Confidential

TITLE: **A phase I/II trial of pembrolizumab (MK-3475) and poly-ICLC in patients with metastatic mismatch repair-proficient (MRP) colon cancer**

IND NUMBER: **129974**

PROTOCOL #: **CC-16047**

ClinicalTrials.gov #: **NCT02834052**

PROTOCOL SPONSOR/PI: **Asha Nayak-Kapoor, M.D.**

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Investigational Agent(s):

Drug Name:	**Pembrolizumab**	**Poly-ICLC**
Other Identifier:	MK-3475	Polyinosinic-Polycytidylic acid – poly-L-lysine carboxymethylcellulose
IND Number:	123,482	43984
Manufacturer:	Merck	Oncovir

Protocol History

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CONTENTS

TABLES

1 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab and Poly-ICLC in MRP colon cancer
Trial Phase	*1/2*
Clinical Indication	Phase 1: All solid tumors; Phase 2: Metastatic Mismatch Repair Proficient (MRP) Colon Cancer, which includes disease that is microsatellite instability status low (MSI-low) and microsatellite stable (MSS).
Trial Type	Interventional
Type of control	Historical
Route of administration	Pembrolizumab IV, Poly-ICLC IM
Trial Blinding	None
Treatment Groups	1
Number of trial subjects	31
Estimated enrollment period	18 months
Estimated duration of trial	*30 months*
Duration of Participation	2-3 years
Estimated average length of treatment per patient	6 months

2 TRIAL DESIGN

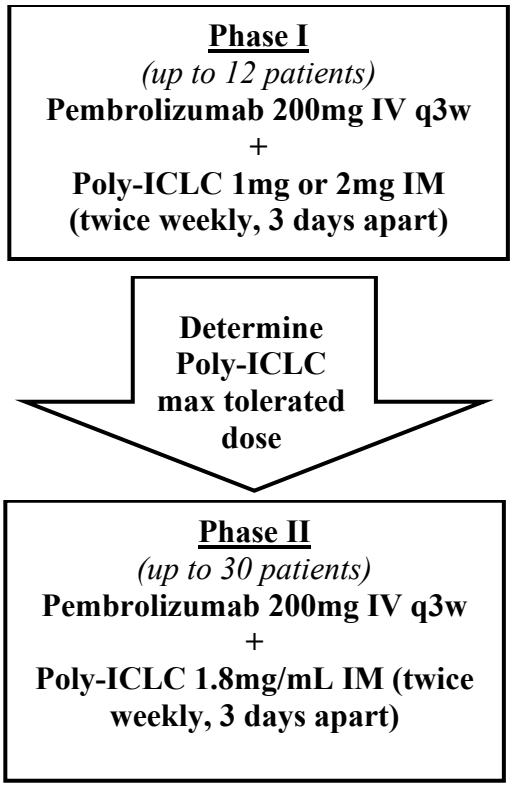
2.1 Trial Design

This study will enroll its patients into two separate phases:

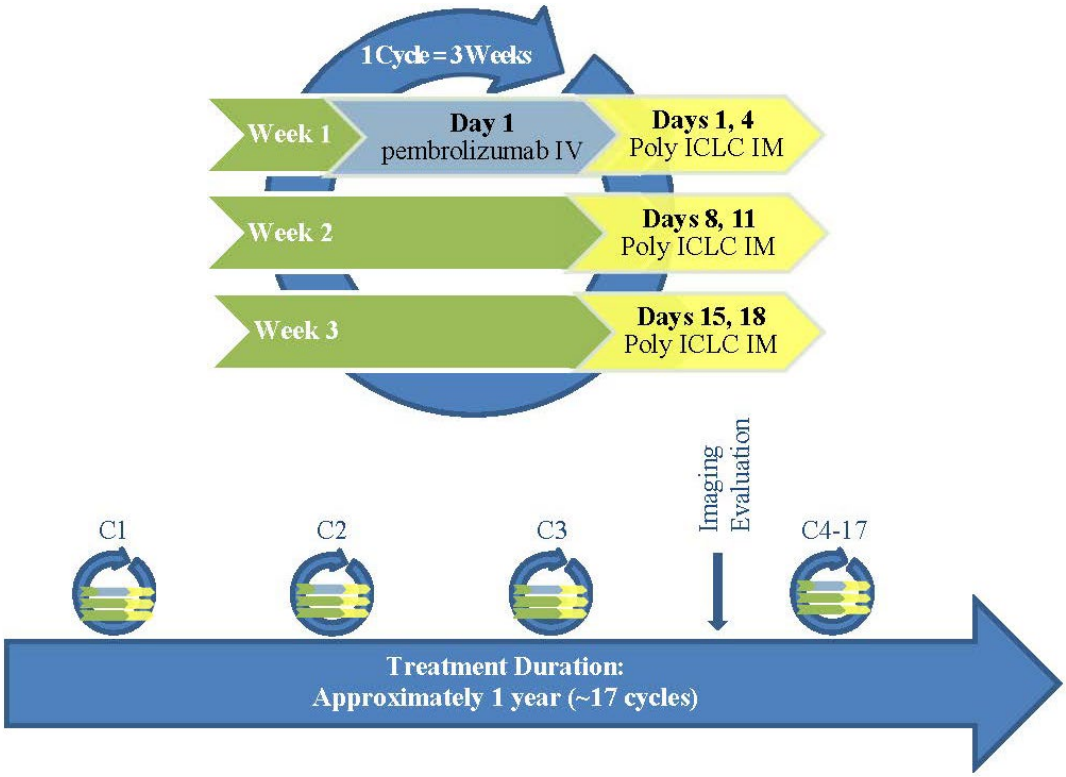
1) Run In phase
    a. Aimed to determine if poly-ICLC can be safely combined with standard dosages of pembrolizumab.
        i. Poly-ICLC will be administered intramuscularly twice weekly at two dose levels: 1 mg or 2 mg
        ii. Pembrolizumab will be administered 200 mg IV q3w
    b. Each dose level enrolls 3-6 patients, with the potential for 12 patients if dose limiting toxicity (DLT) occurs at each dosing level.
    c. Patients with any solid tumor that is unresponsive to at least one line of therapy are eligible for the dose escalation phase unless curative options exist
2) Phase II trial expansion
    a. The combination will then be administered at the recommended phase II dose in up to 27 patients with metastatic MRP colon cancer

2.2 Trial Diagrams

2.2.1 Trial Phases



2.2.2 Trial Treatments



3 OBJECTIVES & HYPOTHESES

3.1 Primary Objectives & Hypotheses

3.1.1 Objectives:

a. Phase 1: Determine the maximum tolerated dose of poly-ICLC that can be combined with pembrolizumab
b. Determine the response rate, as assessed by RECIST 1.1, of metastatic MRP colon cancer that has progressed following two lines of therapy in the metastatic setting to the combination of pembrolizumab and poly-ICLC

3.1.2 Hypotheses:

a. Poly-ICLC will generate an inflammatory response increasing epitope recognition and development of tumor reactive T cells at the tumor site. However, interferon alpha and gamma produced by the poly-ICLC will increase PD-L1 expression and limit new T cell development. Thus, PD1 blockade will increase the effectiveness of the therapy.
b. Phase 1 – Combination of Poly-ICLC and Pembrolizumab is tolerable at the doses proposed for this intervention
c. Phase 2 – Combination of poly-ICLC and pembrolizumab has increased efficacy compared to pembrolizumab alone in patients with colon cancer. The RR will increase to 20% for the combination treatment from an expected 5% response rate for pembrolizumab alone.

3.2 Secondary Objectives

a. Phase I and II - Determine the adverse event profile and dose limiting toxicities of the combination of pembrolizumab and poly-ICLC
b. Determine the progression free survival rate, overall survival rate and duration of response of recurrent metastatic MRP colon cancer to the combination of pembrolizumab and poly-ICLC

3.3 Exploratory Objectives

a. Evaluation of inflammatory state in tumor biopsies with specific attention to definition of tumor infiltration with hematopoietic cells, cell surface signaling molecule expression
b. Evaluation of pre-treatment and post-treatment microarray panels in tumor samples and peripheral blood
c. Determine response rate by irRECIST

4 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on Pembrolizumab (MK-3475). Refer to the Investigator's Brochure (IB) for detailed background information on Poly-ICLC

4.1.1 Pharmaceutical and Therapeutic Background for pembrolizumab

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 immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various 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.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United 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.

4.1.2 Pharmaceutical and Therapeutic Background for poly-ICLC

Polyinosinic-Polycytidylic acid stabilized with poly-L-lysine and carboxymethylcellulose (Poly-ICLC, Hiltonol®) is a synthetic double-stranded ribonucleic acid (dsRNA) 'host-targeted' therapeutic viral-mimic and Pathogen-associated molecular pattern (PAMP) with broad innate and adaptive immune enhancing, vaccine adjuvant, antiviral and anti-proliferative effects. These effects are mediated partly by its induction of a 'natural mix' of interferons (IFNs), cytokines, and chemokines, activation of natural killer [NK] cells, myeloid dendritic cells via TLR3 and MDA5, T4 and T8 cells, and activation of several nuclear and cytoplasmic enzyme systems, including the oligoadenylate synthetase [OAS], the dsRNA dependent protein kinase [PKR], RIG-I Helicase, and MDA5 that are involved in antiviral and antitumor host defenses. It has been shown to have broad gene regulatory actions as well.

Poly-ICLC was used intravenously as an IFN inducer some years ago in patients with various types of cancers, including leukemia, lymphoma, gliomas, myeloma, juvenile laryngeal papillomatosis, renal cell carcinoma, breast cancer, ovarian cancer, and melanoma.[1-9] In most of these early trials, about 6 mg/m2 Poly-ICLC was generally used intravenously. Few objective responses were reported in these high dose clinical trials and Poly-ICLC was generally abandoned when recombinant IFN became available. It was subsequently determined that lower doses (10 to 50 µg/kg) of Poly-ICLC resulted in a broader host defense stimulation, a potent adjuvant and antiviral effects.[10] Consequently, Poly-ICLC is currently being developed for use only at doses up to about 30 µg/kg and the data presented in the following sections focus on studies using Poly-ICLC in this target dose range.

Pharmacokinetics and Product Metabolism in Humans

Poly-ICLC is not detectable in serum 24 hours after administration. However, the clinical half-life of the OAS response to 30 µg/kg IM Poly-ICLC in healthy human volunteers is about 2.5 days, suggesting an optimum dose schedule of two or three times per week. Twenty-four of 29 patients treated with 10 to 20 µg/kg Poly-ICLC by IM injection showed at least a 300% increase in serum OAS. A significant association of serum OAS with tumor response has been observed in patients with malignant glioma participating in an open pilot trial.

Mechanism of Action

Poly-ICLC stimulates at least 4 interrelated systems, any of which (alone or in combination) might be responsible for its possible antitumor and antiviral activity; induction of IFN and multiple other cytokines, chemokines and costimulatory factors, a broad immune-enhancing effect,[5] direct antiviral/antineoplastic effect, and modulation of gene expression.

Poly-ICLC induces a 'natural mix' of interferons, cytokines and chemokines, including IFN production. As expected, the amount of these measurable in serum is dose-dependent, although biologically significant induction likely occurs locally. In previous studies, the minimal serum IFN levels induced by the currently recommended low doses of Poly-ICLC have not been associated with antitumor or antiviral action. A study of the immunomodulatory effect of Poly-ICLC in cancer patients showed no detectable serum IFN in patients receiving 1 mg/m^2 poly-ICLC by IM injection.[1] In contrast, IFN was detectable in the serum of patients receiving 4 mg/m^2 IV poly-ICLC.

Low-dose Poly-ICLC directly stimulates the immune system through activation of NK cells, myeloid dendritic cells via TLR3 and MDA5, T-cells, macrophages and by inducing a 'natural mix of interferons, cytokines and chemokines'. Some of these actions are related to the potent PAMP-adjuvant actions of poly-ICLC with various vaccine platforms, as well as to the broad antiviral state induced by the drug.

The third action of poly-ICLC is a more direct broad host-targeted antiviral and perhaps antineoplastic effect mediated by the two IFN-inducible nuclear enzyme systems, the 2'5'-oligoadenylate synthase (OAS) and the double stranded RNA kinase P1/eIF2a kinase, also known as the PKR,[3-5] as well as RIG-I helicase and MDA5. The concentration of the 2'5'-OAS was elevated in the peripheral blood mononuclear cells of all Poly-ICLC-treated patients. Intramuscular administration of low-dose Poly-ICLC increased NK cells and growth inhibitory activities and 2'5'-OAS levels to a greater extent than high-dose IV infusion. Clinically, a maximal OAS response was observed at an IM dose of 30 μg/kg Poly-ICLC, and was greatly decreased at greater than 100 μg/kg in normal volunteers.[11] The hypothesis that OAS and/or PKR may be involved in the antineoplastic effect of Poly-ICLC may thus explain the relative ineffectiveness of high dose Poly-ICLC in early cancer trials. However, further studies are needed to confirm this.

A fourth aspect of the action of Poly-ICLC involves modulation of the expression of a broad range of innate immune and other genes in a pattern closely paralleling that of a live virus vaccine (YF).[11,12] Some of these genes play critical roles in the body's natural defenses against a variety of neoplasms and microbial infections, and in controlling other cell functions, including protein synthesis, programmed (apoptotic) cell death, cell metabolism, cellular growth, the cytoskeleton and the extracellular matrix.

Immune Effects of Poly-ICLC administration

A randomized trial of poly-ICLC administration to normal volunteers was conducted to establish the signaling effects of the molecule and to establish its comparability to live viral vaccines. Eight volunteers received poly-ICLC and four received placebo. In addition, another group of volunteers received a live viral vaccine to yellow fever to allow a comparison with the poly-ICLC treated subjects. Poly-ICLC was administered at a dose of 1.6 mg subcutaneously in this study. RNA samples from peripheral blood were obtained at multiple time points (6 hr, 12 hr, and 1, 2, 3, 7, 14, and 28 days after treatment). The peak response was observed at day 1 in five of the eight subjects and at 12 hours in the others. There was no change in microarray expression patterns observed in the placebo group following injection whereas there were 31, 212 and 52 genes showing more than a 2 fold increase at 12 hr, day 1 and 2 respectively and the expression patterns were comparable. An examination of the time course of the total number of differentially expressed genes following poly-ICLC administration shows a peak effect at 24 hours with a return to pretreatment levels on day three. Based on this and other observations a twice weekly dosing regimen would provide optimal results for enhancement of Poly-ICLC effects. Poly-ICLC induced a broad array of interferon-regulated genes (IRGs) associated both with viral control and enhancement of viral replication. Using pathway analysis the expression of other innate signaling pathways was stimulated including NF-κB, dendritic cell maturation, antigen presentation and inflammasome-associated genes. Poly-ICLC also induced expression of BAFF which triggers Ig class switching and increased the expression of components of the complement system (C1QB, C3AR1 and SERPING1). A comparison with the effects of yellow fever vaccine on peripheral blood microarray showed that

poly-ICLC induced a similar pattern although the time course was different with peak activation at 1 day for poly-ICLC and 7 days for yellow fever vaccine.

Safety and Tolerance of Poly-ICLC

The side effects of poly-ICLC depend on several factors including dose, route of injection, and health status of the patient. Early Phase I trials in advanced cancer patients studies reported a maximum tolerated dose (MTD) of about 12 mg/m^2 IV; at this dose, the mean serum type I IFN level was 2000 IU/mL, well above that attainable with exogenous IFN. Patients typically showed fevers of 40ºC, myalgia, arthralgia, malaise, and some nausea and vomiting, similar to symptoms seen with high dose interferon (IFN). While the dose in most of the early cancer trials, was about 6 mg/m^2 poly-ICLC IV, it was subsequently found that a much lower IM dose (<1mg/ m^2) was better for enhancing immune effects, with much milder side effects than IV administration [13] [14] More specific side effects of IM poly-ICLC are listed below. Please note that these are generally at higher doses than that proposed for this trial.

Discomfort at IM injection site:

The most common adverse effect is mild, transient discomfort at the site of IM injection. With subcutaneous (SC) injections there is a transient mild to moderate grade 1 or 2 erythematous skin reaction. [15]. However, when combined with peptide vaccine plus Montanide SC, it can produce a transient skin reaction with induration or sterile abscess. Biopsy of such lesions has demonstrated infiltration by T-cells sensitized to the peptide. Such responses have not been reported with poly-ICLC alone or mixed with other vaccines.

In a recent pilot study of intratumoral Poly-ICLC in patients with large metastatic tumors, most patients showed tumor necrosis and or inflammation of the injected tumor. Two of those patients had large facial lesions that became infected and were treated with antibiotics. The necrosis resulted in a void where the tumor had been. In one patient, the inflammation was treated transiently with corticosteroids.

Flu-like symptoms:

Approximately 8 to 12 hours after doses of 10 to 50 mcg/kg IM, patients may develop a mild flu-like syndrome with fever of less than 38ºC, which may last for about 12 hours, but responds readily to acetaminophen or aspirin. Mild myalgia, arthralgia, sometimes nausea, and malaise can be present during this period of time. This flu-like syndrome typically diminishes markedly after the first few poly-ICLC treatments. On very rare occasions in the course of treatment, patients who have been tolerating treatment uneventfully may develop an earlier, more pronounced fever with chills and malaise (typical of higher dose IV poly-ICLC) in response to an IM injection. This will typically resolve over 12 to 24 hours, responds to acetaminophen, and does not typically recur on subsequent dosing.

Hematologic abnormalities:

Several cases of transient leukopenia have been reported. Poly-ICLC was restarted after a drug holiday in most cases, but leukopenia recurred in only one patient, with rapid resolution within two days after discontinuation of drug for the second time. This was felt to represent transient migration and compartmental sequestration of WBC rather than myelotoxicity. High dose Poly-ICLC has been associated with a coagulopathy in dogs, but not in other species including primates. There has been no change in the expected incidence of deep venous thrombosis,

pulmonary embolus, or coagulopathy in multiple sclerosis, AIDS or malignant glioma patients on low dose IM poly-ICLC. One paralyzed multiple sclerosis patient treated with 100 mcg/kg IV suffered a fatal pulmonary embolus, which was not judged to be due to the drug.

Hepatic enzyme elevation:
Mild (grade 1), transient (<7 days) hepatic enzyme elevations were described in a trial of 100 mcg/kg poly-ICLC given IV in multiple sclerosis patients. In three patients, this was prolonged for >7 days, but in all patients the enzymes returned to normal after temporary discontinuation of the poly-ICLC. Enzyme elevation was not typically seen with doses of 10 to 50 mcg/kg three times weekly. However, one patient receiving 20 mcg/kg three times per week had to be dropped from study because of a transient enzyme elevation that persisted slightly longer than the 4-week protocol cutoff. In addition, preclinical studies have shown increased hepatic NK cells, as well as suppression of the P450 hepatic enzyme system by poly-ICLC, as well as by IFN, but the clinical implications of this finding are not clear.[16] [17]

Seizures:
Three glioma patients with epilepsy had seizures during a high febrile episode, but recovered uneventfully.

Transient peritumoral inflammation or edema:
In a pilot brain tumor trial, a few patients showed an increase in their gadolinium enhancing lesions after 3-6 months of IM poly-ICLC, followed by an apparent tumor response at 6-12 months and prolonged survival on continued treatment.[18] Decadron was used as needed in first few months of treatment on that study. In a more recent follow-up open study in patients with advanced recurrent gliomas, several patients have shown increased peritumoral edema after several weeks of poly-ICLC therapy. This has resolved in all cases on continued poly-ICLC, with or without concomitant steroids. (Merchant, Young et al, 2000) Biopsy data in at least two patients treated with poly-ICLC also showed a peritumoral inflammatory response. These findings support the possibility that poly-ICLC may at times be facilitating a relatively early immunologic response to the tumor, perhaps manifested by transient increased inflammation or gadolinium enhancement.

Multicenter glioma Clinical trials
In a recent multi-center study of glioblastoma patients, 21 of the 24 subjects (88%) receiving 20 mcg/kg poly-ICLC alone three times weekly reported at least one adverse event. The incidence of adverse events was reported by the worst grade for an event for an individual subject. The majority of adverse events were classified as either grade 1 (71 of 104 or 68%) or grade 2 (28 of 104 or 27%) toxicity. There were only 3 of 104 (3%) and 2 of 104 (2%) events reported as a grade 3 or grade 4 event, respectively. The most frequently reported events (toxicities) were fatigue (15 subjects), local 'pain-other' (10 subjects), and myalgia (9 subjects). Only 57 out of 380 events were definitely or probably ascribed to Poly-ICLC. [19,20]

In a separate trial in patients with multiply recurrent anaplastic glioma receiving the same dose IM, all 24 subjects treated (100%) reported at least one adverse event. The majority of adverse events reported were classified as either grade 1 (41 of 63 or 65%) or grade 2 (14 of 63 or 22%). There were 7 of 63 (11%) grade 3 events and only 1 of 63 (2%) grade 4 event. The most frequently reported adverse events were fatigue (9 subjects), transient increases in SGOT, SGPT

and alkaline phosphatase (4 subjects each) and pain, type not specified (4 subjects). Only 19 out of 406 events were definitely or probably ascribed to the Poly-ICLC. [21]

SC Poly-ICLC in Normal volunteers

In a trial of a single dose of 1.6mg SC Poly-ICLC in normal volunteers, no treatment-related, grade 4, or serious adverse events were reported. Nonetheless, volunteers receiving poly-ICLC developed erythema and induration at the site of injection. Systemic reactogenicity included transient flu-like symptoms, such as malaise, headache, fever, and chills, which were generally mild to moderate in severity). In addition, there were no clinically significant changes in complete blood cell counts and serum chemistries, including liver function tests, 3 and 7 d after poly-ICLC administration.[11]

4.1.3 Preclinical and Clinical Trial Data

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

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

A significant challenge to the development of effective immunotherapy of cancer is the induction and maintenance of T cells that recognize tumor antigens. Vaccination to defined tumor antigens is being used in the treatment of many cancers including melanoma and cervical cancer but for many tumors no defined tumor antigens have been characterized. Alternative vaccination strategies using whole cell vaccines, dendritic cells pulsed with peptides or RNAs derived from tumors are being investigated in this situation. There is currently one FDA approved vaccine for the treatment of cancer, specifically Sipuleucel-T for the treatment of prostate cancer. A strategy to induce a T cell response without the need for a specific vaccine for each type of cancer would provide a major advance in the immunotherapy of cancer. The combination of poly-ICLC and PD-1 blockade produced by antibodies directed at PD-1 or its ligand PD-L1 were recently shown to induce CD8 T cell responses in the absence of peptide vaccines or with irrelevant peptide vaccines. In the B16 melanoma and MC38 colon carcinoma models enhanced tumor regression compared to either agent alone was observed. This effect was associated with long-term immunity that protected from subsequent tumor challenge.

In a review of 97 patients treated with monoclonal antibodies directed at PD-1 or its ligand PD-L1 only a single response was observed in patients with colorectal cancer. The one response was also unusual as it was a complete response (CR) that has been maintained. Subsequently it was found that the patient had a mismatch repair defect that would allow for production of multiple new antigens with potential for recognition by the immune system. This led to a phase 2 clinical trial in patients with colorectal cancer stratified on the basis of microsatellite DNA stability.

Microsatellite instability (MSI) is caused by the loss of DNA mismatch repair activity and is associated with increased numbers of mutations in the cellular genome (mean 1782 somatic mutations per tumor in MSI compared with 73 in MRP tumors). MSI colon cancer represents approximately 15% of patients with most cases due to acquired hypermethylation of the promoter of the MLH1 gene. It has been postulated that patients with microsatellite instability would possess more immunogenic tumors and these patients have a slightly better prognosis than microsatellite stable patients. This has now been demonstrated in a phase 2 trial with 4 of 10 patients with MSI colon cancer responding, whereas no MRP patients responded, as had been observed in the earlier

trials. In a follow up to this manuscript at ASCO2015 it was reported that the response rate was 62% (Susan Topalian ASCO 2015 meeting, unpublished). It will therefore require a large numbers of patients to demonstrate an improvement in outcome with MSI colon cancer whereas the lack of response in MRP (microsatellite stable) colon cancer will provide a means to evaluate the toxicity of the regimen and a preliminary evaluation of its ability to enhance immune responses and clinical benefit. The use of chemotherapy has the potential to impair the development of immunity to tumor-associated neoantigens in animal models and could potentially have a similar effect in humans.[22,23] We therefore selected patients with progressive disease following two lines of chemotherapy for metastatic cancer as the patient population for investigation. The additional third line regimen of pembrolizumab with poly-ICLC could impair the activity of PD-1 blockade in reinvigorating exhausted T cell populations that are reactive to tumor neoantigens.

4.2.2 Rationale for Dose Selection/Regimen/Modification

Pembrolizumab (MK-3475) dosing

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

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). Pharmacodynamics data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamics 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.

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

Poly-ICLC dosing

Poly-ICLC at high doses was ineffective in the therapy of cancer but at low doses produces activation of multiple pathways that are similar to those associated with viral vaccines. Induction of these pathways was associated with protective tumor immunity in three mouse tumor models. The dosing studies in normal volunteers provides a rationale for selection of a low dose regimen of poly-ICLC to maximize its effects on the innate immune system. In that study a dose of 1.5 mg of poly-ICLC was used as a subcutaneous injection. The microarray studies of peripheral blood lymphocytes from normal volunteers showed that the maximal effect of poly-ICLC in terms of numbers of differentially expressed genes following administration is noted at 24 hours and returned to pretreatment levels by three days. We will use an IM route of administration as it has a much greater safety profile and will use two doses bracketing that level, 1 or 2 mg. Poly-ICLC will be given IM and followed by infusion of pembrolizumab. Patients will be instructed on self-administration of poly-ICLC.

4.2.3 Rationale for Endpoints

Efficacy Endpoints

Clinical response is a standard endpoint for clinical trials of new cancer agents. The immune RECIST and RECIST response criteria will be used in the study. The immune RECIST response rate as determined by Dr. Nayak will be the primary endpoint. Therapy will be continued until patients have confirmed disease progression unless there is clinical decompensation or alternative options are selected.

Biomarker Research

Expression of PD-L1 has been associated with response to PD-1 blockade in multiple tumor types and will be evaluated in this study. Microarray analysis of peripheral blood lymphocytes will be used to characterize the response to poly-ICLC alone and in combination with pembrolizumab.

5 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

5.1.1.1 Phase 1 – Presence of histologically confirmed malignancy that has progressed following at least one therapy and able to be visualized on imaging. Measureable disease is not required. Patients with known targetable mutations must have progressive disease on the appropriated targeted drug therapy.

5.1.1.2 **Phase 2 –** Diagnosis of mismatch repair proficient "MRP" (includes microsatellite stable [MSS] and MSI-low) colon cancer that has progressed following at least two lines of therapy. Tissue for microsatellite testing is required to document microsatellite status. Using MSI Analysis System (Promega) is preferred, but the assay may be performed by any accredited laboratory. Ten patients will be included who have disease that can be biopsied pre- and post-therapy (on treatment biopsies).

5.2 Subject Inclusion Criteria

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

1. Be willing and able to provide written informed consent/assent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Have measurable disease based on RECIST 1.1 **(Phase 2 only)**. For definition of measurable, non-measurable, target and non-target lesions, see *Appendix 11.4, RECIST 1.1 Guidelines*.
4. All subjects (Phase I and Phase II) will be consented for access of archival tissue (paraffin block or unstained slides) for immunohistochemistry analysis (Phase I patients will be reconsented for this).
5. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. **(Phase 2 only)** *Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1. Optional fresh tissue biopsies may be obtained before Cycle 4, end of treatment visit and follow-up period if relapse is encountered. Subjects 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 Sponsor.*
6. Have a performance status of 0 or 1 on the ECOG Performance Scale.
7. Demonstrate adequate organ function as defined in Table 1; all screening labs should be performed within 10 days of treatment initiation.

Table 1. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR**	≤1.5 X upper limit of normal (ULN) **OR**

Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

8. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
9. Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in *Section 5.9.2 – Contraception*, for the course of the study through 120 days after the last dose of study medication.

   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

10. Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in *Section 5.9.2- Contraception*, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

5.2.1 Subject Exclusion Criteria

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

1. Microsatellite instability-high (MSI-H) tumor status detected by Promega or an accredited laboratory per local procedures **(Phase 2 only)**.
2. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
3. 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 with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.

4. Has a known history of active TB (Bacillus Tuberculosis)
5. Hypersensitivity to pembrolizumab or any of its excipients.
6. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
7. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.
    - Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
    - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
8. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
9. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
10. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
11. Has known history of non-infectious pneumonitis that required steroids, or any evidence of current pneumonitis.
12. Has an active infection requiring systemic therapy.
13. 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.
14. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
15. 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.
16. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
17. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
18. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

19. 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 are not allowed.

5.3 Trial Treatments

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

Table 2. Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
Poly-ICLC	1.8mg/mL *	Twice weekly	Intramuscular injection	Day 0/1, 4, 8, 11, 15, 18 of each cycle	Experimental

*Per manufacturer, drug product is now formulated at the original 1.8/mg/mL "dry" weight which is equivalent to 2.0mg/mL "wet" concentration of Poly-ICLC. This is a label correction for residual water of hydration in the lyophilized components and represents no change in the product or formulation, but simply a calculation correction.

The treatment to be used in this trial will follow the same regimen in both phases; all subjects will receive both poly-ICLC and pembrolizumab on Day 1of each cycle. The Day 1dose of poly-ICLC should be administered in the clinic for all cycles, in both phases. This will allow for assessment of AEs/SAEs and application of dose modifications, if needed, prior to dispensing drug for that cycle.

Trial treatment will be given for 17 cycles. If therapy is not interrupted this will be one year of therapy but therapy may extend for more than one year if interruptions are needed. A subject who, after completing 17 cycles of study treatment and, at that time, has a radiologic disease status of SD, PR or CR, may continue to receive study treatment without interruption for an additional year (up to a total of 35 cycles) of study treatment (Second Course Phase/Retreatment Period, section 7.2.13). See section *5.4.2, Dose Administration*, for details regarding drug administration.

5.4 Dose Selection

The rationale for selection of doses to be used in this trial is provided in *Section 4.0, Background and Rationale.*

5.4.1 Dose Modification (Escalation/Titration/Other)

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 3* below. See *Section 5.8.1* for supportive care guidelines, including use of corticosteroids.

Table 3. Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or 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	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of

			prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

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

[a] For 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.

[b] 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 pre-medicated for the next scheduled dose; Refer to Infusion Treatment Guidelines for further management details.

[c] 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.

5.4.1.1 Determining the Recommended Phase 2 Dose (RP2D) of Poly-ICLC:

For the Phase I component of the trial, classical 3+3 design will be employed and will include dose-escalation to determine the RP2D of Poly-ICLC to be combined with pembrolizumab.

a. We will consider two dose levels, 1 and 2 mg of Poly-ICLC.
b. A minimum of 3 patients will be treated depending on DLT. Dose level 1 (1mg) will be administered to a cohort of 3 patients.
c. If 0 out of 3 experience DLT, then dose escalation will proceed to the dose level 2 (2mg).
d. If one out of three patients experience DLT, a cohort of additional three patients will be assigned to the same dose level (1mg).
e. If two or more patients of three (or six) patients experience DLT at the first dose level, then enrollment of patients will be stopped.
f. If a maximum one patient experiences DLT at dose level 2, then the dose will be declared the RP2D.
g. If 2 or more out of 6 patients experience DLT at the second dose level, then the first dose level (1mg) will be declared the RP2D.

h. The RP2D should have at least 6 patients enrolled at the dose level with a maximum of 1 patient experiencing DLT. Toxicities that occur during the phase II portion of the study will be taken into account in determining the RP2D.

5.4.1.2 Dose Limiting Toxicity (DLT) Criteria for poly-ICLC escalation phase:

A DLT will be defined as any Grade ≥ 3 or higher treatment-related toxicity that occurs during the DLT-evaluation period. Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition. The following will be DLTs, regardless of relatedness:

- Any Grade 4 irAE
- Any Grade 4 non-hematologic toxicity
- Any Grade ≥ 3 diarrhea or vomiting that does not resolve within 3 days
- Any Grade 3 irAE, excluding colitis or pneumonitis, which does not downgrade to ≤ Grade 2 within 3 days after onset of the event despite maximal medical supportive care including systemic corticosteroids or does not downgrade to ≤ Grade 1 or baseline within 14 days.
- Any ≥ Grade 3 colitis irrespective of duration
- Any Grade ≥ 3 non-infectious pneumonitis irrespective of duration
- Liver transaminase elevation ≥ 5 × but ≤ 8 × ULN that does not downgrade to Grade 2 within 5 days after onset with optimal medical management, including systemic corticosteroids. Transaminase elevation > 8 × ULN or total bilirubin > 5 × ULN will be considered a DLT regardless of duration or reversibility
- Any increase in AST or ALT > 3 × ULN and concurrent increase in total bilirubin > 2 × ULN (Hy's Law).

The definition of DLT *excludes* the following conditions:

- Grade 3 fatigue for ≤ 7 days
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy
- Grade 3 inflammatory reaction attributed to a local antitumor response that resolved to ≤ Grade 1 within 30 days
- Concurrent vitiligo or alopecia of any AE grade
- Grade 3 infusion-related reaction (IRR; first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management.
- Grade 3 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days.
- Grade 3 or Grade 4 lymphopenia (unless clinically significant)
- Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention, and improves by at least 1 grade within 7 days
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days
- Grade 3 fever lasting ≤ 24 hours with or without medical therapy and is not considered a serious adverse event

The period for definition of DLT will be the first 3 weeks of treatment. Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 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.

5.4.2 Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

5.4.2.1 Pembrolizumab Preparation, Storage and Administration

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion on an outpatient basis 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). Preparation and administration of the investigational agent, pembrolizumab, will follow the same guidelines as for the FDA-approved agent, pembrolizumab, known commercially as Keytruda.

Preparation for Intravenous Infusion

- Visually inspect the solution for particulate matter and discoloration prior to administration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.
- Dilute pembrolizumab injection (solution) or reconstituted lyophilized powder prior to intravenous administration.
- Withdraw the required volume from the vial(s) of pembrolizumab and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.
- Discard any unused portion left in the vial.

Storage of Diluted Solutions

The product does not contain a preservative. Store the diluted solution of pembrolizumab either:

- At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the infusion solution in the IV bag, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration. Do not freeze.

Administration

- Administer infusion solution intravenously over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter.
- Do not co-administer other drugs through the same infusion line.

- The first injection of Pembrolizumab will be administered in clinic one hour after the first IM injection of Poly ICLC in the concurrent treatment group under the supervision of study clinical staff. Pembrolizumab will be administered one day after Poly ICLC injection in the subsequent treatment group. These two groups apply to phase II, while phase I will follow similar schedule as concurrent treatment group.
- The patient will be monitored for at least 30 minutes including a determination of blood pressure, heart rate, and respiratory rate before and after each injection.

5.4.2.2 Poly-ICLC Preparation, Storage and Administration

Poly-ICLC is provided in vials containing 1.8mg (1 ml). Excess volume is expected for the first cohort of subjects (1 mg/ .5ml). Unless labeled otherwise, the poly-ICLC vials being provided for this trial are labeled as single-use; therefore excess volume will be discarded. For doses that are administered at the clinical site, staff will dispose of the vials according to local protocol. For doses that are administered at the subject's home, used vials should be kept and returned to clinical staff at the following visit for reconciliation/compliance assessment.

Study subjects will receive intramuscular (IM) injections of 1 or 2 mg poly-ICLC on Days 1, 4, 8, 11, 15, 18 of each three-week cycle (twice weekly). The first injection of each cycle will be administered in clinic under the supervision of study clinical staff. The subject will be monitored for at least 30 minutes after the first IM injection; blood pressure, heart rate, and respiratory rate should be assessed before and after injection. Approximately one hour after the poly-ICLC injection is given, the subject will begin pembrolizumab IV infusion.

Following the first treatment, subsequent poly-ICLC injections may be administered at home by the study subject or the study subjects' person of choice (e.g., family member, friend). Study subjects will be given a set of written instructions to follow, and a diary sheet that they are required to maintain showing the dates and times when injections were given and the injection sites (extremities). At the investigator's discretion, subsequent injections may be scheduled to be given in the outpatient clinic instead of at-home administration.

IM injections will be performed using standard technique into the thighs or upper arms. Injection site may be rotated based on study subjects' and investigator preference and will be recorded in the diary. The study nurse will train the study subjects or the study subjects', person of choice on how to inject IM Poly-ICLC during the first treatment.

The investigational pharmacy will follow its standard operating procedures (SOPs) when dispensing the study drug for distribution to the study subjects. Study subjects will be instructed to administer (or have their person of choice administer) the second IM injection 3 days following the first injection (Day 4). The clinical staff will provide study subjects with a sufficient supply of Poly-ICLC, sterile syringes with needles and alcohol swabs for this purpose. Study subjects will be instructed to store the vials in the refrigerator, in a location that prevents the study drug from freezing, until it is time to administer the study drug. They will be told to exchange any vials of Poly-ICLC that inadvertently becomes frozen.

The study subjects will also be provided with a diary wherein the date, time and injection site of the study drug is to be noted as well as comments on any side effects. The diary will be reviewed by the clinic staff with the study subject at clinic visits and collected from the study subject at the following

study visit. Study subjects and/or their person of choice will be instructed to allow a 72-hour interval between each injection. Study subjects will be instructed to contact the study doctor with any concerns regarding injections.

5.4.3 Trial Blinding/Masking

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

5.5 Treatment Allocation

5.6 There will be no randomization utilized in this study. Aside from the predetermined dose-escalation (and individual dose modifications, if needed, all subjects will receive the same treatment). Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations accepted or prohibited to use in this trial are detailed in following paragraphs. If there is a clinical indication for one of these medications or vaccinations prohibited during the trial, discontinuation from trial therapy may be required. The investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.6.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the electronic Case Report Form (eCRF) in OnCore 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 eCRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.3.

5.6.2 Prohibited Concomitant Medications

Subjects 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 and Poly-ICLC
- 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, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

The Exclusion Criteria describes other medications which are prohibited in this trial. There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.7 Rescue Medications & Supportive Care

5.7.1 Supportive Care Guidelines

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

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to the dose modification section.

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

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

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

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

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

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

- **Hyperthyroidism or Hypothyroidism**:
  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - **Grade 2** hyperthyroidism events (and **Grade 2-4** 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.

- **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 corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

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

Table 4. Supportive Measures

Toxicity	Grade	Supportive Treatment
Pneumonitis[1]	2	Treat with systemic corticosteroids[2]
	3-4	Immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed
Diarrhea/Colitis[3,4]	2	Administer oral corticosteroids[2]
	3-4	Treat with intravenous steroids followed by high dose oral steroids.
Type 1 diabetes mellitus (if new onset) or Hyperglycemia[5]	T1DM or 3-4	Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
Hypophysitis	2	Treat with oral corticosteroids[2,6]
	3-4	Treat with intravenous steroids followed by high dose oral steroids[6]
Hyperthyroidism	3	Non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
	4	Treat with an initial dose of IV corticosteroid followed by oral corticosteroids
Hypothyroidism	2-4	Thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care[2]
Hepatic Reaction	2	Monitor liver function tests more frequently until returned to baseline values (consider weekly)
	3-4	Treat with intravenous corticosteroids for 24 to 48 hours[2]
Renal Failure or Nephritis	2	Treat with oral corticosteroids[2]
	3-4	Treat with intravenous steroids followed by high dose oral steroids[2,6]

1) Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
2) When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
3) All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
4) For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
5) Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
6) Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

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

Table 5. Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	**Treatment**	**Premedication at subsequent dosing**
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the 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 pre-medicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine	
Grade 4: Life-threatening; pressor or ventilatory support indicated	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.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.8 Diet/Activity/Other Considerations

5.8.1 Diet

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

5.8.2 Contraception

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

Female subjects will be considered of non-reproductive potential if they are either:
(1) Postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);
OR
(2) Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;
OR
(3) Has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:
(1) Practice abstinence† from heterosexual activity;
OR
(2) Use (or have their partner use) acceptable contraception during heterosexual activity.
Acceptable methods of contraception are‡:

- Single method (one of the following is acceptable):
  - Intrauterine device (IUD)
  - Vasectomy of a female subject's male partner
  - Contraceptive rod implanted into the skin

- Combination method (requires use of two of the following):
  - Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
  - Cervical cap with spermicide (nulliparous women only)
  - Contraceptive sponge (nulliparous women only)
  - Male condom or female condom (cannot be used together)
  - Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.
‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception.

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

5.8.3 Use in Pregnancy

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

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject

impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 7.3.2.

5.8.4 Use in Nursing Women

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

5.9 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in *Other Procedures* section.

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

- The subject withdraws consent.
- Confirmed radiographic disease progression
  Note: For unconfirmed radiographic disease progression, please see Appendix 11.4, *RECIST 1.1 Guidelines, Confirmation of Progression*.
  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved; please see Appendix 11.4, *RECIST 1.1 Guidelines, Confirmation of Progression*.
- Unacceptable adverse experiences such as dose-limiting toxicities
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 12 months of uninterrupted treatment with pembrolizumab and poly-ICLC (17 administrations of combination study treatment [study diagram 2.2.2]).
  Note: 12 months of study medication is calculated from the date of first dose. Subjects who stop combination study treatment after 12 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 7.2.13, Second Course Phase (Retreatment Period).
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.2.12 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.3). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.9.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab and poly-ICLC via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.2.13, *Second Course Phase (Retreatment Period)*.

5.10 Subject Replacement Strategy

Subjects who withdraw from therapy prior to completion of cycle 1 of therapy will be replaced during the phase I portion of the trial to allow for evaluation of at least 3 subjects at each dose level. Similarly, if patients withdraw before assessment of tumor response in the phase II portion of the trial, they will be replaced unless withdrawal is due to clinical disease progression.

5.11 Clinical Criteria for Early Trial Termination

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

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug

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

6 TRIAL FLOW CHART

Trial Period:	**Screening**	**Treatment Cycles[1]**									**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Study Screening (Visit 1)	1	2	3	4	*To be repeated, cycles 9-17* 5	6	7	8	Second Course Phase (Retreatment Period)[13]	Discon	Safety Follow-up[2]	Follow UpVisits[3]	Survival Follow Up[4]
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 12 wks post discon	Every 12 wks post discon
Administrative Procedures														
Informed Consent	X													
Inclusion/Exclusion Criteria	X													
Demographics and Medical History	X	X	X	X	X	X	X	X	X	X	X	X	X	
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X				
Trial Treatment Administration														
Pembrolizumab[5]		X	X	X	X	X	X	X	X	X				
Poly-ICLC[6]		X	X	X	X	X	X	X	X	X				
Clinical Procedures/Assessments														
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X										X	X		
Directed Physical Examination		X	X	X	X	X	X	X	X	X			X	
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG[7]	X													
Post-study anticancer therapy/Survival Status											X	X	X	X
Laboratory Procedures/Assessments (analysis performed by LOCAL laboratory)														
Pregnancy Test – Urine or Serum β-HCG	X	X	X	X	X	X	X	X	X	X				
PT/INR and aPTT	X		X											
CBC with Differential	X	X	X	X	X	X	X	X	X	X	X	X	X	
Comprehensive Serum Chemistry Panel	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X				X				X	X				
Infections work up: Hepatitis B, Hepatitis C, HIV	X													
FreeT3, FreeT4 and TSH[8]	X		X		X		X		X	X	X	X	X	
Correlative Studies Blood Collection (CENTRAL labs, analysis performed by Cancer Research Center)[9]														
1 ABI TEMPUS tube (~3ml blood) for RNA microarray analysis	X	X		X										
1 DNA PAXgene tube (~8.5 ml blood) for DNA analysis	X	X		X										

Trial Period:	Screening	Treatment Cycles[1]								End of Treatment	Post-Treatment		
						To be repeated, cycles 9-17				Second Course Phase (Retreatment Period)[13]			
Treatment Cycle/Title:	Study Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Safety Follow-up[2]	Follow UpVisits[3]	Survival Follow Up[4]
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 12 wks post discon	Every 12 wks post discon
1-2 EDTA BD Vacutainer tubes (at least 10 ml, ideally up to 20 ml) for PBMC, plasma collection/separation	X	X		X									
Efficacy Measurements[10]													
Tumor Imaging (CT/MRI of Chest, Abdomen, Pelvis; bone scan if clinically indicated)	X									X	X		
Tumor Biopsies/Archival Tissue Collection													
Archival or Newly Obtained Tissue Collection[11,12] for microsatellite testing and immune evaluation; any sequence-based CLIA certified analysis system may be used. PD-L1, IDO, CD3, CD4. CD8, and FOXp3 will be evaluated. Other markers may also be analyzed.	X				X[11]						If disease progression (optional)		If disease progression (optional)	

[1] Cycles should be scheduled continuously; however, initiation of subsequent cycles may be extended up to 3 days.
[2] All subjects should have a Safety Follow Up visit, approximately 30 days after the last dose of trial treatment, or before the initiation of a new anti-cancer treatment, whichever comes first.
[3] Subjects who discontinue treatment for a reason other than disease progression will move into the Follow Up phase and should be assessed every 12 weeks to monitor disease status.
[4] Subjects with confirmed disease progression will move into the Survival Follow Up phase and should be contacted by telephone every 12 weeks to assess survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.
[5] Pembrolizumab is only administered on Day 1 of each 3-week cycle
[6] Poly-ICLC is to be administered IM on Days 1, 4, 8, 11, 15, 18 of each cycle. Subjects will be instructed on self-administration.
[7] Collect at baseline, and as clinically indicated.
[8] Thyroid labs to be drawn every other cycle.
[9] Blood for correlative studies to be collected at Screening, Cycle 1 Day 1 at 4-6 hours post-treatment, and Cycle 3 Day 1 at 4-6 hours post-treatment. Preferably, blood should be drawn 6 hours post-dose, but between 4-6 hours is acceptable, depending on individual patient's circumstances. See Lab Manual (Appendix 11.6) for details.
[10] Baseline scans must be obtained within 28 days prior to the first dose of trial treatment. The first on-study scan should be performed after Cycle 3, before beginning Cycle 4 treatment. Subsequent scans should be performed every 3 cycles (approximately every 9 weeks). The same method should be used for tumor measurement throughout therapy. After discontinuation of therapy scans will be performed every 12 weeks.
[11] Archival tissue may be used for MSI testing; all other testing should be done on fresh tissue, if available. Fresh tissue biopsy at cycle 4, at end of treatment visit and during follow-up is **optional** for subject.
[12] Beginning with Amendment 4, tissue collection was expanded to include Phase 1 subjects; in previous protocol versions, tissue was only to be collected for Phase 2 subjects.
[13] Subjects who have a radiologic status of SD, PR or CR after completing 17 cycles of study therapy may continue without interruption for an additional year (up to a total of 35 cycles of trial treatment).

7 TRIAL PROCEDURES

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

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

7.1 Administrative Procedures

7.1.1 Informed Consent

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

Consent must be documented by the subject's dated signature on a consent form along with the dated signature of the person conducting the consent discussion. A copy of the signed and dated consent form should be given to the subject before participation in the trial.

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

Specifics about a trial and the trial population will be added to the consent form template at the protocol level. The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.2 Inclusion/Exclusion Criteria

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

7.1.3 Medical History

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

7.1.4 Prior and Concomitant Medications Review

Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days

before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

Concomitant Medications
The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded in the *Concomitant Medications* eCRF, and as defined in Section 7.2.

7.1.5 Disease Details and Treatments

Disease Details
The investigator or qualified designee will obtain prior and current details regarding disease status. These details should be captured in the *Disease History* eCRF in OnCore.

Prior Treatment Details
The investigator or qualified designee review all prior cancer treatments including systemic treatments, radiation and surgeries. These details should be captured in the *Prior Therapies* eCRF in OnCore.

Subsequent Anti-Cancer Therapy Status
The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.1.6 Assignment of Study Subject Number

After the study subject has been consented and has met all eligibility criteria, the subject must be registered for active study treatment. The following should be provided to the Augusta University Cancer Clinical Research Unit (CCRU) multi-center coordinator, either in hard copy, or emailed to Cancer_Center_Trials@augusta.edu:

- A copy of the signed consent form
- A completed registration Eligibility Checklist, with investigator signature

After confirmation of eligibility, the CCRU multi-center coordinator will email the study staff to confirm enrollment, including the assigned Study Subject number that will be associated with the subject for all study activities. The study staff may forward this correspondence to their on-site pharmacy for release of investigational agents.

7.2 Clinical Procedures/Assessments

7.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.03 (see Section 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse

events, or irAEs); see the separate ECI guidance document in Appendix 4 regarding the identification, evaluation and management of potential irAEs.

Please refer to section 7.3 for detailed information regarding the assessment and recording of AEs.

7.2.2 Full Physical Exam

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

7.2.3 Directed Physical Exam

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

7.2.4 Electrocardiograms

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study. ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.

At Screening, a single ECG will be obtained on which QTcF must be <470 ms. In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, two additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding. A physician should be available to read these ECGs and make a decision if they are found to be abnormal.

Situations in which ECG results should be reported as AEs are described in Section 7.3.

7.2.5 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.2.6 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 11.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.2.7 Tumor Imaging and Assessment of Disease

CT, MRI, PET, ultrasound and bone scan may be used for evaluation of disease. Tumor measurements should be performed on the same type of scan throughout treatment and it is preferred that CT or MRI be used.

7.2.8 Tumor Tissue Collection and Correlative Studies Blood Sampling

Blood sample volumes for the purposes of this study are restricted. The amount of blood drawn from adults (those 18 years of age or older) for research purposes shall not exceed 10.5 mL/kg or 550 mL; whichever is smaller, in an 8-week period. Blood will be drawn into TEMPUS blood collection tubes from Applied Biosystems for extracting RNA for flow cytometry evaluation. See Appendix 11.6 for details regarding specimen processing.

Archival tumor tissue will be obtained on all patients (Phase I and Phase II) if possible. Formalin fixed paraffin embedded (FFPE) tumor sample or unstained slides will be accepted. All patients with tumors that are accessible utilizing reasonable clinical interventions will be requested to consent to tumor biopsy. Approaches which may be utilized include but are not necessarily limited to needle aspiration, true-cut biopsy or incisional biopsy of superficial lesions or lesions accessible by interventional radiology. Patients will be requested to undergo biopsy prior to/beginning of cycle 4 therapy. Patients may be asked again for tissue biopsy at attainment of disease stabilization and at the time of disease progression, or toxicity leading to discontinuation of treatment. Specimens will be processed as outlined below.

7.2.9 Archival Tumor Sample/Tumor Biopsy Specimens

Archival tumor tissue samples (paraffin block or unstained slides) will be obtained, if possible, on all subjects (Phase I and Phase II) for immunohistochemistry analysis.

Tumor Biopsy Specimens (Phase II Only)

Tumor biopsies are required prior to the beginning of treatment. Optional, repeated biopsies at cycle 4 (±3 days), end of treatment visit and during the follow-up period are performed if relapse is encountered. Where possible, 4 samples should be obtained at each biopsy.

- The first will be preserved in standard formalin fixative. This specimen should be accessioned and submitted to the Pathology Department for routine staining with hematoxylin and eosin. After processing, the remaining block should be sent to tumor repository bank led by Dr. Roni Bollag.
- The second will be preserved in a specialized fixative for analysis of fresh frozen tissue.
- The third specimen will be snap frozen in liquid nitrogen for later protein and/or RNA analysis.
- The 4th should be complimentary and hence either frozen or fixed with formalin based on size of tissue

When needle aspiration is the only mechanism for acquisition of neoplastic tissue, cytospins will be collected and immediately processed to optimize protection of protein and/or RNA integrity.

All biopsy specimens must include the study name, patients name, hospital number, date and time of collection and site of biopsy. Questions regarding specimen collected may be directed to Drs. Roni Bollag or Asha Nayak-Kapoor.

7.2.10 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

Table 6. Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Hematology	**Chemistry**	**Urinalysis**	**Other**
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Free Total triiodothyronine (FreeT3)
Absolute Neutrophil Count	Carbon Dioxide	results are noted	Free thyroxine (FreeT4)
Absolute Lymphocyte Count	*(CO_2 or bicarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		Hepatitis A, B, C antibody‡
	Calcium		HIV 1/2 antibody
	Chloride		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		Blood for correlative studies
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
‡ If any antibody test is reactive, follow up with PCR testing.

Laboratory tests for screening or entry into the Second Phase should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.2.11 Other Procedures

Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.3, *Assessing and Recording Adverse Events*. Subjects who a) attain a CR or b) complete 12 months of treatment with pembrolizumab and poly-ICLC may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.2.13, *Second Course Phase (Retreatment Period)*. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit and then proceed to the Follow-Up Period of the study.

Blinding/Unblinding

Not applicable.

7.2.12 Visit Requirements

Visit requirements for screening and the treatment periods are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab (as described in Section 7.2.13, *Second Course Phase (Retreatment Period)* may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 6 weeks (42 ± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 9 weeks (± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section 7.2.13, *Second Course Phase (Retreatment Period)*. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab and poly-ICLC according to the criteria in Section 7.2.13, *Second Course Phase (Retreatment Period)* will move from the follow-up phase to the Second Course Phase when they experience disease progression.

Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.2.13 Second Course Phase (Retreatment Period)

Subjects who stop the combination pembrolizumab and poly-ICLC treatment 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 study drugs 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 12 months of study therapy for reasons other than disease progression or intolerability
- A subject who, after completing 17 cycles of study treatment and, at that time, has a radiologic disease status of CR, PR or SD may continue to receive study treatment without interruption for an additional year (up to a total of 35 cycles of study treatment).

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab and poly-ICLC
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab and poly-ICLC
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 5.1.2
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.9.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male subject should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might 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.

Subjects who are eligible to restart treatment will be retreated at the same dose levels of poly-ICLC (to be determined) and pembrolizumab (standard 200mg) that were initiated for their treatment. Additionally, subjects who have received study treatment with a radiologic response of CR, PR or SD may continue study treatment without interruption for an additional year (for up to 35 cycles of study treatment). Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

7.3 Assessing and Recording Adverse Events

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

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time. Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an adverse event.

All adverse events that occur after the consent form is signed but before treatment allocation must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment allocation through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.3.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

7.3.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck

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

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

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

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

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

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment allocation through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatid form 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)

7.3.3 Immediate Reporting of Adverse Events to the Sponsor and to Merck

7.3.3.1 Serious Adverse Events

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is another important medical event

  Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
  - Is a new cancer (that is not a condition of the study);
  - Is associated with an overdose.

Refer to Table 6 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.3.3.3 for additional details that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject 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 through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject 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 other than progression of the cancer under study (reference Section 7.3.3.3 for additional details), 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.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck Global Safety.

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

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

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross-reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

7.3.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

For the time period beginning when the consent form is signed until treatment allocation, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject 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 through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.3.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

7.3.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section 7.3.3, *Immediate Reporting of Adverse Events to the Sponsor and to Merck*, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor within 24 hours and to Merck Global Safety within 2 working days either by electronic or paper media.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Merck Global Safety as a SAE within 2 working days of determination that the event is not progression of the cancer under study. Hospitalization related to convenience (e.g. transportation issues etc.) will not be considered a SAE.

7.3.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.03. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets. All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 7. Evaluating Adverse Events

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

V4.03 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to Merck within 2 working days.	

	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause Merck product to be discontinued?	
Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

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

7.3.5 Sponsor Responsibility for Reporting Adverse Events

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

8 STATISTICAL ANALYSIS PLAN

8.1 Introduction

This study has two parts:

a. Phase I dose-escalation to determine the recommended phase II dose of Poly-ICLC to be combined with the standard dose of pembrolizumab. Patients with any solid tumor that is unresponsive to at least two lines of therapy is eligible for the dose escalation phase unless curative options exist.
b. The combination will then be administered at the recommended phase II dose to in up to 27 patients with relapsed metastatic colon cancer. MSI-high patients will be excluded.

Descriptive statistics will be presented for primary and secondary endpoints. Summary statistics for continuous variables will include the mean, standard deviation, median, and range (minimum/maximum). Categorical variables will be presented as frequency counts and percentages; and time-to-event variables will be summarized by Kaplan-Meier medians and survival plots. Data listings will be created to support each table and to present all data. The data will be tabulated and analyzed with respect to patient enrollment and disposition, demographic and baseline characteristics, for primary efficacy and safety measures per study part (Phase I, II), and on a per dose level for phase I part. The primary efficacy analysis will be conducted on the efficacy evaluable population and safety analysis will be performed on the safety evaluable population. Maximum tolerated dose for of Poly-ICLC to be combined with pembrolizumab will be estimated based on the data from the 3+3 dose escalation. RP2D will then be determined based on the estimated MTD, which should not exceed 1/6 of RLT. SAS 9.3 software, or higher will be used for data analysis.

8.2 Study Objectives

8.2.1 Primary Objectives

a. Phase 1: Determine the maximum tolerated dose of poly-ICLC that can be combined with pembrolizumab
b. Phase II: Determine the response rate of metastatic MRP colon cancer that has progressed following two lines of therapy in the metastatic setting to the combination of pembrolizumab and poly-ICLC by RECIST 1.1.

8.2.2 Secondary Objectives

a. Phase I and II - Determine the adverse event profile and dose limiting toxicities of the combination of pembrolizumab and poly-ICLC
b. Determine the progression free survival rate, overall survival rate and duration of response of recurrent metastatic MRP colon cancer to the combination of pembrolizumab and poly-ICLC

8.2.3 Exploratory Objectives

a. Evaluation of inflammatory state in tumor biopsies with specific attention to definition of tumor infiltration with hematopoietic cells, cell surface signaling molecule expression.
b. Evaluation of pre-treatment and post-treatment microarray panels in tumor samples and peripheral blood.

8.3 Study Design/Endpoints

Phase I: Classical 3+3 design will be employed and will include dose-escalation to determine the RP2D of Poly-ICLC to be combined with pembrolizumab. We will consider two dose levels, 1 and 2 mg of Poly-ICLC.
Phase II: Primary endpoint is the response rate defined according to RECIST 1.1 criteria. irRECIST response will be assessed as an exploratory endpoint.

8.4 Sample Size/Accrual Rate

For part 1: 3 to 12 patients will be used for the dose escalation part. The actual number of patients will depend on the DLT and MTD. We are expecting 3 patients per month to be enrolled in the study.
For Part 2: With the assumption that the RR rate for pembrolizumab alone is about H0=5%, 27 patients are needed to detect an increase in RR to H1=20% for the treatment combination to achieve 80% power and keep the probability of type I error (α) at 0.05. We are expecting accrual rate of 5 patients per month during the phase II portion of the study.

8.5 Analysis of Endpoints

8.5.1 Analysis of Primary Endpoints

a. A minimum of 3 patients will be treated depending on DLT. Dose level 1 (1mg) will be administered to a cohort of 3 patients. If 0 out of 3 experience DLT, then dose escalation will proceed to the dose level 2 (2mg). If one out of three patients experience DLT, a cohort of additional three patients will be assigned to the same dose level (1mg). If two or more patients of three (or six) patients experience DLT at the first dose level, the trial, then enrollment of patients will be stopped. If a maximum one patient experience DLT at dose level 2, then the dose will be declared the RP2D. If 2 or more out of 6 patients experience DLT at the second dose level, then the first dose level (1mg) will be declared the RD2D. The RP2D should have at least 6 patients enrolled at the dose level with a maximum of 1 patient experiencing DLT.
b. To assess preliminary evidence of antitumor activity, in terms of Objective Response Rate (ORR). ORR will be calculated as the number of participants with complete response (CR) or partial response (PR) by RECIST criteria, divided by the total number of participant in the dataset. The ORR will be estimated for every estimated and the associated exact 95% CI will be provided.

8.5.2 Analysis of Secondary Endpoints

a. The adverse event profile will be presented by dose level of the combination treatment for the phase I portion.
b. The progression free survival rate, overall survival rate and duration of response of recurrent metastatic MRP colon cancer to the combination of pembrolizumab and poly-ICLC administered at RP2D will be estimated along with the correspondent 95%

confidence interval. In addition, the 20-week PFS rate along with its 95% CI will be estimated and presented.

8.6 Analysis Datasets

Analysis will be conducted on the modified intent-to-treat set (mITT), which Includes all enrolled subjects treated with at least 1 dose (or partial dose) of the study medications. The mITT set will be used for all safety and preliminary efficacy analysis.

8.7 Interim Analysis

No interim analysis is applicable for the proposed study.

9 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

Table 8. Product Descriptions

Product Name & Potency	Dosage Form
Poly-ICLC 2mg/vial	Suspension for injection (IM)
Pembrolizumab 100 mg/ 4mL	Solution for injection (IV)

9.1 Investigational Products

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

The use of both pembrolizumab and poly-ICLC are considered investigational in this clinical trial, which is conducted under IND#129974, held by Dr. Asha Nayak-Kapoor.

9.1.1 Pembrolizumab (MK-3475, Keytruda®)

Pembrolizumab will be provided by Merck for use in this investigational setting. Pembrolizumab is provided as a white to off white lyophilized powder (50 mg/vial) or as a liquid solution (100 mg/vial) in Type I glass vials intended for single use only. Pembrolizumab Powder for Solution for Infusion, 50 mg/vial, is reconstituted with sterile water for injection prior to use. The drug product is stored as a stable lyophilized powder or liquid solution under refrigerated conditions (2 to 8°C).

The lyophilized drug product after reconstitution with sterile water for injection, and the liquid drug product are a clear to opalescent solutions, essentially free of visible particles. The reconstituted lyophilized product and the liquid product are intended for IV administration. The reconstituted drug product solution or the liquid drug product can be further diluted with normal saline or 5% dextrose in the concentration range of 1 to 10 mg/mL in intravenous (IV) containers made of polyvinyl chloride (PVC) or non-PVC material. Reconstituted vials should be immediately used to prepare the infusion solution in the IV bag and the infusion solution should be immediately administered. Diluted pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion. In addition, IV bags can be stored at 2 to 8°C for up to a cumulative time of 20 hours. This recommendation is based on up to 24 hours of room temperature and up to 24 hours of refrigerated stability data of diluted MK-

3475 solutions in the IV bags. For each individual trial, clinical supplies are to be stored in accordance with specific instructions on the label.

9.1.2 POLY-ICLC (Hiltonol®)

Poly-ICLC is classified as an investigational new drug. It is a synthetic complex of polyinosinic and polycytidylic acid, stabilized with polylysine and carboxymethyl cellulose.

How supplied

Poly-ICLC is supplied by the manufacturer (Oncovir) in vials containing 1.8mg/mL opalescent solution. Drug supply for "at home" study drug administrations will follow local investigational pharmacy procedures.

Each vial poly-ICLC supplied by the manufacturer will be labeled with the following information:

Drug Name
Concentration
Storage Conditions
Lot Number
Date of Manufacture, Manufacturer
Investigational Use Statement

Storage and stability

Poly-ICLC is stable at room temperature for at least 4 weeks. Treatment sites are asked to store the drug at approximately 2-8 °C. Study subjects will have Poly-ICLC administered at home, and will be advised to store their doses in a standard refrigerator. The vials should not be frozen.

Supplier

The drug to be used in this study is prepared and packaged using GMP conditions, under contract to Oncovir, Inc. It is then tested for quality, activity, sterility and pyrogenicity before release to the site pharmacy for clinical use.

Drug ordering information

Order Poly-ICLC supplies by contacting:

Andres M. Salazar, MD
CEO & CSO, Oncovir, Inc
529 Jefferson Street
Winchester, VA 22601
asalazar@oncovir.com

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

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

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

10 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

Only the investigator, the members of the research team, the sponsor, authorized officials from state and federal governments such as the Food and Drug Administration (FDA) or the Office of Human Research Protections (OHRP), and authorized representatives of the Western Institutional Review Board (WIRB) and Augusta University will have access to confidential data which would identify participants, unless specifically required to be disclosed by state or federal law. Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. The results of this study may be presented at meetings or in publications. However, participants will not be identified in any reports or publications resulting from the study. All reasonable steps will be taken to ensure confidentiality.

10.2 Compliance with Financial Disclosure Requirements

Investigators participating in the study will comply with federal and Augusta University financial disclosure requirements.

10.3 Compliance with Law, Audit and Debarment

Investigators will comply with federal and state laws. This study will be audited by the Georgia Cancer Center's auditing team. Investigators who have been debarred from clinical trial participation by the FDA may not participate in this trial.

10.4 Compliance with Trial Registration and Results Posting Requirements

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

10.5 Quality Management System

10.6 Data Management

The DM (Data Monitor) Console is OnCore's data management tool and is the validation and management workspace for online forms in OnCore.

Electronic case report forms (eCRFs) are created in the eCRFs Console, and attached to specific protocol calendar visits for completion by the coordinator.

10.6.1 Data Entry

Recording and handling data

In OnCore, when a subject visit as occurred, forms that need to be completed are listed on the Forms by Status > To Do Forms tab. Data is recorded specific to each form/visit. By opening the form, it becomes "Active," and the coordinator can continue to work on the form until the "Complete" button is selected. In declaring a form as complete, coordinators are in effect stating that the form is completely filled-out and is ready for a data monitor (DM) to validate the data.

Subject documents (questionnaires, diaries)

Subject documents, such as questionnaires and diaries, completed by the subject on paper, is then manually transcribed and entered into OnCore by the research staff.

10.6.2 Query Management

In the DM Console, forms are categorized by the following statuses:

To Do

Assigned to forms for a subject visit marked as Occurred. This status will remain until form data entry begins.

Started

Assigned to a form when the data entry process is started. This status is set the first time the form is accessed.

Completed

Assigned when the form is declared as Completed.

Queried

Assigned when the Data Monitor adds a note questioning the form data. The CRA is expected to respond.

Amended

Assigned when the CRA responds to a Queried form. The response is sent to the Data Monitor.

Missed

Assigned to a form that has been marked as Missed or occurs on a visit or procedure that was marked as Missed.

Additional
Assigned to an additional form instance created for a subject's visit.

Validated
Assigned when a Data Monitor declares the form data is valid. Validated forms are not editable.

Locked
Assigned when a Data Monitor locks the form, declaring the form data as unchangeable. A special security privilege is required to undo this status.

N/A
Assigned to a form that has been marked as Not Applicable or occurs on a visit or procedure that was marked as Not Applicable.

10.6.3 Study Data Flow

Validation
As online forms are declared as Completed, the data monitor validates the data and either raise a query or locks the form. If the data is accurate and the monitor has no questions, the form can be validated by clicking the Validate button (shown for Completed and Amended forms) in the DM Console. After all queries have been resolved, the form can be **Locked**.

Queries
Raising a query sends the form and a question back to the person who entered the data within OnCore. A queried form can be amended and then validated and locked. The process of querying and amending a form may have multiple iterations.

Database lock
In OnCore, individual validated forms are locked, preventing further edits. After all forms are validated, the database is essentially locked.

10.7 Data Export & Reporting

Data export formats
OnCore's Biostat Console is used to extract data from OnCore for use in statistical analysis tools. The subject's full name is never included in the export. The Biostat Console can also be used to view the current progress of protocols related to accruals, forms, and adverse events. From the Data Export page, selected data can be exported into Excel spreadsheets or files formatted for easier import into SAS.

11 APPENDICES

11.1 ECOG Performance Status

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

11.2 Common Terminology Criteria for Adverse Events V4.03 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

11.3 Immune Related Response Criteria (irRC) with Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

Responses will be evaluated in all subjects. Because of direct clinical observations of immune cell influx into tumor causing enlargement in some patients prior to sustained response, recently it has been suggested that clinical trials involving the use of immunotherapy use alternative guidelines, called immune related response criteria (irRC) to determine radiographic response or progression after therapy. The criteria for evaluation of response are those defined in Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: Immune-related response criteria. Clin Cancer Res 2009; 15:7412-7420.

These recommendations have been used in recent clinical trials. One study of 227 subjects with metastatic melanoma showed that the approximately 10% of patients who had PD by modified WHO criteria but either CR, PR or SD by irRC had a similar overall survival as those patients who had SD, PR or CR by both criteria. The irRC was created using bidimensional measurements (as previously widely used in the WHO criteria). We have taken the concepts of the irRC and combined them with the recently revised RECIST 1.1 to come up with the modified irRC used in this protocol. Consistent with the irRC, the main changes from RECIST 1.1 are (a) a requirement for confirmation of both progression and response by imagining at least 4 weeks

after initial imaging and (b) not automatically calling the appearance of new lesions progressive disease if the total measurable tumor burden has not met criteria for progressive disease.

For immune-related response criteria (irRC), only index and measurable new lesions are taken into account. At baseline tumor assessment on this trial, target lesions will be measured along the longest axis and the measurements will be summed, called sum of largest diameter (SLD). These lesions must be a minimum of 10mm per lesion, maximum of 5 target lesions, maximum of 2 per organ system. At each subsequent tumor assessment, the unidimensional measurement of target lesions and of new measureable lesions are added together to provide the total tumor burden: As per the modified definitions below, all responses and progression except stable disease (SD) required confirmation on a consecutive scan at least 4 weeks from the initial observation).

Definitions of irRC:

Response	**irRC**
New measurable lesions	**Incorporated into tumor burden**
New non-measurable lesions	**Do not define progression (but precludes irCR)**
Non-index lesions	Contributes to defining irCR (complete disappearance required)
Overall irCR	100% disappearance of all lesions, whether measurable or not, and no new lesions, in two consecutive observations not less than 4 wks from the date first documented. All measurable lymph nodes also must have reduction in short axis to <10mm.
Overall irPR	≥ 30% decrease in SLD compared with baseline confirmed by a consecutive assessment at least 4 wk after first documentation
Overall irSD	Not meeting criteria for irCR or irPR, in absence of irPD: 30% decrease in SLD compared with baseline cannot be established nor 20% increase compared with nadir.
Overall irPD	At least 20% increase in SLD compared with nadir (minimum recorded tumor burden) and an increase of at least 5mm over the nadir, confirmed by a repeat, consecutive observation at least 4 wk from the date first documented.

Overall responses derived from changes in index, non-index and new lesions as demonstrated in the following table:

Measurable response	**Non-measurable response**		**Overall response using irRC**
Index and new, measurable lesions (tumor burden)* %	**Non-index lesions**	**New, non-measurable lesions**	
Decrease 100%	Absent	Absent	irCR[&]
Decrease 100%	Stable	Any	irPR[&]
Decrease 100%	Unequivocal progression	Any	irPR[&]
Decrease ≥ 30%	Absent / Stable	Any	irPR[&]
Decrease ≥ 30%	Unequivocal progression	Any	irPR[&]
Decrease < 30% to increase < 20%	Absent / Stable	Any	irSD
Decrease < 30% to increase < 20%	Unequivocal progression	Any	irSD
Decrease ≥ 20%	Any	Any	irPD

* Decreases assessed relative to baseline

[&] Assuming response (irCR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 weeks apart.

11.4 Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria

RECIST 1.1 TABLE OF CONTENTS

LIST OF TABLES

1. INTRODUCTION

This appendix details the implementation of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines (Eisenhauer et al 2009) for the CC-16047 study with regards to Investigator assessment of tumor burden including protocol-specific requirements for this study.

2. DEFINITION OF MEASURABLE, NON-MEASURABLE, TARGET AND NON-TARGET LESIONS

Only patients with measurable disease at baseline should be included in the study.
Measurable disease is defined by the presence of at least 1 measurable (by RECIST 1.1) lesion which has not been previously irradiated. A tumor lesion in a previously irradiated field can be assessed as measurable disease provided the lesion has been deemed to demonstrate progression.

Measurable:
A lesion, not previously irradiated per the protocol prior to enrollment, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and that is suitable for accurate repeated measurements. A tumor lesion in a previously irradiated field can be assessed as measurable disease provided the lesion has been deemed to demonstrate progression.

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis at baseline.
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, or abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Lesions <2 cm biopsied within the screening period (newly acquired tumor biopsy)
- Previously irradiated lesions that have not demonstrated progression[1,2]
- Brain metastasis

Special cases:

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.
- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected as target lesions (TLs).

Target lesions:
A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TLs at baseline.

Non-target lesions:

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

1. METHODS OF ASSESSMENT

The same method of assessment and the same technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits. A summary of the methods to be used for RECIST assessment is provided in *Table 1*, and those excluded from tumor assessments for this study are highlighted with the rationale provided.

Table 1 Summary of methods of assessment

Target lesions	Non-target lesions	New lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Clinical examination	Clinical examination
	X-ray, Chest X-ray	X-ray, Chest X-ray
		Ultrasound
		Bone scan
		FDG-PET

CT: Computed tomography; FDG-PET: 18-Fluoro-deoxyglucose positron emission tomography; MRI: Magnetic resonance imaging.

3.1 CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and identification of any new lesions.

In the CC-16047 study, the methods of assessment of tumor burden used at baseline and follow-up visits are contrast-enhanced CT/MRI of the neck, chest, and abdomen (including liver and adrenal glands). Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients. CT examination with intravenous contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For brain lesion assessment, MRI is the preferred method.

3.2 Clinical examination

In the CC-16047 study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as TLs if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

3.3 X-ray

In the CC-16047 study plain X-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

3.4 Ultrasound

In the CC-16047 study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumor size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

3.5 Endoscopy and laparoscopy

In the CC-16047 study, endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor assessment.

3.6 Tumor markers

In the CC-16047 study, tumor markers will not be used for tumor response assessments as per RECIST 1.1.

3.7 Cytology and histology

In the CC-16047 study histology will not be used as part of the tumor response assessment as per RECIST 1.1.

3.8 Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

In the CC-16047 study, isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and X-ray is recommended where bone scan findings are equivocal.

3.9 FDG-PET scan

In the CC-16047 study, 18-Fluoro-deoxyglucose positron emission tomography (FDG-PET) scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive 18-Fluoro-deoxyglucose uptake[3] not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

[3] A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

2. TUMOR RESPONSE EVALUATION

4.1 Schedule of evaluation

RECIST assessments will be performed using contrast-enhanced CT/MRI assessments of chest, abdomen, and pelvis. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before start of study treatment, and ideally should be performed as close as possible to the start of study treatment. The first on-study scan should be performed after Cycle 3, before beginning Cycle 4 treatment. Subsequent scans should be performed every 3 cycles (approximately every 9 weeks) thereafter until confirmed objective disease progression as defined by RECIST 1.1 (irrespective of the reason for stopping treatment or subsequent therapy). The same method should be used for tumor measurement throughout therapy. After discontinuation of therapy scans will be performed every 12 weeks.

Additional assessments will be performed post confirmed objective disease progression for patients remaining on assigned treatment, re-treatment, or until subsequent cancer therapy according to the clinical study protocol. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimize any unintentional bias caused by some patients being assessed at a different frequency than other patients.

4.2 Target lesions

4.2.1 Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.

- If a TL splits into two or more parts, then record the sum of the diameters of those parts.
- If two or more TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion. Although a visit response of PD will be assigned in the vast majority of these cases, a case should be flagged and reviewed by the Study Physician in a blinded fashion if use of the estimated size in the calculation of TL would not give an overall visit response of PD.
- When a TL has had any intervention eg, radiotherapy, embolization, surgery, during the study, the size of the TL should still be provided where possible.

4.2.2 Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumor visit response for TL (see Table 2).

Table 2 Evaluation of target lesions

Complete Response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TLs, taking as reference the baseline sum of diameters.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progression of disease (PD)	At least a 20% increase in the sum of diameters of TLs and an absolute increase of at least 5 mm, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study).
Not Evaluable (NE)	Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. Note: if the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response.

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; SD Stable disease; TL Target lesion.

4.3 Non-target lesions

4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit (see Table 3).

Table 3 Evaluation of non-target lesions

Complete response (CR) must	Disappearance of all NTLs since baseline. All lymph nodes be non-pathological in size (<10 mm short axis).
Non CR/Non PD progression.	Persistence of one or more NTL with no evidence of
Progression (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: for patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; NTL Non-target lesion; TL Target lesion.

To achieve "unequivocal progression" on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of stable disease or partial response in TLs, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more NTLs is usually not sufficient to qualify for unequivocal progression status.

4.4 New lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor.

If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

4.5 Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with "symptomatic deterioration" requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumor assessments where possible until objective disease progression is observed.

4.6 Evaluation of overall visit response

The overall visit response will be derived using the algorithm shown in Table 4.

Table 4 Overall visit response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No or NE	CR
CR	NA	No or NE	CR
CR	Non CR/Non PD	No or NE	PR
CR	NE	No or NE	PR
PR	Non PD or NE or NA	No or NE	PR
SD	Non PD or NE or NA	No or NE	SD
NE	Non PD or NE or NA	No or NE	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR Complete response, PR Partial response, SD Stable disease, PD Progression of disease, NE Not evaluable,
NA Not applicable (only relevant if there were no non-target lesions at baseline).

3. CONFIRMATION OF PROGRESSION

In the CC-16047 study, imaging for confirmation of response (complete response or partial response) should be performed at next scheduled visit (and no less than 4 weeks) following the date the criteria for response were first met.

Disease progression in this immunomodulatory therapy requires confirmation. The confirmatory scan should occur preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of progression of disease (PD) in the absence of clinical deterioration.

Progression would be considered confirmed if the following criteria are met:

- ≥20% increase in the sum diameters of TLs compared with the nadir at 2 consecutive visits with an absolute increase of 5mm [(3)]
- And/or significant progression (worsening) of NTLs or new lesions at the confirmatory PD time-point compared with the first time point where progression of NTLs or new lesions identified
- And/or additional new unequivocal lesions at the confirmatory PD time-point compared with the first time point new lesions identified

(3) *The assessment of progression requires a ≥20% increase in the sum diameters of target lesions at the first progression timepoint relative to the nadir. The nadir is the smallest sum of diameters, and this may be at baseline or subsequent follow-up assessments. The confirmatory scan confirms the persistence of the ≥20% increase relative to the nadir. The minimum absolute increase in the sum of diameters of target lesions is at least 5 mm at both assessments.*

In the absence of significant clinical deterioration the Investigator should continue assigned treatment until progression is confirmed. If progression is not confirmed, then the patient should continue on assigned treatment and on treatment assessments.

If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression, then the patient should still continue to be followed until confirmed objective disease progression.

4. RECIST GUIDELINE REFERENCES

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

Nishino et al 2013
Nishino M Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH, Hodi FS. Developing a common language for tumor response to immunotherapy: Immune-related response criteria using unidimensional measurements. Clin Cancer Res, 2013;19(14):3936-43.

11.5 Lab Specimens Summary

Sample Type	Collection Tube	Screening	Collection Cycle(s)	D1	Amount of Blood (approx.)	Teaspoon Equivalent
Blood						
Hematology	Lavender top (EDTA)	X	All cycles (Q3W)	X	5 mL	1 tsp per draw
Chemistry	light green top tube (lithium heparin)	X	All Cycles (Q3W)	X	5 mL	1 tsp per draw
Other: b-HCG,TSH, PT/PTT, etc	light green top tube (lithium heparin) or as indicated by Path manual[1]	X	Only Screening or as needed			
Correlative Blood Studies						
RNA Microarray Sampling	TEMPUS tube	X	Cycle 1, 6-hr post-infusion	X	2.5 mL	½ tsp
			Cycle 3, 6-hr post-infusion	X	2.5 mL	½ tsp
DNA Analysis	PAXgene tube	X	Cycle 1, 6-hr post-infusion	X	8.5 mL	1 ½ tsp
			Cycle 3, 6-hr post-infusion	X	8.5 mL	1 ½ tsp
PBMC, Plasma Collection/ Separation Analysis	1-2 10 ml Lavender top EDTA tubes (at least 10 ml, ideally up to 20 ml)	X	Cycle 1, 6-hr post-infusion	X	10-20 mL	2-4 tsp
			Cycle 3, 6-hr post-infusion	X	10-20 mL	2-4 tsp
Experimental Biopsies (Phase II only)						
Pre-therapy tumor biopsy sample	Formalin + Fresh Frozen	X	Only screening	N/A	N/A	N/A
Post-therapy tumor biopsy sample (5-10) (optional)	Formalin + Fresh Frozen		C4	N/A	N/A	N/A
Post-therapy tumor biopsy sample (5-10) (optional)	Formalin + Fresh Frozen		End of treatment visit and follow-up period	N/A	N/A	N/A
Diagnostic Biopsy						
Historical Biopsy or repeat biopsy if no historic biopsy	Formalin + Fresh Frozen	X	Only Screening or as needed	N/A	N/A	N/A
Archival tumor tissue on all subjects	Paraffin-embedded block or unstained slides	X				

[1]https://paws.gru.edu/pub/pathology/Pages/Pathology-Lab-Manual.aspx#

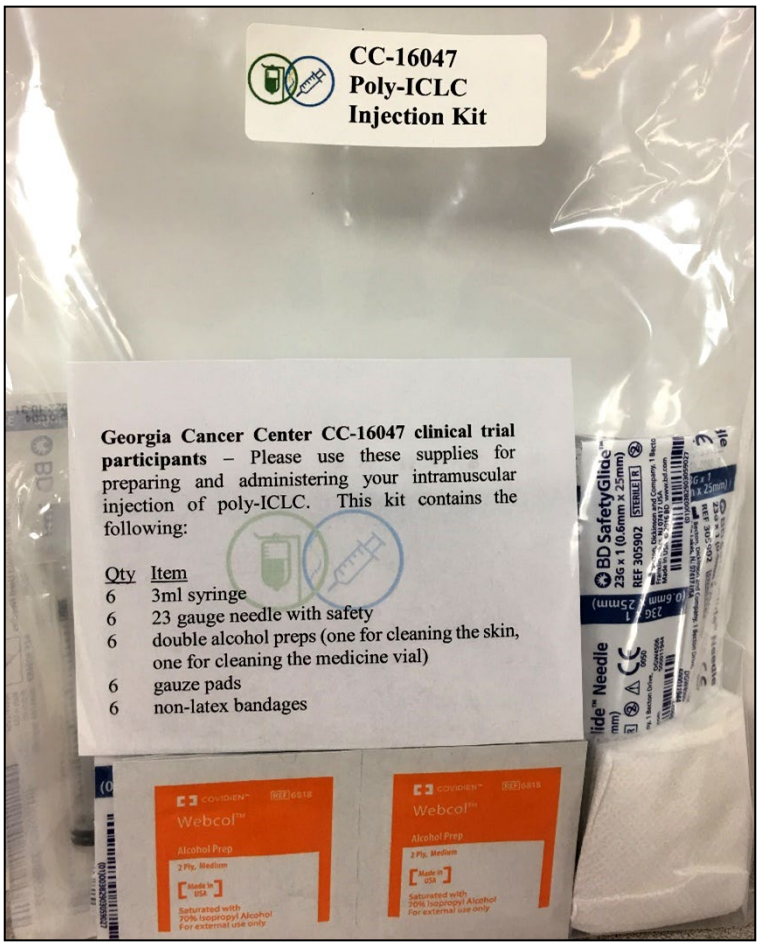
11.6 Laboratory Manual

11.6.1 Patient Guide (for at-home administration of poly-ICLC)

A folder containing printed documents that describe how to handle, prepare, and administer the poly-ICLC intramuscular injections will be provided to each enrolled subject. The study coordinator should review the guide with the patient and caregiver to ensure understanding, and to answer any questions. The subject may also use the folder to keep up with their injection diary sheets.

11.6.2 Patient Injection Kits

When poly-ICLC vials are dispensed to the subject for at-home injection, the study subject should be given a patient injection kit (pictured below). The GCC CTO has assembled injection kits with supplies from the AU Health/AU Medical Center Central Distribution office. Supply refills will be managed by the Multi-Center Research Coordinator.



Standard kits (for a full cycle with six injections of poly-ICLC) should include the following:

- Six 3ml syringes (single-use, sterile)
- Six 23 gauge needles with safety (single-use, sterile)
- Six double alcohol preps (one for cleaning the skin, one for cleaning the medicine vial)
- Six gauze pads
- Six non-latex bandages

If sharps containers are available from other sources within the clinic, they may be provided to the patient. Otherwise, patients and caregivers should be instructed to identify a puncture-proof container (with lid) to throw out their used needles and syringes. Sharps containers may be purchased at a drugstore or medical supply store, or a common household container such as an empty laundry detergent bottle or similar container may be used.

Patients and caregivers should also be instructed to return full sharps containers to the clinic to be disposed of properly.

Correlative Study Sample Collection, Processing, and Storage

Tempus Blood Collection Tubes from Applied Biosystems have been selected for extracting RNA from whole blood to be used for the research in this protocol.

When collecting whole blood into a TEMPUS tube for RNA extraction please follow these steps; failure to follow all of these steps can significantly affect the RNA yield of the sample:

1. Draw the 3 ml whole blood sample either directly into the TEMPUS tube with a straight needle or butterfly collection system or by drawing blood into a syringe and then transferring it into the TEMPUS tube. Be sure to position the TEMPUS tube below the butterfly tubing or below the patient's arm to ensure that the buffer in the TEMPUS tube does not flow toward the patient.

2. Immediately cover the filled TEMPUS tube with a gloved thumb or gauze square and shake the tube **extremely vigorously** for a full 15 seconds. The shaking should be vigorous enough to cause some foaming of the sample. It is important to shake the tube hard enough to break up any small clots that have begun to form during drawing, and the break the cells themselves, allowing the buffer to protect the RNA inside.

3. Leave the tube upright at room temperature for 2-4 hours, then store in refrigerator for up to 24 hours or transfer to Tumor Bank.

4. Transfer the sample, with a refrigerated cool-pack, to Tumor Bank for storage at -80 °C.

5. Samples may be stored for up to 6 years. (Duale et al. BMC Research Notes 2014, 7:633)

Contact for RNA sequencing, microarray analysis, flow analysis:

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Participant's Name: _____
Participant's Medical Record Number: _____

AUGUSTA UNIVERSITY

RESEARCH INFORMED CONSENT DOCUMENT

TITLE: A phase I/II trial of pembrolizumab (MK-3475) and poly-ICLC in patients with metastatic mismatch repair-proficient (MRP) colon cancer

PROTOCOL NO.: CC-16047
WCG IRB Protocol #20161318
917962

SPONSOR: Asha Nayak-Kapoor, MD

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Invitation To Take Part In Research
You are invited to take part in a research study of pembrolizumab (MK-3475) and poly-ICLC in patients with solid tumors and metastatic mismatch repair-proficient (MRP) colon cancer. Patients with colon cancer that have a defect in repair of damaged DNA will not be eligible for this study because of the high response rate observed with pembrolizumab alone. This document will tell you about:

- important information about the study
- what will happen if you decide to take part in the study
- the purpose of the study
- and the potential risks and benefits of taking part in the study.

The study doctor and/or study staff will:

- discuss the study with you and
- answer all of your questions.

Taking part in this study is voluntary. Please take the time to read this form carefully. You can take home an unsigned copy of the consent form to discuss with friends and family while you make your decision. Please ask any questions you may have before you agree to take part in the study. If you decide to take part in this study you will be asked to:

- sign this form

Why am I being asked to take part in this study?
You are being asked to take part in this study because you have a cancer that is no longer responsive to at least one standard therapy. For the first part of the study patients with any type of cancer will be eligible. For the second part of the study you must have a cancer of the large bowel without a defect in DNA repair and that did not respond to two standard treatments. Your type of cancer shows specific genetic patterns that make it more resistant to immunologic treatments. Two drugs are being used in this study, pembrolizumab and Poly-ICLC.

Pembrolizumab is an antibody that is made in the laboratory. An antibody is a natural protein made by our immune system that binds other proteins or molecules to fight infection and its ill effects. Pembrolizumab has been approved by the Food and Drug Association (FDA) for melanoma skin cancer and specific types of lung cancer. Pembrolizumab is an experimental drug therapy for many other types of cancer and has shown outstanding effects in certain tumor types like Hodgkin lymphoma and microsatellite repair insufficient tumors particularly of the large bowel. Pembrolizumab binds to another protein in the body and may prevent cancer growth by helping certain blood cells of the immune system eliminate the tumor.

Poly-ICLC is an immunostimulating agent. This means that it activates your immune system against infections and tumor cells. It is an experimental drug that has not yet been approved by the FDA.

Both Pembrolizumab and Poly-ICLC are investigational as used in this study.

What Is the Purpose of This Study?
The main purpose of this study is to determine the dose of poly-ICLC that is safe and tolerable when it is combined with pembrolizumab in subjects with cancer. This study will also evaluate how the combination of pembrolizumab and poly-ICLC activates your immune system in your blood and inside the tumor and how it affects the size and number of tumor(s) in your body and how effective the combination is in patients with colon cancer that is unlikely to respond to pembrolizumab alone.

The study also determines how you benefit from the treatment by evaluating the tumor response to the treatment, prolonging your survival and duration of the response to the treatment.

The combination of poly-ICLC and pembrolizumab is in a very early stage of development for use in humans. Please carefully read the sections on risk and benefits below.

The information learned in this study may be helpful in the further development of combining immune stimulating agents such as poly-ICLC and pembrolizumab in patients with specific types of tumor that benefit from immunological treatments.

How many people are expected to take part in this study?
This study is exclusively for adult patients over the age of 18. If you choose to take part in the study, you will be one of 31 people at Augusta University who are participating in this clinical trial. Approximately 12 people will take part in the first part of this study. The second phase of the study will enroll up to 27 patients. Both groups will receive pembrolizumab as an infusion

into the vein every three weeks at the outpatient clinic, combined with biweekly intramuscular injections of poly-ICLC. In order to participate in this trial, you must be able to either inject yourself with the poly-ICLC, or identify another person who can be trained to give you the injections. This regimen will be given for 17 cycles. Each cycle is 21 days with pembrolizumab given on day 1 and poly-ICLC injections on days 1, 4, 8, 11, 15, 18.

Study Procedures
This study will enroll its patients into two separate phases:

1) Phase I
   a. Aimed to determine if poly-ICLC can be safely combined with standard dosages of pembrolizumab.
      i. Poly-ICLC will be administered intramuscularly twice weekly at 1.8 mg.
      ii. Pembrolizumab will be administered 200 mg intravenously every three weeks.
   b. Each dose level enrolls 3-6 patients, with the potential for 12 patients. These patients are closely monitored for any possible drug reaction.
   c. Patients with any solid tumor that is unresponsive to at least one line of therapy are eligible for the dose escalation phase unless curative options exist.
2) Phase II trial expansion
   a. Patients with any colon tumor that is unresponsive to at least two lines of therapy are eligible for the dose expansion phase unless curative options exist.
   b. The combination from Phase I with the highest tolerated dose of Poly-ICLC will then be administered at the recommended phase II dose in up to 27 patients with MRP colon tumor.

The total duration of treatment for each phase is one year with total 17 cycles of combination treatment. If your cancer is responding to treatment, you may be able to continue with the study treatment for up to an additional year (or up to 35 cycles of study treatment).

What will happen to me in the study?
Your participation in this research study is expected to last approximately 52 weeks. After you are done participating in the study you need to attend follow up visits with your treating physician at day 30 and every 12 weeks thereafter, for up to 36 months. They will ask if you are in remission (cancer free), whether your cancer has returned, and if so, whether you are on a new form of cancer treatment.

Screening Visit:
The screening visit is done to see if you are eligible (qualify) for and can safely participate in this study. You will be given detailed information about the study and will have an opportunity to ask our doctors any questions. If you are still interested in taking part in the study, we will ask you to sign this consent form. This is not a contract binding you to the study. It is simply to show that you understand what the study is about and that you are willing to participate in the study, if eligible. You are free to withdraw from the study any time.

We will conduct several routine screening procedures that include a physical examination and recording your medical history. In addition, you will have one blood draw of approximately 11.5

tablespoons of which two and a half tablespoons will be used to measure your blood chemistry, kidney/liver function and blood counts. The remaining 9 tablespoons of blood will be used to evaluate your immune responses (how your body recognizes and defends itself against bacteria, viruses, and substances that appear foreign and harmful to the body such as tumors). You will also have urine tests (approximately 4 oz or half a cup), and an electrocardiogram (ECG) to measure and record the electrical activity (heart beat) of your heart. Your doctor may review a tissue sample from the original biopsy that was done to confirm your cancer diagnosis.

You will have a CT-scan of the chest/abdomen/pelvis and a CT scan of any extremity affected by your tumor, and a brain MRI or CT scan of the brain. In some cases you may have a PET/CT scan performed. You may have an ultrasound performed of the lesions to determine whether they can be biopsied under ultrasound guidance. The scanning imaging tests have to be done within 4 weeks of your 1st study treatment.

If you are a female who is able to become pregnant, you will have a pregnancy test taken to determine if you are pregnant. Pregnant women are not allowed to participate in this study because the risks of the study for an unborn fetus are unknown. If you are not pregnant and could become pregnant you must use contraceptives during the course of this study, and for 120 days after going off study (completion or involuntary). If you are a male you must use contraceptives (abstinence, condoms, outercourse) while on study and for 120 days after going off study (completion or involuntary).

After we receive your test results we will contact you to let you know the outcome. If you qualify for enrollment onto the study and you still want to take part in it, you will be asked to return to the study doctor to begin your study treatment as described in the following pages.

- In Phase 1, study medication poly-ICLC will be given via intramuscular injections twice weekly combined with the standard dose of pembrolizumab as a single intravenous infusion on Day 1 of each cycle. The lower dose will be given to a small number of subjects. If they can tolerate it, the higher dose will be given to another small group. Every week, two intramuscular injections of poly-ICLC will be given three days apart: on days 1, 4, 8, 11, 15, and 18.
- Phase II: Combination treatment with the highest tolerated poly-ICLC dose and standard intravenous pembrolizumab will be continued in up to 27 patients with the proposed schema mentioned above. Treatment cycles are continued for total duration of one year (17 cycles) unless you or your study physician decide not to continue the study protocol.
- Blood tests are done before every cycle. Urine tests are done every 4 cycles and specific thyroid tests will be checked every 2 cycles during both phase I and II of treatment. For each blood sampling, a single blood draw will be performed of approximately 6.5 tablespoons. Half a tablespoon will be used to measure your blood chemistries, assess kidney/liver function and to count your red and white blood cells and platelets, and 6 tablespoons will be taken to evaluate how your immune system is functioning. Urine tests (approximately 4 oz or half a cup) will also be performed. Immune response will be re-evaluated based on the blood test samples provided on cycle 1, 3 and 7 of treatment protocol.

- All patients in Phase II of the study will have a biopsy taken from the tumor at the beginning/during cycle 4 of poly-ICLC. There may also be optional repeated biopsies at the beginning of cycle 4, during the end of study visit and follow-up period if relapse is encountered. The biopsy is provided by local anesthesia with the guide of CT scan or ultrasound. During the follow up, tumors might need a repeated biopsy if they show progression or appearance of new lesions. Biopsy samples are taken by special needles that may leave a minimal scar of few millimeters. These studies are optional but are important to learn how the therapy works and what happens in the tumor when it stops working.

If you decide to take part in this research study you will be responsible for the following things:

- Being able to give yourself, or having your person of choice (e.g., family member, friend) give you the poly-ICLC injections at home. The first injection will be administered in the clinic under the supervision of study clinical staff. The study nurse will provide training on how to give yourself the injection. You will be monitored for at least 30 minutes after the first injection to watch for any adverse reactions. Following the first injection, subsequent injections will be administered at home. You will be given a set of written instructions to follow, and a diary sheet to show the dates and times of your injections, as well as where you received the injection (injection site).
- Tell the study doctor how you feel and about any side effects.
- Tell the study doctor about any medication, over-the-counter products, herbal remedies, or alternative therapies that you use while you are in this study. **Certain medications cannot be taken while you are in this study.** The study doctor will explain what these medications are. If you need treatment with any medications that are not allowed during this study, you must tell the study doctor or the study staff. You will not be denied medications required to treat an illness you may have, but you may be required to stop taking the study medication. This is for your safety, since some medications may not work well with Poly-ICLC, and you might have physical problems. You must check with the study doctor first if you need to take any new over-the- counter medications or herbal supplements, or if you need to change your usual prescription medications during this study.
- You should not have any immunizations (vaccinations) without the study doctor's approval.
- Tell the study doctor about any medical treatments that you will have to get during the study (such as elective surgery).
- If you decide to take part in the study, it is important that you follow the instructions and advice given to you by the study doctor.
- You should not donate blood for 3 months following the last dose of study treatment.
- You may be able to return to work or stay home at the time you receive your study drug. Normal daily activities need not to be changed unless you experience drug related serious adverse events or your study physician recommends you limited activities or special considerations.

What Research Procedures Will Be Done Only Because I Am Taking Part In This Study?

Based on the information provided before, your blood samples will be withdrawn for further evaluation of kidney, liver and thyroid function as well as hematology and immune response assays. Urine samples are taken and tumor biopsies will be taken. Imaging studies for evaluation of the tumor size will be done within 4 weeks before enrollment as well as every 4 cycles during the study protocol and every 12 weeks during the follow up.

What procedures will be done as part of my normal clinical care?

- History and physical examinations, review of current medicinal products taken by the patient. You will be asked about any adverse events you experience in every visit and each post treatment follow up visit.
- Blood samples will be taken every cycle during the treatment and every 3 weeks for the whole duration of follow up.
- Imaging studies by CT scan with contrast media will be done before enrollment and every 3 cycles during the study and every 12 weeks thereafter.
- Electrocardiogram (ECG) will be performed during screening, and thereafter as needed.

Archival Tumor Samples

Your tumor sample from tissue that was already collected from you through a previous surgery will be obtained for the study. In such cases, the tumor sample (also called a "paraffin block") is already stored in a pathology lab.

RISKS

What are the possible risks or discomforts?

Possible adverse events include those associated with venipuncture, study drug administrations, and tumor biopsies. Imaging studies with CT scan as well as electrocardiography (ECG) may also show their own adverse reactions. Certain of the expected events listed below are also due to activation of the patient's own immune system against the tumor, with potentially beneficial inflammation and tumor necrosis.

There may be more risks that are not known or not expected as this is the first time this combination of drugs is being administered.

Possible Risks Associated with Poly-ICLC:

Following are risks and discomforts that you may experience during your participation in this research study.

1) Discomfort at the injection site: You will likely experience discomfort, soreness and redness at the injection site, both during and afterwards.
2) You may also develop pain and swelling at the tumor sites that could cause symptoms, which would vary depending on the location of the tumor. Inflammation at other tumor sites could also be an indication that your body is fighting the tumor.
3) Flu- like symptoms: You may develop flu like symptoms several hours after injection, which may last up to several days. These include muscle aches, fevers, headaches, chills, fatigue and general symptoms of having a viral infection. These symptoms should be

better with acetaminophen (Tylenol).

4) Low white blood cell counts: While on study treatment it is possible that you could develop low white blood cell counts. Low white cell counts put you at risk for serious infection so if this were to happen, the dose of Poly-ICLC may have to be adjusted. If you get an infection while your white count is low you may have to be hospitalized and receive antibiotics.

5) Liver abnormalities: While you are on study we will be checking your liver function by monitoring your blood work results. You may develop a temporary elevation in your liver function tests. There are no reported cases of this causing any clinical symptoms.

6) Clotting abnormalities: This was reported in animal studies in non-human primates but never in humans, so is possible but unlikely.

7) Anemia (low red blood cell counts): Due to repeated blood draws it is possible that you could develop anemia. Anemia causes people to feel week and have low energy. If anemia causes you symptoms or reaches levels of concern, no further blood draws will be obtained except as medically necessary until your levels return to the range that is normal for you.

8) **Seizures:** Have been reported, but are extremely unlikely. Three patients who experienced seizures had brain tumors and were highly susceptible to seizures and may have had a history of such. They all recovered without a problem.

Possible Risks Associated with pembrolizumab:

Most of the possible side effects listed below are mild to moderate. However, some side effects can be very serious and life-threatening and may even result in death. Some side effects do not need treatment while others generally get better with treatment. Some patients may need to delay doses of pembrolizumab to allow the side effects to get better. The most important possible side effects, which are listed below, may occur because of the way pembrolizumab works on the immune system and they have been seen in patients treated with pembrolizumab in clinical studies. Side effects like these have also been seen in clinical studies with other drugs that are very similar to pembrolizumab.

Very Common Side Effects (Out of 100 people who receive prembrolizumab, 20 or more people may have the following):

- Diarrhea (loose or watery stools)
- Rash/dry itchy skin
- Cough

Common Side Effects (Out of 100 people who receive pembrolizumab, at least 5 but less than 20 people may have the following):

- Joint pain
- Rash
- Fever
- Back pain
- Pain in your belly
- Loss of skin color
- Not enough thyroid hormone, so you may feel tired, gain weight, feel cold or have

infrequent or hard stools (hypothyroidism)
- Low levels of salt in the blood that may cause you to feel tired, feel confused, have a headache, have muscle cramps, and/or feel sick to your stomach (hyponatremia)

Uncommon Side Effects (Out of 100 people who receive pembrolizumab, at least 1 but less than 5 people may have the following):
- Inflammation of the lungs, so you may feel short of breath and cough (pneumonitis)
- Too much thyroid hormone, so you may feel anxious, feel angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools (hyperthyroidism)
- Infusion reaction, where you may feel dizzy or faint, feel flushed, get a rash, have a fever, feel short of breath, experience a decrease in your blood pressure at the time of receiving your infusion (IV) or just after, or have pain at the site of infusion
- Inflammation of the bowels/gut, which may cause severe pain in your belly with loose or watery stools, and black, tarry, sticky stools or stools with blood or mucus (colitis)
- Inflammation of the skin so you may have peeling of the skin, itchiness, and/or skin redness. The skin inflammation (i.e., peeling, itching and redness) could also be widespread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body which can cause severe infection (Severe skin reactions, including Stevens-Johnson syndrome or toxic epidermal necrolysis)

Rare (Out of 100 people who receive pembrolizumab, less than 1 person may have the following):
- Inflammation of the nerves that may cause pain, weakness, or tingling in your hands and feet, and may spread to your legs, arms, and upper body, leading to severe muscle weakness and possible temporary paralysis (Guillain-Barré syndrome)
- Inflammation of the muscles, so you may feel weak or have pain in your muscles (myositis)
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels), so you may have severe pain in the top part of your belly that may move to your back, feel sick to your stomach, and have vomiting that gets worse when you eat (pancreatitis)
- Inflammation of the eye, so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters, or have headaches (uveitis)
- Inflammation of the liver that may make you feel sick to your stomach and vomit, feel like not eating, feel tired, have a mild fever, a pain in the right side of your belly, yellow eyes and skin, and dark urine (hepatitis)
- Inflammation of the pituitary gland (a gland in the head), which may cause you to feel sick to your stomach or have headaches, changes in your behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness, or fainting (hypophysitis)
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, having joint, muscle, and bellyaches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan (adrenal insufficiency)
- Type 1 diabetes, a condition that can cause too much sugar in your blood, feeling thirstier than usual, frequent urination, and weight loss. You are likely to need regular insulin shots
- Inflammation of the kidney, so you may pass less urine or have cloudy or bloody urine,

swelling, and low back pain (nephritis)

- Inflammation of the middle layer of your heart wall that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath, and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting (myocarditis)
- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to change in your heart rate, blood pressure, body temperature, and the rate at which food is converted into energy (thyroiditis)
- A condition that may make you feel weak and tired and may cause drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing (myasthenic syndrome/myasthenia gravis including exacerbation)
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs (sarcoidosis)
- Inflammation of the brain with confusion and fever. This may also include: disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness (encephalitis)
- Hypoparathyroidism which is a rare condition where the parathyroid glands, located in the neck near the thyroid gland, produce too little parathyroid hormone (causing low calcium level and high level of phosphorus in the blood)
- Inflammation of the spinal cord with pain, numbness, tingling, or weakness in the arms or legs, bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating, and constipation (myelitis)
- Inflammation of the blood vessels (vasculitis). Symptoms will depend on the particular blood vessels that are involved in the inflammatory process, for example: if it is your skin, you may get a rash. If your nerves are not getting enough blood, you could have numbness and weakness. You may also experience fever, weight loss, and fatigue.

Additionally, since pembrolizumab was approved in September 2014, the following side effects have been reported by people receiving pembrolizumab. These side effects were voluntarily reported from a group of people of unknown size. It is not possible to estimate the frequency of these side effect:

- Inflammation of the joints which may include joint pain, stiffness and/or swelling (arthritis)
- Severe responses of the immune system that cause the body to attack its own blood cells, spleen, liver, lymph nodes, skin and brain. This may include fever, rash, inflammation of the liver, yellowing of the skin, an enlarged liver and spleen, low blood counts, and enlarged lymph nodes. The nervous system may also be affected and cause confusion, seizures, and even coma (hemophagocytic lymphohistiocytosis)
- Changes in eyesight, eye pain, whitish patches on the skin and hearing loss (Vogt-Koyanagi-Harada syndrome)
- Inflammation and scarring of the bile ducts (tubes that carry digestive fluid that is made in the liver). This can cause symptoms similar to those seen with inflammation of the liver (hepatitis) such as pain in right side of your belly, yellow eyes and skin, feeling tired, and itching (sclerosing cholangitis).

As well as the important possible risks described above patients with different types of cancer who have been treated with pembrolizumab in clinical trials have very commonly (i.e., more than 10% of patients) reported: feeling tired, nausea, vomiting, decreased appetite, shortness of breath, cough, fever and pain in muscles and joints.

Biopsy: If you have easily accessible tumors, you will have a biopsy sample taken before beginning treatment and before receiving the fourth cycle of the treatment. There may also be optional repeated biopsies of the tumor at the end of study visit and follow-up period if relapse is encountered. The biopsies are done under the guidance of either ultrasound or CT scan and up to 3 core needle biopsies less than 1mm in width will be taken of each lesion. These procedures are done to evaluate how your body recognizes and defends itself against cancer. A biopsy is a relatively safe surgical procedure. As with any surgical procedure, you may experience side effects that include pain, infection, temporary swelling/bleeding, tenderness, scarring at the surgical site and allergic reaction to the drugs. The study doctor will give you specific instructions on how to care for your biopsy site and contact information in case of an emergency.

Blood Draw: Symptoms may include bleeding, fainting, injection site infection and/or anemia (low red blood cell levels that could result in tiredness, dizziness, sleeplessness, shortness of breath, leg cramps). Fainting can occur during or after a blood draw in some individuals. Your red blood cell level will be monitored periodically during the study. You may be asked to take iron supplements if your level decreases.

Radiation Exposure: If you take part in this research, you will have a number of radiation procedures or examinations that are part of the regular medical care for your condition and you would have them whether or not you participate in this research. You will not be exposed to any additional radiation because you are participating in this research.

These tests include X-rays, CT scans, and or PET scans, all of which are used routinely to follow up on your condition. The study doctor will decide which test you have, and when you have it, based upon your disease, where it is located, and your progress. You may also have MRI scans, but these do not involve radiation exposure.

Some of the scans could involve "contrast", which is like a dye injected into the bloodstream, which makes things appear more clearly on the test. Since some of the contrast dyes contain iodine, it is important that you tell the study doctor if you are allergic to iodine.

The study doctors will always try to keep radiation exposure as low as reasonably achievable by choosing tests and procedures that involve the lowest possible exposure while providing the necessary information about your condition.

Women of Childbearing Potential
You cannot participate in this study if you are or plan to become pregnant, or if you are breastfeeding. There may be unknown risks to you, the embryo/fetus or nursing infant if you become pregnant during the study.

You must be using adequate contraception for the duration of the study and for 120 days following your participation. If you become pregnant, suspect pregnancy, if you have a change in your menstrual cycle, or in your contraception method you should immediately contact the study doctor. Should you become pregnant during the study, you will be withdrawn from the study immediately and should seek care from a doctor who specializes in pregnant women (an OB/GYN, or obstetrics and gynecologist physician). The study doctor or any investigator on this study, or Merck and Oncovir, the manufacturers of the drugs are **not** responsible for any financial aspects of obstetrical, child or related care.

Psycho/Social/Economic Risks: Risks and discomforts not only include physical injury, but also possible psychological, social or economic harm, discomfort or inconvenience, or breach of confidentiality.

Privacy Risk: There always exists the potential for loss of private information; however, there are procedures in place to minimize this risk.

Unknown Risks: It is possible that the study treatment or procedures may involve risks to you that are not currently known or foreseeable. It is important that you should consult with the treating physician regarding any questions or concerns you may have about the study treatments.

If I take part in this study, can I take part in other studies?
You are not allowed to enter any clinical study while you are enrolled in this study and during the follow up unless your study physician or you decide to withdraw/be withdrawn from the study.

Can I take other medication while I am taking part in the study?
You must tell the study team about any medicines (prescription or over-the-counter), and herbal, vitamins, or mineral supplements:

- That you take now.
- That you or your doctors add or take away.

The combination of these medicines and the research study medicine is not known at this time. The combination may result in increased risk to you. You must contact the research team at **706-721-2505** if any changes are made to your current medicines and supplements.

You agree not to drink alcohol while you are taking poly-ICLC and pembrolizumab since the combination of either experimental medication and alcohol may be harmful to you.

<u>Reproductive Risks</u>
Women who can get pregnant or are breastfeeding
The effects of (name of study drug) on an embryo or fetus are not known. You may not take part in this study if you are:

- breastfeeding
- pregnant

- think that you may be pregnant
- Or are trying to get pregnant. The risks to an unborn child are not known. Your study doctor does not want you to become pregnant while you are taking part in this study.

If you are female, from the time of informed consent through 120 days following the last dose of study medication, you must agree to the following:

- Avoid pregnancy unless you are unable to become pregnant (e.g. have had your "tubes tied", had a hysterectomy or are at least 1-year post-menopausal). If sexually active and able to become pregnant, you must agree to use 2 effective methods of birth control as noted in the table below. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method and the withdrawal method are not acceptable methods of contraception.
- Refrain from breastfeeding and egg cell donation.

Effective Methods of Contraception (Two Methods Must be Used)

Barrier Methods	Intrauterine Device Methods	Hormonal Methods
• Male condom plus spermicide • Cap plus spermicide • Diaphragm plus spermicide	• Copper T • Levonorgestrel-releasing intrauterine system (e.g. Mirena®) [a]	• Implants • Hormone shot or injection • Combined pill • Minipill • Patch

[a] This is also considered a hormonal method.

Men

If you are a male who is sexually active with a female partner who may become pregnant, from the time of informed consent through 120 days following the last dose of study medication, you must agree to the following:

- Be unable to get a female partner pregnant (eg, had a vasectomy).
- If sexually active you must agree to use 2 effective methods of birth control as noted in the table below. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method and the withdrawal method are not acceptable methods of contraception.
- Refrain from sperm donation.

If during the study and through 120 days after your last dose of study medication, you learn that you are pregnant (female subject) or your female partner becomes pregnant (male subject), you must contact the Study Doctor immediately for further instructions about follow-up. The study team will ask you about any pregnancy during the study visits and may continue to follow-up with female subjects for 120 days after your last dose of study medication. If at any time you report a pregnancy of either you or your partner, the study team will collect information about the results of the pregnancy and/or birth and will schedule any follow-up visits that may be necessary. The study doctor will ask the pregnant partner of a male subject to sign a separate

consent form to allow the collection of this information. This health information will become part of the clinical trial records and will be shared with the Sponsor so that the Sponsor may determine if there are any effects of the study medication on unborn children.

If I get sick or become hurt because of the study, what will happen?
Augusta University:
If you think that you have suffered a research related injury, seek medical care right away and contact the study team as soon as possible at 706-721-2505. In the event that this research related activity results in an injury, treatment will be made available including first aid, emergency treatment, and follow-up care as needed. Cost for such care will be billed in the ordinary manner to you or your insurance company. No reimbursement, compensation, or free medical care is offered by Augusta University (AU), AU Medical Center, AU Medical Associates, AU Dental Associates, AU Nursing Associates, Inc., AU Health Professions Associates, Inc. collectively designated AU Affiliates [or any other facility involved with this study]. You do not give up your legal rights by participating in this study.

COSTS
The study drugs, pembrolizumab and poly-ICLC, will be provided for this study by Merck and Oncovir respectively. There will be no charges for the laboratory tests related to the research part of the study.

If you agree to participate in this study, you and/or your insurance will not be billed for the tests and treatments that are being done only for research. However, you are still responsible for paying for the usual care you would normally receive for the treatment of your illness. You will be responsible for all co-pays, deductibles, and denied claims.

You have the right to ask specifically what it will cost you to take part in this study. You have the right to contact your insurance company to discuss the costs of your routine care and whether these will be covered if you participate in this study. You may choose not to be in this study if your insurance does not pay for your routine care. In that case, your doctor will discuss other treatment plans with you.

No other compensation, such as lost wages or other damages, will be offered.

BENEFITS
How could I benefit from being in this study?
Since this study is the first time poly-ICLC is administered in combination with pembrolizumab in patients with colon tumor, there is no way to know if there will be any benefit from this treatment. The combination of poly-ICLC and pembrolizumab is experimental. It is possible that the combination will have no direct benefit to you. Even in the future if it is found that either pembrolizumab or poly-ICLC can benefit cancer patients, a few patients on this study may receive a low dose of any of them for safety reasons; a low dose is given in this study to make sure that the drug does not have serious side effects and you do not have a choice what dose of pembrolizumab or poly-ICLC you will receive. The likelihood of you benefiting from this study is low. Other people, including those with cancer, may benefit from what is learned in this

study.

Will the researchers tell me if they learn something new that may change my decision to continue in the study?
You will be told of any new information about the study. This new information may change your mind about being in the study.

ALTERNATIVES/OTHER OPTIONS

What other options do I have if I decide not to take part in the study?
You are not required to take part in this study. There are no curative options for your cancer. There are additional therapies available that have been shown to prolong the life of patients on average by 1-2 months such as regorafenib, trifluridine/tipiracil, or EGFR-directed antibodies if your tumor is RAS wild type. You may still receive these therapies if the therapy given during this study is not effective. If you do not want to take part in the study, your Study Doctor will discuss different options that are available to you. These options may include:

- Treatment with other chemotherapy drugs;
- Treatment with medications that will make you feel more comfortable, but have no effect on your cancer;
- Other experimental treatments;
- No treatment but palliative care to relieve your symptoms

If you decide that you don't want any more active treatment, one of your options is called "comfort care." Comfort care includes pain medication and other support. It aims to maintain your comfort and dignity rather than cure disease. Usually this care can be provided at home.

The study staff will discuss these other options with you.

ENDING THE STUDY

Can I stop taking part in the study?
Joining this study is voluntary. You can decide not to take part or at any time after joining the study and for any reason, you can withdraw from the study without any penalty or loss of benefits to which you are otherwise entitled. Your decision to leave the study will have no effect on your future care or treatment by physicians or by this institution.

If you leave the study early, you are recommended to go through such study exit procedures as may be considered necessary by the doctor doing this study. Your study doctor may ask if he/she can continue to collect relevant information for the study during your normal clinic visits.

Can the study doctor remove me from the study?
Yes, the study doctor may stop your taking part in the research study for many reasons. Some examples are:

- The sponsor or study doctor decides to stop the study.
- The study doctor stops your taking part in the study for your safety.
- You are not eligible to take part in the study.

- Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- You do not follow the instructions from the study staff.
- Failure to keep appointments, follow directions or take medications as instructed.
- A serious adverse reaction to study treatment.
- The need for treatment that is not allowed in the study.
- Worsening of your disease.

If you decide to stop taking part in the study for any reason, you must contact the study staff immediately at 706-721-2505 (24 hours/day, 7 days/week).

What's the best way to stop taking part in the study?
Before you stop taking part in the study, contact the study staff. You should follow the instructions they give you to safely stop the study.

Could there be any harm to me if I decide to stop participating in the study before it's finished?
If you decide to stop taking part in the study, the study staff will discuss ways to safely remove you from the study. You should follow the instructions the study staff gives you.

If I withdraw from the study, can information about me still be used and/ or collected?
If you stop taking part in the study the study staff will not collect any more information from you. The information that the study staff had about you before you decided to stop being in the study can be used.

Will I be paid for taking part in the study?
You will not be paid for taking part in this study. You will be responsible for the costs of transportation to participate in the study.

CONFIDENTIALITY
By signing this form you consent to the Study Doctor and his or her staff ("Study Team") collecting and using personal data about you for the study ("Study Data"). This includes: your date of birth/age as permitted by local laws, your sex, your ethnic origin, and personal data on your physical or mental health or condition.

Your consent to the use of Study Data does not have a specific expiration date, but you may withdraw your consent at any time by notifying the Study Doctor. If you withdraw your consent, any Study Data collected prior to that time may still be given to and used by the Sponsor but your Study Doctor will not collect any new Study Data.

The Study Data given to and used by the Sponsor is protected by the use of a subject identification number (SID), which is a number specific to you. The Study Data given to the Sponsor does not include identifying information such as your name. The Study Doctor maintains a confidential list that links the SID to you. A person appointed by the Sponsor,

regulatory authorities, or other supervisory bodies may review any Study Data held by the Study Doctor and the Study Doctor's institution. The reason these people may look at your health information is to make sure the study has been done the right way and that the Study Data are accurate.

The Study Doctor and his/her Study Team will use Study Data to conduct the Study. The Sponsor may use Study Data to conduct the Study and to support research and development of pharmaceutical products, diagnostics, or medical aids. The Sponsor may use the Study Data to apply for approval to market pembrolizumab as well as poly-ICLC. The Study Doctor's institution and the Sponsor are each responsible for their handling of Study Data in accordance with applicable Data Protection law(s) and each act as a data controller of the Study Data for this purpose.

The Sponsor may share Study Data with other companies within its group, with its service providers, its contractors, and with research institutions and research-based commercial organizations who will use Study Data only for the purposes described above. The Sponsor may transfer Study Data to countries outside of the United States for the purposes described in this document. Please be aware that the laws in such countries may not provide the same level of data protection as in the United States and may not stop Study Data from being shared with others. The Sponsor will take all steps reasonably necessary to ensure that any Study Data transferred is treated securely and in accordance with this form to the extent permitted by law.

Although information about this study, including the results, may be published for scientific purposes or posted electronically (for example, in a clinical trials registry database) or presented to scientific groups, your identity will not be revealed.

You have the right to request to see your Study Data held by the Study Doctor and the Sponsor. You also have the right to request that any inaccuracies in your data be corrected. If you wish to make a request, then please contact the Study Doctor, who can help you contact the Sponsor if necessary.

How will the researchers protect my privacy and keep information about me confidential (private)?
Any study information about you will be kept private and will only be given out with your permission. If the results of this study are published, your name will not be used. Your research records will be private to the extent allowed by law. In order to make sure the research is done properly, the Institutional Review Board may need access to information about your participation in this study. If you sign this consent form, you are giving us permission to collect, use and share your health information.

Research records that identify you will be kept private. You will not be identified in study records or publications disclosed outside Augusta University and except as detailed in the following sections, if applicable.

Authorization to Use or Disclose (Release) Health Information that Identifies You for a

Participant's Name: _____
Participant's Medical Record Number: _____

Research Study

If you sign this document, you give permission to Augusta University and AU Affiliates to use or disclose your health information that identifies you for the study described earlier in this document.

The health information Augusta University and AU Affiliates may use or disclose for this study includes information in your medical or dental record, results of physical exams, medical or dental history, lab tests or certain health information indicating or relating to your condition.

The health information listed above may be used by and/or disclosed to the following, as applicable:

- Researchers and their staff;
- The sponsor of the study including its agents such as data storage banks or contract research organizations monitoring the study;
- Other institutions and investigators participating in the study;
- Data Safety Monitoring Boards;
- Accrediting agencies;
- Clinical staff not involved in the study whom may become involved if it is relevant;
- Health insurers or payers in order to secure payment for covered treatment;
- Parents/Guardians of children younger than 18 years
- Vendors to facilitate payment or reimbursement for your participation in this study;
- Federal/state agencies and Augusta University and AU Affiliates committees having authority over the study. These may include, but are not limited to:
    - The Institutional Review Board (IRB) overseeing this study;
    - Committees with quality improvement responsibilities;
    - Office of Human Research Protections;
    - Privacy and security staff for oversight and investigations;
    - Food and Drug Administration;
    - National Institutes of Health;
    - Other governmental offices as required by law.

Augusta University and AU Affiliates are required by law to protect your health information. By signing this document, you authorize Augusta University and AU Affiliates to use and/or disclose your health information for this research.

Once your information has been disclosed outside Augusta University and AU Affiliates, it may no longer be protected by federal laws and regulations and might be further disclosed by the persons or institutions receiving the information.

Please note that:

You cannot receive research-related treatment if you do not sign this Authorization.

Augusta University and AU Affiliates may not withhold treatment whether or not you sign this Authorization.

You may change your mind and take back (revoke) this Authorization at any time. If you revoke this Authorization, Augusta University and AU Affiliates may still use or release health information and any data and/or specimens they already have obtained about you as necessary for this study. If you revoke this Authorization, you cannot continue to participate in this study. To revoke this Authorization, you must write to the Principal Investigator listed at the top of this document.

You may not be allowed to see or copy the study information described on this Authorization as long as the study is in progress. Feel free to ask the study staff if this applies to this study. When the study is complete, you have a right to request a copy of your personal health information collected for the study.

Your health information will be used or disclosed when required by law. Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury or disability and for conducting public health surveillance, investigations or interventions. No publication or public presentation about the study will reveal your identity without another signed authorization from you.

You will be given a copy of this Authorization. This Authorization does not have an expiration date. If you have questions or concerns about this Authorization or your privacy rights, please contact the Augusta University and AU Affiliates Privacy Officer at 706-721-0900.

Regulations require that you be given a copy of the Augusta University and AU Affiliates Notice of Privacy Practices describing the practices of Augusta University and AU Affiliates regarding your health information.

Contact Information for Answers to Your Questions:

You have read this form that serves as an informed consent document. This form also serves as your authorization for Augusta University and/or to use and release (disclose) your PHI in the manner described as a study subject. You have been given the opportunity to ask questions about the information on this form. You will be given a signed copy of this form for your records.

You can ask questions about the study at any time. Please contact Asha Nayak-Kapoor, MD or the study staff at 706-721-2505 (24 hrs/day) if you have questions about:

- More information of the study
- Study procedures or treatments
- Report an illness, injury, or other problem
- Leaving the study before it is finished
- Expressing a complaint or concern about the study

- Any other questions you may have about the study

If you have questions about your rights as a research subject, or if you have questions, concerns, or complaints about the research you may contact:

WCG IRB
1019 39th Avenue SE Suite 120
Puyallup, Washington 98374-2115
Telephone: 855-818-2289
E-mail: researchquestions@wcgirb.com

WCG IRB is a group of people who perform independent review of research.

WCG IRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WCG IRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Voluntary Participation:
Taking part in this research study is voluntary and your choice. You may say no if you do not want to take part in the study. If you take part in the study, you may stop at any time.

You do not need to give a reason. You will not be treated differently if you choose not to take part in the study now. You will not be treated differently if you later decide to stop taking part in the study. If you stop, contact the study staff immediately and follow instructions that they may give you.

What documents will be given to me if I decide to be in the study?
☐ This "Research Informed Consent Document"

STATEMENT OF CONSENT

I have read this form and the information in it was explained to me. I agree to take part in this research study. All of my questions were answered. My taking part in the study is voluntary. I will receive a copy of this form for my records. I am not giving up my legal rights by signing this form.

_____
Subject's Name (print)

Participant's Name: _____
Participant's Medical Record Number: _____

_____ _____/_____
Subject's Signature Date Time (00:00)

_____ _____/_____
Witness' name (print) Date Time (00:00)

_____
My signature indicates that I was present during the informed consent process and that informed consent was given freely by the subject. My signature also indicates that I was present when the subject signed the form.

INVESTIGATOR STATEMENT

I acknowledge that I have discussed the above study with this subject and answered all of his/her questions. They have voluntarily agreed to participate. I have documented this action in the subject's medical record source documents or research chart source documents, as applicable. A copy of this signed document will be placed in the subject's medical record or research chart, as applicable. A copy of this document will be given to the subject.

_____
Printed name of Investigator obtaining consent

_____ _____/_____
Signature of Investigator obtaining consent Date Time (00:00)