An Unanticipated Problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given:
  a) The research procedures that are described in the study-related documents, including study deviations, as well as issues related to compromise of participant privacy or confidentiality of data.
  b) The characteristics of the participant population being studied.

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized and if in relation to an AE is also deemed **Serious** per **Section 10.2**.

10.7.2 Reporting Unanticipated Problems

Unanticipated problem reporting will begin at the time of participant consent. The Unanticipated Problem Form will be submitted to the CRS Compliance Office within 1 business day of becoming aware of the Unanticipated Problem. After review, CRS Compliance will submit the UP to the IRB.

When becoming aware of new information about an Unanticipated Problem, submit the updated information to CRS Compliance with an updated Unanticipated Problem Form. The site Investigator or designated research personnel will report all unanticipated problems, whether related or unrelated to the investigational agent(s) to the **IRB in accordance with their local institutional guidelines**.

10.8 FDA Reporting

When RPCI is the IND holder the following describes the FDA reporting requirements by timeline for AEs and new safety findings that meet the criteria outlined below:

Within 7 Calendar Days

Any adverse event that meets **ALL** the following criteria:

- Related or possibly related to the use of the study drug;
- Unexpected; and
- Fatal or life-threatening.

Within 15 Calendar Days

Any adverse event that meets **ALL** the following criteria:

- Related or possibly related to the use of the study drug;
- Unexpected; and
- Serious but not fatal or life-threatening;

Or, meets **ANY** of the following criteria:

- A previous adverse event that is not initially deemed reportable but is later found to fit the criteria for reporting (report within 15 days from when event was deemed reportable).
- Any findings from other studies, including epidemiological studies, pooled analysis of multiple studies, or other clinical studies conducted with the study drug that suggest a significant risk in humans exposed to the drug.

- Any findings from animal or in vitro testing that suggest a significant risk for human participants including reports of mutagenicity, teratogenicity, or carcinogenicity or reports of significant organ toxicity at or near the expected human exposure.
- Any clinically important increase in the rate of occurrence of a serious, related or possibly related adverse event over that listed in the protocol or investigator brochure.

Sponsors are also required to identify in IND safety reports, all previous reports concerning similar adverse events and to analyze the significance of the current event in the light of the previous reports.

Reporting Process

The principal investigator or designee will complete and submit a FDA Form 3500A MedWatch for any event that meets the above criteria. Forms will be submitted to the CRS Compliance Office via email to CRSCompliance@RoswellPark.org.

11 DATA AND SAFETY MONITORING

The RPCI Data and Safety Monitoring Board will assess the progress of the study, the safety data, and critical efficacy endpoints. During the Phase Ib study, the study conduct will be reviewed by the RPCI Phase I Committee on a weekly basis. The DSMB will review the study annually and will make recommendations that include but not limited to; (a) continuation of the study, (b) modifications to the design (c) or termination of the study.

12 STATISTICAL METHODOLOGY

This is a single-arm phase Ib\II study of pembrolizumab and cetuximab in patients with metastatic colorectal cancer.

The primary objectives of this study are:

- To estimate the objective response rate of patients with metastatic colorectal cancer treated with pembrolizumab and cetuximab
- To estimate the 6-month progression-free survival (PFS) rate of patients with metastatic colorectal cancer treated with pembrolizumab and cetuximab
- To examine the adverse event profile of combining pembrolizumab and cetuximab

The secondary (exploratory) objectives of this study are:

- To examine the PFS of patients with metastatic colorectal cancer treated with pembrolizumab and cetuximab
- To examine the overall survival of patients with metastatic colorectal cancer treated with pembrolizumab and cetuximab
- To determine estimate the objective response rate by immune-related response criteria (irRECIST) of patients with metastatic colorectal
- To explore peripheral blood and tumor biomarkers of response and/or resistance to the study treatment

12.1 Sample Size Determination

We utilize two primary efficacy endpoints for this study: the proportion of patients achieving complete or partial RECIST objective response rate and the proportion surviving progression-free for at least six months. While the addition of pembrolizumab to cetuximab may have cytotoxic effect, it may act primarily in a cytostatic fashion; therefore, it is important to consider both endpoints, and thus declare the agent worthy of further investigation if it shows activity on either endpoint. We utilize a single-stage version of the bivariate design of Sill, et al (24) (2012). Based on historical data, the response rate for cetuximab alone in this patient population is approximately 20%, and the proportion of patients surviving progression-free for at least six months is approximately 30% (5). We set the following null and alternative hypotheses indicating inactivity or activity for the two endpoints.

Endpoint	**H_0 (regimen inactive)**	**H_1 (regimen active)**
Objective tumor response	20%	40%
6-Month PFS	30%	50%

We will target 42 eligible and treated patients, but will require at least 38 eligible and treated patients in order to have ≥80% power to detect activity based on response alone, ≥80% power to detect activity based on 6-month PFS alone, and ≥97% power if the regimen is active on both endpoints. This assumes independence of the two endpoints; slight losses of power occur for moderate dependence between the two endpoints. Type I error is controlled at <0.10. An exact binomial test will be used to compare the observed response and 6-month PFS percentages versus the null values in the table above. Only patients who are not treated with study therapy will be replaced.

12.2 Demographics and Baseline Characteristics

Descriptive statistics (as appropriate: n, percent, mean, median, min and max) will be used to summarize demographic and baseline characteristics.

12.3 Efficacy Analysis

Objective tumor response and six-month PFS will be tabulated and will be compared to the null values using exact tests. All treated patients with study therapy will be considered evaluable for response and 6-month PFS. Patients who receive at least one full dose of both drugs and come off study therapy prior to 6 months and receive off-protocol therapy will be considered treatment failures with regard to the 6-month PFS endpoint. Patients who have infusions reactions to cetuximab, such that continuation of treatment is not deemed feasible, will be replaced.

All patients treated with study therapy will be considered evaluable for response and 6-month PFS. Patients who come off study therapy prior to 6 months and receive off-protocol therapy will be considered treatment failures with regard to the 6-month PFS endpoint. Objective tumor response will not be considered after patient receives off-study therapy.

Objective tumor response using immune-related RECIST (irRECIST) will be tabulated.

Analysis of secondary endpoints will be hypothesis generating and descriptive in nature. Distributions of PFS and OS will be estimated using the Kaplan-Meier method.

12.4 Safety Analysis

12.4.1 Adverse Event

The frequency of toxicities will be tabulated by maximum grade by preferred term within a patient across all cycles. All participants who receive any study treatment will be considered evaluable for toxicity.

12.5 Phase Ib Analysis and Criteria for Early Termination of the Study

There will be an initial Phase Ib cohort to examine the safety and tolerability of the combination. After up to nine patients are enrolled, and at least 6 have completed at least two cycles of chemotherapy, the study will be suspended, and the safety/tolerability of the combination will be examined. If ≥2 patients out of 6 (or ≥2/7, ≥2/8, or ≥3/9) patients have DLTs, the study will be modified or stopped after review of all safety data. The Roswell Phase I Committee, Study PI, and study statistician will all be involved in the discussion. At that time, the study team will decide what action to take, e.g., continue the study as is, make changes to the study with regard to treatment or dose modifications, or discontinue the study. Should the study team elect to continue the study with additional modifications, the revised protocol must be submitted to the FDA for further review prior to implementation in the clinical study.

The dose limiting toxicity (DLT) will be defined as any ≥ grade 3 clinically significant toxicity, which is deemed possibly treatment related and occurs within the first 6 weeks of therapy. This will be exclusive of rash, fatigue and hypomagnesemia, but inclusive of grade 4 rash or hypomagnesemia which does not revert to grade ≤ 2 within 24 hours.

Following the phase Ib cohort, no interim analyses for efficacy are planned for this study. The study adds an agent (pembrolizumab) to a standard of care agent (cetuximab), so we expect efficacy to be at least as good as standard of care.

13 CORRELATIVE DATA ANALYSIS

Biomarker Analyses: Pre- and post-treatment levels and changes from pre- to post-treatment in biomarkers will be summarized overall and by response and 6-month PFS categories using summary statistics (e.g., mean or median, with dispersion measures, and using transformed values as appropriate). Depending on the number of responses, logistic regression models may be used to compare response rates across pre-treatment biomarker levels. Proportional hazards models may be used to examine progression-free survival and overall survival across biomarker levels.

14 ETHICAL AND REGULATORY STANDARDS

14.1 Ethical Principles

This study will not be initiated until the protocol and informed consent document(s) have been reviewed and approved by a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Each participant (or legal guardian) shall read, understand, and sign an instrument of informed consent prior to performance of any study-specific procedure. It is the responsibility of the investigator to ensure that the participant is made aware of the investigational nature of the treatment and that informed consent is given.

The Investigator is responsible for the retention of the participant log and participant records; although personal information may be reviewed by authorized persons, that information will be treated as strictly confidential and will not be made publicly available. The investigator is also responsible for obtaining participant authorization to access medical records and other applicable study specific information according to Health Insurance Portability and Accountability Act regulations (where applicable).

This study will be conducted in compliance with all applicable laws and regulations of the state and/or country and institution where the participant is treated. The clinical trial should be conducted in accordance with the ethical principles embodied in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, consistent with good clinical practice and the applicable regulatory requirements and according to the guidelines in this protocol, including attached appendices.

14.2 Informed Consent

The Investigator (or IRB specified designee) is responsible for obtaining written consent from each participant or the participant's legally authorized representative in accordance with applicable GCP guidelines using the approved informed consent form, before any study specific procedures (including screening procedures) are performed. The informed consent form acknowledges all information that must be given to the participant according to GCP guidelines, including the purpose and nature of the study, the expected efficacy and possible side effects of the treatment(s), and specifying that refusal to participate will not influence further options for therapy. Any additional information that is applicable to the study must also be included. Additional national or institutionally mandated requirements for informed consent must also be adhered to. The participant should also be made aware that by signing the consent form, processing of sensitive clinical trial data and transfer to other countries for further processing is allowed.

The Investigator shall provide a copy of the signed consent form to the participant and the signed original shall be maintained in the Investigator File. A copy of the signed consent form must be filed in the participant file. At any stage, the participant may withdraw from the study and such a decision will not affect any further treatment options.

15 STUDY RESPONSIBILITIES

15.1 Data Collection

Data entry into the database is to be completed in a timely fashion (within 30 days) after the participant's clinic visit. If an AE is considered serious it is captured on both the Adverse Event page and the Serious Adverse Event Source Form, which is handled in an expedited fashion.

Data management activities will be performed using eClinical. eClinical is a suite of software tools that enables the collection, cleaning and viewing of clinical trial data. CRS data management will design the study-specific database and facilitate its development by the eClinical Information Technology team. Once the database design is approved by the Investigator, Statistician, and Clinical Research Coordinator, the database will be put into production and data entry can begin. Data can be entered and changed only by those with the rights to do so into the eCRFs (via the EXPeRT Module). eClinical is compliant with all relevant technical aspects of relevant GCP guidelines.

- The system can generate accurate copies of stored data and audit trail information in human readable form.
- System access is limited to authorized individuals through the controlled assignment of unique ID and password combinations.
- The system is designed to periodically force users to change their passwords and verifies that user ID and password combinations remain unique.
- The system automatically generates a permanent time-stamped audit trail of all user interactions.

When data entry is complete, data management will review the data and will query any missing, incomplete, or invalid data points for resolution by the Clinical Research Coordinator and Investigator. Once all queries have been resolved, the data can be released to the statistician for analysis.

15.2 Maintenance of Study Documents

Essential documents will be retained per RPCI's policy for 6 years from the study termination date. These documents could be retained for a longer period, however, if required by the applicable local regulatory requirements or by an agreement with RPCI.

16 ADMINISTRATIVE RULES

16.1 Revisions to the Protocol

RPCI may make such changes to the protocol as it deems necessary for safety reasons or as may be required by the U.S. FDA or other regulatory agencies. Revisions will be submitted to the IRB/ERC for written approval before implementation.

16.2 Termination of the Study

It is agreed that, for reasonable cause, either the RPCI Investigators or the Sponsor, may terminate this study, provided a written notice is submitted within the time period provided for in the Clinical Trial Agreement. In addition, RPCI may terminate the study at any time upon immediate notice if it believes termination is necessary for the safety of participants enrolled in the study.

16.3 Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

17 APPENDICES

Appendix A Instructions for Network Sites

1. CONTACT INFORMATION

All questions related to the protocol or study implementation should be directed to:

Roswell Park Cancer Institute
CRS Network Office
ASB K 104
Buffalo, New York 14263
Telephone:
Monday - Friday; 8: 00 AM to 4: 30 PM EST
716-845-8084
After hours, weekends, and holidays request the RPCI Investigator
716-845-2300
Fax: 716-845-8743

2. INFORMED CONSENT

- Informed consent must be obtained by the **site Investigator/designee** from any participants wishing to participate, **prior to any study specific procedures.**
- An informed consent template is provided by RPCI and can be amended to reflect institutional requirements.
- All consent changes **must** be reviewed by RPCI Network Office prior to submission to the site IRB.
- The informed consent must be IRB approved.
- Always check that the most up to date version of the IRB approved consent is being used.
- Within 5 business days, notify the RPCI Network Office of all participant withdrawals or consent to limited study participation and appropriately document the discontinuation and the reason(s) why.

3. PARTICIPANT REGISTRATION

The participant completes the Gender, Race, and Ethnicity Form and this is placed in the study binder.

RPCI does not grant exceptions to eligibility criteria.

Phase 1 Protocol Registration Instructions

Contact the RPCI Network Monitor to verify that a slot is available in the open cohort when a participant has been identified. **Do not have the participant sign consent prior to verifying an open slot.**

- After the participant signs consent, the Subject Screening and Enrollment Log must be faxed or emailed to the RPCI Network Monitor within 1 business day. The RPCI Network Monitor

will confirm receipt of the Subject Screening and Enrollment Log and email the participant ID number.

- When the participant has met eligibility, a signed eligibility checklist and other requested documentation will be faxed or emailed to the RPCI Network Monitor.
- Within 1 business day of receipt of the eligibility check list, the RPCI Network Monitor will fax or email the cohort assignment and dose level.
- An email must be sent by the site to confirm receipt of the cohort assignment and to provide the planned treatment start date.

Phase 2 Protocol Registration Instructions

The Subject Screening and Enrollment Log must be faxed or emailed to the RPCI Network Office within 1 business day of the date the participant is consented. Once the Investigator has determined that eligibility has been met, complete the eligibility check list and fax or email it to the RPCI Network Monitor at 716-845-8743.

4. STUDY DEVIATIONS

- If a deviation has occurred to eliminate hazard, this must be reported to the RPCI Network, site IRB and any other regulatory authority involved in the study.
- ALL study deviations will be recorded on the **Study Deviation Log**.
- Participants inadvertently enrolled with significant deviation(s) from the study-specified criteria will be removed from the study, at the discretion of the Principle Investigator.

5. STUDY DOCUMENTATION

- Study documents must be filled out completely and correctly. Ditto marks are not allowed.
- If an entry has been documented in error put a single line through the entry and initial and date the change. The RPCI Network Monitor must be able to read what has been deleted.
- Do **NOT** use white-out, magic marker, scratch-outs.
- Do **NOT** erase entries.
- Use only black ink for documentation on the accountability form and any other study forms.
- It is the responsibility of RPCI to inform the Investigator/ institution as to when these documents no longer need to be retained. If, for any reason, the Investigator desires to no longer maintain the study records, they may be transferred to another institution, another investigator, or to RPCI upon written agreement between the Investigator and RPCI.

6. DRUG ACCOUNTABILITY

Drug accountability must be strictly maintained.

- Responsibility rests solely with the Investigator but can be delegated as appropriate (e.g., to pharmacy personnel).
- A drug accountability record form (DARF) will record quantities of study drug received, dispensed to participants and wasted, lot number, date dispensed, participant ID number and initials, quantity returned, balance remaining, manufacturer, expiration date, and the initials of the person dispensing the medication.
- Study drug supply will only be used in accordance with the IRB approved study.
- Drug accountability forms are protocol and agent specific, they are study source documents and will be used to verify compliance with the study.
- An inventory count must be performed with each transaction. Any discrepancies shall be documented and explained.
- Drug accountability forms must be stored with study related documents.
- Each medication provided for this study and each dosage form and strength must have its own DARF.
- Dispensing the wrong study supply is considered a **medication error**.
- **NEVER** replace investigational agents with commercial product.
- Do **NOT** "transfer", "borrow" or "replace" supplies between studies.

7. SERIOUS ADVERSE EVENT REPORTING

The site Investigator or designated research personnel will report all SAEs, whether related or unrelated to the investigational agent(s) to the **IRB in accordance with their local institutional guidelines**. The site will notify the RPCI Network Monitor within 1 business day of being made aware of the SAE. A preliminary written report must follow within 1 business day of the first notification using the following forms:

- RPCI SAE Source form
- MedWatch 3500A
- See section 10.4 for additional reporting information

A complete follow-up report must be sent to the RPCI Network Monitor when new information becomes available.

8. UNANTICIPATED PROBLEM REPORTING

An unanticipated problem (UP) is any incident, experience, or outcome that meets all of the criteria in **Section 10.7**.

For all adverse events occurring that are unanticipated and related or possibly related to the research drug, biologic or intervention, the participating physician or delegated research staff

from each site will notify their local **IRB in accordance with their local institutional guidelines**. The site must also notify the RPCI Network Monitor within 1 business day of being made aware of the Unanticipated Problem by completing the **RPCI Unanticipated Problem Report Form** and faxing or emailing it to the RPCI Network Monitor.

Appendix B ECOG Performance Status Scores

Description	Status
Fully active, able to carry on all pre-disease performance without restriction.	0
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.	1
Ambulatory and capable of all self-care but unable to carry out any work activities.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4
Dead	5

Appendix C Calculation for Creatinine Clearance

Cockroft-Gault Equation*

Men: CrCl = [(140-YR) x ABW] / (SCr x 72)

Women: CrCl = 0.85 x [(140-YR) x ABW] / (SCr x 72)

Where:

CrCl is creatine clearance (mL/min)

ABW is Actual body weight (kg)

SCr is serum creatinine (mg/dL)

YR is age (years)

*Cockcroft D, W, Gault M, H, Prediction of Creatinine Clearance from Serum Creatinine. Nephron. 1976; 16 (1):31-41)

Appendix D Adaptation of the Immune-Related Response Criteria: irRECIST

The following is taken from Bohnsack et al, 2014, 1070P-Adaptation of the Immune Related Response Criteria: irRECIST, Ann Oncol, 25 (suppl 4): iv369 doi:10.1093/annonc/mdu342.23 [25].

1. Baseline

A. Measurable Lesion Definitions and Target Lesion Selection

- Follow the definitions from RECIST 1.1
- Measurable lesions must be accurately measured in at least one dimension with a minimum size of:
    - 10 mm in the longest diameter by CT or MRI scan (or no less than double the slice thickness) for non- nodal lesions and ≥ 15 mm in short axis for nodal lesions
    - 10 mm caliper measurement by clinical exam
    - 20 mm by chest X-ray

B. Non-measurable Lesion Definitions

- Follow the definitions from RECIST 1.1
- Non-target lesions will include
    - Measurable lesions not selected as target lesions
    - All sites of non-measurable disease, such as neoplastic masses that are too small to measure because their longest uninterrupted diameter is < 10 mm (or < two times the axial slice thickness), i.e., the longest perpendicular diameter is ≥ 10 and < 15 mm.
    - Other types of lesions that are confidently felt to represent neoplastic tissue, but are difficult to measure in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural or pericardial effusions, ascites, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill-defined abdominal masses, skin lesions, etc.

C. Target and Non-target Lymph Node Lesion Definitions

- Follow the definitions from RECIST 1.1

D. Non-target Lesion Selection

- All lesions or sites of disease not recorded as target lesions should be recorded as non-target lesions at baseline. There is no limit to the number of non-target lesions that can be recorded at baseline.

E. Bone Lesions

- Follow the definitions from RECIST 1.1
- Regardless of the imaging modality blastic bone lesions will not be selected as target lesions. Lytic or mixed lytic-blastic lesions with a measurable soft tissue component ≥ 10 mm can be selected as target lesions.

F. Brain Lesions

- Brain Lesions detected on brain scans can be considered as both target or non-target lesions.

G. Cystic and Necrotic Lesions as Target Lesions

- Lesions that are partially cystic or necrotic can be selected as target lesions.
- The longest diameter of such a lesion will be added to the Total Measured Tumor Burden (TMTB) of all target lesions at baseline.
- If other lesions with a non-liquid/non-necrotic component are present, those should be preferred.

H. Lesions with Prior Local Treatment

- During target lesion selection the radiologist will consider information on the anatomical sites of previous intervention (e.g. previous irradiation, RF-ablation, TACE, surgery, etc.).
- Lesions undergoing prior intervention will not be selected as target lesions unless there has been a demonstration of progress in the lesion.

I. No Disease at Baseline

- If a patient has no measurable and no non-measurable disease at baseline the radiologist will assign ‘No Disease’ (irND) as the overall tumor assessment for any available follow-up time-points unless new measurable lesions are identified and contribute to the TMTB.

2. <u>Follow-Up</u>

A. Recording of Target and New Measurable Lesion Measurements

- The longest diameters of non-nodal target and new non-nodal measurable lesions, and short axes of nodal target and new nodal measurable lesions will be recorded. Together they determine the Total Measured Tumor Burden (TMTB) at follow-up.

B. Definition of New Measurable Lesions

- In order to be selected as new measurable lesions (≤ 2 lesions per organ, ≤ 5 lesions total, per time-point), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions.

C. Non-target Lesion Assessment

- The RECIST 1.1 definitions for the assessment of non-target lesions apply.
- The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN).
- Non-target lesions do not affect irPR and irSD assessments.
- Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD.

D. New Non-Measurable Lesions Definition and Assessment

- All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively.
- Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the time-point.
- Persisting new non- measurable lesions prevent irCR.

3. <u>irRECIST Overall Tumor Assessments</u>

- **<u>irCR</u>**: complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis. Confirmation of response is not mandatory.

- **irPR**: decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions.
- **irSD**: failure to meet criteria for irCR or irPR in the absence of irPD.
- **irNN**: no target disease was identified at baseline and at follow-up the patient fails to meet criteria for irCR or irPD.
- **irPD**: minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment.
- **irNE**: used in exceptional cases where insufficient data exists.
- **irND**: in adjuvant setting when no disease is detected.

For additional information, refer to the following article and online supplemental information:
Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, Lin NU, Litiere S, Dancey J, Chen A, Hodi FS, Therasse P, Hoekstra OS, Shankar LK, Wolchok JD, Ballinger M, Caramella C, de Vries EG, group Rw. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18(3):e143-e52. doi: 10.1016/S1470-2045(17)30074-8. PubMed PMID: 28271869.
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