Phase II Study to Evaluate the Efficacy of MEDI4736 in Immunological Subsets of Advanced Colorectal Cancer

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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List of Abbreviations

Abbreviation or Specialized Term	Definition
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
ALT	alanine aminotransferase
APC	antigen presenting cells
AST	aspartate aminotransferase
CD	cluster of differentiation
CI	confidence interval
CIS	carcinoma in situ
C_{max}	maximum observed concentration
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CRF	case report form
CT	computed tomography
CTC	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte antigen 4
DC	disease control
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme-linked immunosorbent assays
EMA	European Medicines Agency
EOI	end of infusion
EU	European Union
Fc	fragment crystallizable
FFPE	formalin fixed paraffin embedded
FTIH	First-time-in-human
GCP	Good Clinical Practice

Abbreviation or Specialized Term	Definition
GI	gastrointestinal
HCl	hydrochloride
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN	interferon
IgG1κ	immunoglobulin G1 kappa
IHC	immunohistochemistry
IL	interleukin
IM	immunogenicity
IRB	Institutional Review Board
irAE	immune-related adverse event
irRC	immune-related response criteria
IV	intravenous(ly)
IVRS	interactive voice response system
IWRS	interactive web response system
MAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MDSC	Myeloid derived suppressor cell
miRNA	micro ribonucleic acid
MMR	mismatch repair
mRNA	messenger ribonucleic acid
MRI	magnetic resonance imaging
MRSD	maximum recommended starting dose
MTD	maximum tolerated dose
NCI	National Cancer Institute
NOAEL	no-observed adverse-effect-level
NSCLC	non-small cell lung cancer
OBD	optimal biological dose
ORR	objective response rate
OS	overall survival

Abbreviation or Specialized Term	Definition
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed death 1
PD-L1	programmed death ligand 1
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
Q2W	every 2 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SID	subject identification
SMC	Safety Monitoring Committee
SPD	sum of products of diameters
SRT	Safety Review Team
SUSAR	suspected unexpected serious adverse reaction
TIL	tumor infiltrating lymphocyte
TNF-α	tumor necrosis factor alpha
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US FDA	United States Food and Drug Administration
USA	United States of America
WFI	water for injection
WHO	World Health Organization
w/v	weight/volume

1.1 PROTOCOL SUMMARY AND/OR SCHEMA

Name of Investigational drug: MEDI4736	
Title of Study: Phase II Study to Evaluate the Efficacy of MEDI4736 in Immunological Subsets of Advanced Colorectal Cancer	
Study Centers: MSKCC	
Study Period: 24 months	**Phase of Development:** II

Objectives:

The **primary objective** of this study is to determine the objective response rate of MEDI4736 in subjects with DNA mismatch repair deficient (dMMR) or Tumor Infiltrating Lymphocyte-positive (TIL+) advanced/metastatic Colorectal Cancer (CRC), according to RECIST 1.1.

The **secondary objectives** are to determine**:**

- The objective response rate according to immune-related RECIST (irRECIST) of MEDI4736 in dMMR or TIL+ CRC
- Progression-free survival of MEDI 4736 in dMMR or TIL+ advanced/metastatic CRC
- Overall survival of MEDI4736 in dMMR or TIL+ advanced/metastatic CRC
- Safety and tolerability of MEDI4736 in subjects with CRC

The **exploratory objective** of this study is to evaluate biomarkers that may correlate with activity of MEDI4736 in CRC, or prospectively identify CRC patients likely to respond to MEDI4736 treatment.

Study Design: This will be a Simon two-stage design, single arm, phase II study. It will be conducted to determine the efficacy and safety of MEDI4736 in subjects with CRC. Subjects will be stratified to ensure that we include CRC tumor-types that are considered to be immunogenic and therefore more likely to be effectively targeted by an augmented immune response. These include patients with DNA mismatch repair proficient tumors that are characterized by increased TILs at baseline, as well as subjects with hereditary (Lynch syndrome) or acquired dMMR.

All subjects will receive MEDI4736 via IV infusion at 10 mg/kg every two weeks (Q2W). Subjects will continue treatment Q2W for 12 months, or until progression of disease, initiation of alternative cancer therapy, unacceptable toxicity, or other reasons to discontinue treatment occur. Following the 12-month treatment period, subjects without evidence for progressive disease or other reason to discontinue treatment will be monitored without further treatment. Upon evidence of PD during the monitoring period, administration of MEDI4736 may resume at the Q2W schedule, for up to another 12 months. Treatment of isolated, non-target, lesions for palliative/therapeutic intent is acceptable after discussion with the Principal Investigator (e.g. by ablation, surgery or radiation). Tumor measurements and determination of tumor responses for this study will be performed according to RECIST 1.1. Subjects may continue to receive MEDI4736 beyond radiographic progression in the absence of clinical deterioration, and after discussion with the Principal Investigator. All subjects will be followed up to 2 years for survival or until the study closes.

The primary endpoint of this trial is the best response rate in dMMR CRC (cohort 1) and TIL+ CRC (cohort 2) patients. A two-stage Simon"s optimal design will be employed to test the null hypothesis that the true response rate is ≤5% versus the alternative hypothesis that the true response rate is at least 25% with type I and II error rates of 10% each. Each cohort will be evaluated separately for this purpose. In the first stage, we will accrue 9 patients in each cohort. If 0 objective tumor responses (PR or CR) are observed among the 9 subjects treated in a cohort, then subject enrollment will be terminated in that cohort. If at least 1 response is observed among the 9 subjects treated in a cohort, then the study will be expanded to enroll a total of 24 treated subjects in that cohort. At the end of the study, if 2 or fewer objective tumor responses are observed in a cohort, then the study will be considered not worthy of further investigation in that particular cohort. If at the end of the study ≥3 tumor responses per RECIST1.1 are observed in a cohort, then further investigation of MEDI4736 in that patient population will be considered worthwhile. This study requires accrual of a minimum of 18 subjects and up to a maximum of 48 subjects if both cohorts are expanded to the second stage. The accrual time is estimated to be 2 years.

Exploratory research studies to evaluate the effect of MEDI4736 will be performed using research blood draws, archived tissue and tumor biopsies at baseline and at week 8. Tumor biopsies and research blood will be obtained on patients in the first stage only.

Diagnosis and Main Criteria for Inclusion in the Study:

Inclusion Criteria

1. Written informed consent.
2. Histologically- or cytologically- confirmed CRC.
3. Pre-existing Tumor-Infiltrating Lymphocytes or DNA mismatch repair deficiency
4. Locally advanced or metastatic CRC.
5. Subjects have received two or more standard available therapies.
6. Age ≥ 18 years at time of study entry.
7. Eastern Cooperative Oncology Group (ECOG) status of 0 or 1
8. Adequate organ and marrow function, defined as:
    a. Absolute Neutrophil Count ≥ 1,500/$mm^{3.}$
    b. Platelet count ≥ 90,000/$mm^{3.}$
    c. AST and ALT ≤ 3 × institutional upper limit of normal (ULN) or ≤ 5 × ULN for subjects with liver metastases.
    d. Bilirubin ≤ 1.5 × ULN or ≤ 3 × ULN for subjects with documented/suspected Gilbert"s disease
    e. Serum creatinine ≤ 1.5 x ULN.
9. Radiographically measurable disease per RECIST 1.1.
10. Life expectancy ≥ 16 weeks.
11. Consent for tumor biopsies and blood draws for research purposes (required for patients enrolled in stage 1).
12. Consent for use of archived tissue for research purposes.
13. Adequate method of contraception.

Exclusion Criteria

1. Anticancer therapy, monoclonal antibody or major surgery within 4 weeks prior to the first dose of MEDI4736.
2. Any prior Grade ≥ 3 irAE while receiving immunotherapy (including anti-CTLA-4 or anti-CD137 MAb) or any unresolved irAE of any grade (controlled irAE endocrinopathies are allowed).
3. Prior exposure to any anti-PD-1 or anti-PD-L1 antibody.
4. Current or prior use of immunosuppressive medication within 28 days before the first dose of MEDI4736, 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.
5. Any unresolved toxicity CTCAE >Grade 2 from previous anti-cancer therapy.
6. Active autoimmune disease within the past 2 years, except for mild conditions not requiring systemic treatment, such as vitiligo.
7. Any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment. NOTE: Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable (e.g., by local ablation, surgery or radiotherapy).
8. Active or prior documented inflammatory bowel disease (e.g., Crohn"s disease, irritable bowel syndrome, ulcerative colitis).
9. Receipt of radiation therapy within 4 weeks prior to starting investigational product, or limited field of radiation for palliation within 2 weeks of the first dose of investigational product.
10. Known allergy or reaction to any component of the MEDI4736 formulation or its excipients.
11. Known central nervous system (CNS) metastases requiring treatment, such as surgery, radiation or steroids.
12. Known history of confirmed primary immunodeficiency.
13. History of organ transplant requiring therapeutic immunosuppression.
14. Other malignancy within 3 years, except for noninvasive malignancies such as cervical carcinoma in situ (CIS), non-melanomatous carcinoma of the skin or ductal carcinoma in situ (DCIS) of the breast that has/have been surgically cured, or prior malignancy considered by the investigator to be of low likelihood for recurrence.
15. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any patient known to have active hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the patient to give written informed consent.

16. Women who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control.
17. Any other condition(s) that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of subject safety or study results
18. Subjects who are known to be HIV positive.
19. Receipt of live attenuated vaccination within 30 days prior to receiving MEDI4736.

Number of Subjects: Patient population size is 18-48, including patients with acquired or spontaneous DNA mismatch repair deficiency (n=9 to 24) or pre-existing tumor infiltrating lymphocytes identified in a tumor biopsy or surgical specimen (n=9 to 24).

2.1 OBJECTIVES AND SCIENTIFIC AIMS

- The primary objective of this study is to determine the objective response rate of MEDI4736 in subjects with DNA mismatch repair deficient (dMMR) or Tumor Infiltrating Lymphocyte-positive (TIL+) advanced/metastatic CRC, according to RECIST v1.1.

- The secondary objectives are to determine:
    - The objective response rate according to immune-related RECIST (irRECIST) of MEDI4736 in dMMR or TIL+ CRC
    - Progression-free survival of MEDI 4736 in dMMR or TIL+ advanced/metastatic CRC
    - Overall survival of MEDI4736 in dMMR or TIL+ advanced/metastatic CRC
    - Safety and tolerability of MEDI4736 in subjects with CRC

- The exploratory objective of this study is to evaluate biomarkers that may correlate with activity of MEDI4736

3.0 BACKGROUND AND RATIONALE

3.1 COLORECTAL CANCER

Worldwide, CRC is the third most common form of cancer in men, with 663,000 cases (10% of the total) and second most common in women, with 571,000 cases (9.4% of the total) per year. Each year there are about 608,000 deaths from colon cancer which is approximately 8% of all cancer deaths making colorectal cancer the fourth most common cause of cancer death[1]. In 2012 in the U.S. an estimated 103,170 new cases will be diagnosed with 51,690 deaths[2]. Treatment of CRC depends largely on the stage of the disease, which is most commonly rated according to tumor, nodes, and metastasis (TNM) criteria. The initial treatment is surgery. However, post-surgery metastatic disease occurs in 40%-60% of patients and the prognosis for patients who develop advanced metastatic disease is poor. Over the past decade, progress has been made in the role of systemic therapy for the palliation of advanced colorectal cancer. With the introduction of oxaliplatin, irinotecan, anti-VEGF therapies, and anti-EGFR therapies, the median life expectancy of patients has been increased to about 20 months[3]. Despite these therapeutic advances, patients with unresectable, metastatic and/or recurrent CRC, remain incurable. There is a substantial unmet medical need for more effective and less toxic therapies, especially for those patients with advanced disease that have not responded or have become resistant to the existing standard treatments. The development of novel approaches to treatment is greatly needed in order to improve outcomes in such patients.

3.2 IMMUNE THERAPIES

The immune system is capable of identifying tumor-associated antigens and eliminating the cancerous cells expressing them. This process of tumor immune surveillance, or tumor immunoediting, plays an important role in preventing and combating the growth of tumors. The process of immune surveillance is believed to result in a co-evolution of the tumor and immune response termed immunoediting, which is thought to follow three stages[4]. During the initial phase of elimination, the innate and adaptive immune systems detect and eliminate tumor cells. Elimination can result in complete clearance of tumor cells as is seen in rare cases of spontaneous regression

of melanoma [5]. However, if elimination is incomplete, the immune system and tumor may enter a state of equilibrium. During this second phase of immunoediting, the immune response selectively eliminates susceptible tumor cells and may prevent tumor progression. As the equilibrium phase persists, the tumor may evolve mechanisms to avoid or attenuate the immune response. The emergence of tumor cells with reduced immunogenicity or enhanced immunosuppressive mechanisms leads to the escape phase of immunoediting. During escape, many factors may contribute to the failure of the immune system to control tumor growth including expression of T-cell inhibitory molecules, down regulation of tumor antigens, and presence of immunosuppressive regulatory T cells or immunosuppressive cytokines within the tumor microenvironment.

Enhancing the immune response may provide a means to regain control of tumors that have progressed to the escape phase during immunoediting. Programmed death ligand 1 (PD-L1) (B7-H1, CD274) is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. In normal tissue, PD-L1 is expressed on T cells, B cells, dendritic cells, macrophages, mesenchymal stem cells, bone marrow-derived mast cells, as well as various nonhematopoietic cells [6]. Its normal function is to regulate the balance between T-cell activation and tolerance through interaction with its two receptors programmed death 1 (PD-1, CD279) and CD80 (B7-1). PD-L1 is also expressed by tumors and acts at multiple sites to help tumors evade detection and elimination by the host immune system. In the lymph nodes, PD-L1 on antigen presenting cells (APC) binding to PD-1 (CD279) or CD80 (B7-1) on activated T cells delivers an inhibitory signal to the T cell [6]. Likewise, binding of CD80 on APCs to PD-L1 on T cells leads to inhibitory signaling in the T cell. These and bidirectional interactions between CD80 and PD-L1, expressed on both APCs and T cells, lead to further inhibition of T-cell activation. These interactions result in reduced T-cell activation and fewer activated T cells in the circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T cells, preventing them from killing target tumor cells, and protecting the tumor from immune elimination[7].

PD-L1 is expressed in a broad range of cancers with a high frequency, up to 88% in some types of cancer. In a number of these cancers, including lung[8], renal[9-11], pancreatic[12-14], ovarian[15], and colorectal cancer[16], the expression of PD-L1 is associated with reduced survival and unfavorable prognosis. In ovarian cancer, for example, the 5-year survival rate in patients with low levels of PD-L1 was 80.2%, compared to 52.6% in patients with high levels of PD-L1[15]. In lung cancer, only 20% of patients with tumors expressing PD-L1 survived for more than 3 years, compared to 49% of patients with tumors lacking PD-L1[8].

Based on these data, and on assessments of expression of PD-L1 on the surface of human tumors using proprietary immunohistochemistry methods for assessment, MEDI4736 has the potential to affect multiple types of solid tumors, including CRC.

Blocking PD-L1 is a similar approach to that taken by ipilimumab (anti-CTLA-4), but has some potential advantages. Firstly, the expression of CTLA-4 and its ligands is restricted to the hematopoietic system; thus the site of action for molecules targeting CTLA-4 is solely the peripheral lymphoid organs. In contrast, PD-L1 is expressed not only on cells of the hematopoietic system but also on a range of tumor types. Targeting of PD-L1 could therefore have additional effects within the tumor microenvironment. Secondly CTLA-4 plays an early and critical role in controlling T-cell activation. This is reflected in the phenotype of CTLA-4 knockout mice, which die at an age of

between 3 and 4 weeks due to lymphoproliferative disease and tissue destruction. In contrast PD-L1, via binding to PD-1, acts later in the process of T-cell activation[17] and is considered more dispensable for the control of initial T-cell activation. This is reflected in the phenotype of PD-L1 knockout mice, which are viable and have normal T-cell numbers and activation levels, but which have increased T-cell activation in response to antigen and increased susceptibility in certain autoimmunity models[18,19]. Similarly, PD-1 knockout mice show strain-specific phenotypes milder than those seen in CTLA-4 knockouts[20,21]. Based on these data, inhibition of PD-L1 would be expected to have reduced toxicity relative to inhibition of CTLA-4. In support of this, recent Phase 1 clinical studies testing the tolerability of agents targeting PD-1 have shown a more favorable toxicity profile than ipilimumab[22-24].

3.3 IMMUNE THERAPY IN COLORECTAL CANCER

3.3.1 TUMOR-INFILTRATING LYMPHOCYTES

The levels of TILs, and more specifically cytotoxic T cells, have been correlated to improved prognosis in CRC[25], suggesting that an antitumor immune response is beneficial to patients. It has been shown in vitro that an antibody that blocks the interaction between PD-L1 and its receptors can relieve PD-L1-dependent immunosuppressive effects and enhance the cytotoxic activity of antitumor T cells[26]. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance the antitumor immune responses in patients with CRC characterized by increased TILs.

3.3.2 DNA MISMATCH REPAIR DEFICIENCY

dMMR CRC display increased rates of intragenic mutations of short, tandemly repeated DNA sequences known as microsatellites. These tumors are characterized by inactivation, mutational and/or epigenetic silencing of mismatch repair (MMR) genes. The primary function of the MMR system is to eliminate base-base mismatches and insertion/deletion loops that arise as a consequence of DNA polymerase slippage during DNA synthesis. As a result mutation rates in tumors characterized by MMR deficiency are 100- to 1,000-fold more common as compared to normal tissues.

MMR deficiency is characteristic of the hereditary non-polyposis colorectal cancer (HNPCC) syndrome. HNPCC is an autosomal-dominant condition that accounts for approximately 2–3% of all CRC. In most cases, the inherited germline alteration is identified in one of the five human MMR genes: MSH2, MLH1, MSH6, PMS2, and PMS1.

MMR deficiency can also occur in 10–15% of sporadic non-HNPCC colorectal cancers. In these patients, the basis for instability is usually an acquired hypermethylation of the MLH1 promoter with subsequent transcriptional silencing. MMR deficient sporadic colorectal tumors frequently accumulate mutations at microsatellite sequences in coding regions of specific genes that are implicated in tumor progression, such as TGFβRII, IGFIIR, MSH3, MSH6, and BAX.

Clinically, MMR deficient CRC is characterized by a better prognosis and a lower frequency of distant metastases as compared to conventional CRCs. A dense infiltration with lymphocytes is a typical feature of MMR deficient CRCs, suggesting recognition by the host immune system.

This ability of the immune system to recognize MMR deficient CRCs is attributed to the multiple frameshift peptides (FSPs) that are generated as a direct consequence of MMR deficiency and

represent tumor antigens that may be recognized as „„non-self"" by the immune system and elicit an immune response of the host.

3.3 Description of MEDI4736

MEDI4736 is briefly described below. Refer to the current Investigator"s Brochure for details.

3.3.1 Product Derivation

MEDI4736 is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (MAb) directed against human PD-L1. MEDI4736 has an overall molecular weight of approximately 149 kDa, including N-linked oligosaccharides. The antibody is composed of 2 identical heavy chains of approximately 49,670 Da each, and 2 identical light chains of approximately 23,390 Da each. The fragment crystallizable (Fc) domain of MEDI4736 contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to the complement component C1q and the Fcγ receptors responsible for mediating antibody-dependent cell-mediated cytotoxicity (ADCC)[27]. Subsequent to this triple mutation, the anticipated lack of MEDI4736-mediated antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) were confirmed using cell-based functional assays. MEDI4736 is selective for recombinant PD-L1 and blocks the binding of recombinant PD-L1 to the PD-1 and CD80 receptors.

3.3.2 Summary of Nonclinical Experience

MEDI4736 has shown the following activity as an anti-PD-L1 molecule:

- MEDI4736 binds to PD-L1 and blocks its interaction with PD-1 and CD80
- MEDI4736 can relieve PD-L1-mediated suppression of human T-cell activation in vitro
- MEDI4736 or tremelimumab (an anti-CTLA-4 antibody) or the combination does not result in cytokine release when assessed in vitro in assays using whole blood from healthy human donors
- MEDI4736 inhibits tumor growth in a xenograft model via a T-cell dependent mechanism
- A surrogate anti-mouse PD-L1 antibody resulted in improved survival in a syngeneic tumor model as monotherapy and resulted in complete tumor regression in > 50% of treated mice when given in combination with chemotherapy
- In the same study, anti-mouse PD-L1 antibody-treated mice were completely tumor free 3 months after tumor implantation and demonstrated long-term immunity during re-challenge
- In a subsequent study in the same syngeneic model, the combination of an anti-mouse PD-L1 antibody and anti-CTLA-4 antibody resulted in complete tumor regression in all mice treated
- Prevalence of PD-L1 expression on the surface of human tumors ranging from approximately 0-35%, was demonstrated in a broad survey of samples derived from tumor types of interest

The cynomolgus monkey is considered to be the only relevant nonclinical species for evaluation of local and systemic toxicities of MEDI4736. This conclusion was based on the high identity of amino acid sequence of extracellular domain (ECD) of cynomolgus monkey (cyno)PD-L1 and human (h)PD-L1 (95.9% identity), including the conservation of an amino acid in cynoPD-L1 that was

identified to be strongly involved in MEDI4736 binding to hPD-L1, and the similar binding affinity of MEDI4736 for cynoPD-L1 and hPD-L1. In addition, in vivo in cynomolgus monkeys, MEDI4736 suppresses soluble (s)B7 H1 in serum and fully occupies membrane PD-L1 on various leukocyte subsets at doses equal to or more than 0.1 mg/kg (lowest dose tested) with a dose-related duration of suppression and occupancy.

In general, there were no MEDI4736-related adverse effects in toxicology studies conducted in cynomolgus monkeys with MEDI4736 that were of relevance to humans. Adverse findings in the non-Good Laboratory Practice (GLP) PK/PD and dose range-finding study (4 doses over 5 weeks), and a GLP 4-week repeat-dose toxicity study were consistent with anti-drug antibody (ADA)-associated morbidity and mortality in individual animals. The death of a single animal in the non-GLP, PK/PD, and dose range-finding study was consistent with an ADA-associated acute anaphylactic reaction based on the presence of ADA within days of the first dose, acuteness and timing (after repeated dosing) of the death, clinical signs consistent with an anaphylactic reaction, lack of remarkable effects on other study parameters, and lack of histopathologic findings consistent with any other cause of death. In addition, the spectrum of findings, especially the microscopic pathology, in a single animal in the GLP, 4-week, repeat-dose study was also consistent with ADA-mediated effects; similar effects have been observed by MedImmune in cynomolgus monkeys administered other unrelated human monoclonal antibodies and immune-complexes were identified in the affected animal in a subsequent investigative study. Given that immunogenicity of human monoclonal antibodies in nonclinical species is not generally predictive of responses in humans, the ADA-associated morbidity and mortality were not taken into consideration for the determination of the no-observed-adverse-effect level (NOAEL) of MEDI4736, which was 100 mg/kg, the highest dose tested in these studies.

The existing body of knowledge suggests that many tumors express PD-L1 in order to suppress or evade immune-mediated elimination. To aid in the prioritization of tumor types for inclusion in the CD-ON-MEDI4736-1108 study, a wide array of tumor specimens were surveyed for surface expression of PD-L1 and found to vary significantly in both the level of expression across tumor types as well as in the prevalence of expression within a tumor type. Tumor types with a wide range of target expression levels and prevalence of expression were selected for this study in order to test the relevance of PD-L1 surface expression in mediating responses to MEDI4736.

3.3.3 Summary of Clinical Experience

To date (as of 18 Feb 2014), 221 subjects have been enrolled and treated in 5 ongoing clinical studies of MEDI4736 (2 employing MEDI4736 as monotherapy and 3 as combination therapy) and no studies have yet been completed. The majority of the clinical safety data in this IB are from Study CD-ON-MEDI4736-1108, which has the greatest number of enrolled subjects as of 18Feb2014.

Monotherapy Studies:

- Study CD-ON-MEDI4736-1108 is a Phase 1, first-time-in-human (FTIH), multicenter, open-label, dose-escalation, and dose-expansion study to determine the maximum tolerated dose (MTD) or optimal biologic dose (OBD), safety, PK, immunogenicity, and antitumor activity of MEDI4736 in adult subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy exists (N = 198 subjects).
- Study D4190C00002 is a Phase 1 open-label, dose-escalation and dose-expansion study of MEDI4736 in Japanese adult subjects with advanced solid tumors (N =8 subjects).

Combination Therapy Studies:

- Study D4190C00006 is a Phase 1b open-label, dose-escalation, and dose-expansion study of MEDI4736 in combination with tremelimumab in adults with advanced non-small cell lung cancer (NSCLC) (N = 7 subjects).
- Study CD-ON-MEDI4736-1161, is an open-label, dose-escalation study of MEDI4736 in combination with both dabrafenib and trametinib or in combination with trametinib in adults with metastatic melanoma (N = 5 subjects, but no safety data are yet available).
- Study LUD2013-003 is an open-label dose-escalation and dose-expansion study of MEDI4736 in combination with tremelimumab in adults with advance solid tumors (N = 3 subjects, but no safety data are yet available).

3.3.3.1 Monotherapy Studies

Study CD-ON-MEDI4736-1108

As of 18Feb2014 in Study CD-ON-MEDI4736-1108, a total of 198 subjects have been treated with at least one dose of MEDI4736 (ranging from 1 to 27 doses). Of these,

177 subjects received MEDI4736 10 mg/kg every 2 weeks (Q2W). This study has a dose- escalation and a dose-expansion phase. For the purpose of this IB, the safety data were combined from all 177 subjects treated with the 10 mg/kg Q2W regimen of MEDI4736 (i.e., data from subjects receiving 10 mg/kg Q2W from both dose escalation and dose expansion were combined). In addition, 21 subjects have been enrolled in the following dose-escalation cohorts: 4 subjects in each of the 0.1, 0.3, and 1 mg/kg Q2W cohorts; 3 subjects in the 3 mg/kg Q2W cohort, and 6 subjects in the 15 mg/kg Q3W cohort.

Focusing on the largest cohort (177 subjects treated with 10 mg/kg MEDI4736 Q2W), the most frequently reported (≥ 10% of subjects) treatment-emergent adverse events (TEAEs) regardless of grade or causality were fatigue, dyspnea, nausea, constipation, and decreased appetite. The majority of TEAEs were Grades 1 to 2 in severity and manageable by the general treatment guidelines as described in the current MEDI4736 study protocols. The Grade 3 or higher TEAEs occurring in 2 or more subjects included dyspnea, dehydration, abdominal pain, fatigue, sepsis, increased aspartate aminotransferase, increased gamma- glutamyltransferase, hyperbilirubinemia, back pain, pulmonary embolism, respiratory failure, hypotension, and “progression of disease” (verbatim term). Treatment-related TEAEs (all grades) occurring in 2 or more subjects were fatigue, nausea, dyspnea, diarrhea, vomiting, pyrexia, myalgia, hypothyroidism, decreased appetite, dizziness, cough, pruritus, rash, abdominal pain, increased aspartate aminotransferase, arthralgia, asthenia, influenza-like illness, edema peripheral, increased alanine aminotransferase, headache, and dry skin. The SAEs reported for 3 or more subjects were dyspnea, dehydration, abdominal pain, and sepsis. Three subjects had treatment-related SAEs: arthralgia (1 subject); pleural effusion and pneumonitis (both in the same subject); and muscular weakness and “rule out cord compression” (verbatim term) (both in the same subject). For the entire study population, none of the deaths or TEAEs resulting in discontinuation of MEDI4736 in this study were considered related to MEDI4736. No dose-limiting toxicities (DLTs) have been reported.

Partial efficacy data are available for Study CD-ON-MEDI4736-1108. Tumor assessments were based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines with modifications for subjects in the dose-expansion phase. Of the 177 subjects treated with MEDI4736 10 mg/kg Q2W, 77 have had at least one post-baseline disease assessment as of 18Feb2014. Four subjects (5.2%) had a best response of PR (unconfirmed). In addition, 36 subjects (46.8%) had stable disease.

As of 18Feb2014, PK and pharmacodynamic data were available for the first 32 subjects following IV dosing of MEDI4736 in Study CD-ON-MEDI4736-1108. MED4736 exhibited nonlinear PK likely due to saturable target-mediated clearance. Significant target engagement, as measured by soluble PD-L1 (sPD-L1) suppression, was observed following dosing in all individuals tested. Screening for ADA has detected positive samples from 3 of the 31 subjects tested, with evidence for an impact on PK and target suppression in 1 individual.

Study D4190C00002

In Study D4190C00002, 8 subjects have been enrolled and treated with MEDI4736

(1 or 3 mg/kg Q2W) as of 18Feb2014. The TEAEs reported for more than 1 subject were constipation, nausea, vomiting, and nasopharyngitis (each in 2 subjects). All reported TEAEs were Grade 1 or 2. No subjects have discontinued from treatment because of AEs, and no DLTs, or deaths have been reported in this study.

3.3.3.2 Combination Therapy Studies

In Study D4190C00006, preliminary safety data as of 18Feb2014 are available for 7 subjects treated with MEDI4736 and tremelimumab. The only TEAE reported for more than 1 subject was fatigue (3 subjects). All TEAEs were Grade 1 or 2 with the exception of one Grade 3 event of increased aspartate aminotransferase. One subject in this study (MEDI4736 3 mg/kg with 1 mg/kg tremelimumab) was discontinued from treatment because of an SAE of “disease progression” (verbatim term). No DLTs or deaths have been reported in this study.

3.4 CLINICAL EXPERIENCE WITH OTHER MONOCLONAL ANTIBODIES TARGETING THE PD-L1/PD-1 PATHWAY

Other MAbs currently in development that target the PD-1/PD-L1 pathway have shown evidence of clinical activity. An antagonist of PD-1, the primary PD-L1 receptor, has a related mechanism of action to MEDI4736 and is under development. A Phase 1 clinical study of this antagonist (MDX-1106 or BMS-936558) was recently conducted in 39 subjects[22]. No dose-limiting toxicities (DLTs) were observed and an MTD was not identified. One durable complete response (CR) in CRC, 2 partial responses (PRs) in RCC and melanoma, and 2 mixed responses were observed. In a larger Phase 1 study of BMS-936558 (MDX-1106) in 296 subjects, objective responses were seen in NSCLC (18%), melanoma (28%), and RCC (27%). Antitumor activity was observed at all dose levels and in several cases, these responses appeared to be durable, with responses ongoing past 2 years[28]. No objective responses were reported in 19 subjects with CRC. The most common treatment-related AEs of any grade observed during this study were fatigue (24%), rash (12%), diarrhea (11%), and pruritus (10%). Immune-mediated AEs of Grade 3 or higher occurred in 6% of subjects and included pneumonitis (1%), diarrhea (1%), alanine aminotransferase (ALT) increased (1%), and aspartate aminotransferase (AST) increased (1%). Based on the activity seen during this large Phase 1 study, BMS-936558 is being evaluated in 5 Phase 3 studies as of March 2013.

Evidence of activity has also been reported from a Phase 1 clinical study of the anti-PD-L1 antibody, BMS-936559 (MDX-1105)[22]. In this study of 207 subjects, objective responses were seen in melanoma (17%), NSCLC (10%), RCC (12%), and ovarian cancer (6%) at all doses of 1 mg/kg or higher. These responses also appear to be durable, with ongoing responses reported out beyond 23 months. No objective responses were reported in 18 subjects with CRC. The most commonly observed treatment-related AEs of any grade were similar to those observed with BMS-936558 and included fatigue (16%), infusion-related reaction (10%), diarrhea (9%), rash (7%), arthralgia (7%), pruritus (6%), and nausea (6%). Immune-mediated AEs of Grade 3 or higher occurred in 5% of subjects.

Preliminary data from the dose-escalation study of MPDL3280a, another anti-PD-L1 antibody in development, was recently presented[29]. In this dose-escalation study of 30 subjects, antitumor activity was observed in subjects with NSCLC, CRC, SCCHN, RCC, melanoma, gastric, and pancreatic cancer. The most common AEs of any grade included fatigue (67%), nausea (50%), diarrhea (43%), decreased appetite (40%), chills (37%), pyrexia (37%), dyspnea (33%), headache (33%), pain (33%), cough (30%), and night sweats (30%). Three patients experienced Grade 3 or 4 events including asthenia, colitis, and rash. No pneumonitis was reported and no MTD was identified. Taken together, the experience to date with anti- PD-1/PD-L1 MAbs suggests that these agents can provide significant clinical activity across a range of tumor types with a manageable safety profile that is superior to that of the anti-CTLA-4 class.

Studies of other agents targeting the PD-1/PD-L1 pathway are also in early-stage development with limited data available. CT-011 (anti-PD-1 MAb), has been evaluated in a Phase 1 study in advanced hematologic malignancies[24]. In this study of 17 subjects, CT-011 was well tolerated and no treatment-related toxicities were reported. No MTD was identified in this population and clinical benefit was observed in 33% of subjects. MK-3475 (anti-PD-1 MAb) is being evaluated in Phase 1 and 2 studies, with objective responses reported in NSCLC and melanoma[30]. MPDL3280A (anti-PD-L1) and AMP-224 (anti-PD-1 fusion protein) are also being evaluated in Phase 1 clinical studies as monotherapy as well as in combination with standard-of-care chemotherapy.

3.5 RATIONALE FOR DEVELOPING IMMUNE THERAPIES IN COLORECTAL CANCER

The development of immune therapy in CRC is compelling for several reasons: (1) we have described that genetic instability in CRC leads to a diverse number of mutations, each a potential target for a T-cell mediated anti-tumor immune response [31]; (2) several investigators have shown that effector/memory T-cells infiltrate CRC tumors and have prognostic value [25,32]; and (3) dMMR CRC is associated with a profound anti-tumor immune response with evidence of TILs. These tumors are immunogenic because they express tumor antigens generated due to frame shift mutations caused by insertion/deletions at coding microsatellites. Clinically, these patients usually have a more favorable prognosis, possibly from a protective immune response [33-35].

3.6 RESEARCH HYPOTHESIS

The objective of this Phase II study is to determine clinical efficacy and safety of MEDI4736 in immunological subsets of advanced CRC. Subsets will be prespecified to ensure that we include those tumor-types, considered to be immunogenic and therefore more likely to be effectively targeted by an augmented immune response. These include patients with dMMR and/or pre-existing TILs.

The research hypothesis is that MEDI4736 will be adequately tolerated in subjects with CRC and that such administration will result in clinical benefit.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a single arm, phase II study. It will be conducted to determine the efficacy and safety of MEDI4736 in the treatment of immunological subsets of advanced CRC. These subsets will be pre-specified to ensure that we include those tumor-types, considered to be immunogenic and therefore more likely to be effectively targeted by an augmented immune response. These include patients with dMMR and/ or pre-existing TILs.

4.3 Intervention

Subjects with dMMR CRC will enroll into cohort 1 and subjects with TIL+ CRC will enroll into cohort 2). dMMR status will supersede TIL+ status. All subjects will receive MEDI4736 via IV infusion at 10 mg/kg every two weeks (Q2W), as determined from the ongoing phase I study, which is currently enrolling patients into expansion cohorts at this dose. Subjects will continue treatment at Q2W for 12 months, or until progression of disease, initiation of alternative cancer therapy, unacceptable toxicity, or other reasons to discontinue treatment occur.

Following the 12-month treatment period, subjects without evidence for progressive disease or other reason to discontinue treatment will be monitored without further treatment. Upon evidence of PD (with or without confirmation according to RECIST 1.1) during the monitoring period, administration of MEDI4736 may resume at the Q2W schedule, for up to another 12 months. The subject will re-sign consent form prior to retreatment. The same treatment guidelines followed during the initial 12-month treatment period will be followed during the retreatment period, including the same dose and frequency of treatments and the same schedule of assessments. Treatment of isolated, non-target,

lesions for palliative/ therapeutic intent is acceptable after discussion with the Principal Investigator (e.g.: by ablation, surgery or radiation).

Tumor measurements and determination of tumor responses for this study will be performed according to RECIST 1.1.

Subjects may continue to receive MEDI4736 beyond radiographic progression in the absence of clinical deterioration, and after discussion with the Principal Investigator. All subjects will be followed for survival for up to 2 years.

Exploratory research studies to evaluate the effect of this therapy will be performed in patients using research blood draws, and tumor biopsy at baseline and week 8 for research purposes.

4.3 Estimated Duration of Subject Participation

Subjects will be treated until PD, initiation of alternative cancer therapy, unacceptable toxicity, or other reasons to discontinue treatment. All subjects will be followed for survival for up to 2 years unless the Principal Investigator decides to end the study.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

MedImmune will provide the investigators with adequate quantities of investigational product.

MEDI4736 is supplied as a lyophilized powder containing 200 mg MEDI4736. When reconstituted with 4.0 mL of water for injection (WFI), the solution contains 50 mg/mL MEDI4736, 26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02% (weight/volume [w/v]) polysorbate 80, at pH 6.0.

5.1 Storage of MEDI4736

MEDI4736 will be stored at 2-8°C (36-46°F) in a secure area with restricted access.

5.2 Preparation and Dosing Instructions for MEDI4736

The dose of investigational product for administration must be prepared by the investigator"s or site"s designated investigational product manager using aseptic technique. Commercially available WFI and 0.9% (w/v) saline will be supplied by each site. Total in-use storage time from reconstitution of MEDI4736 to start of administration should not exceed 4 hours at room temperature or 24 hours at 2-8°C (36-46°F). If in-use storage time exceeds these limits, a new dose must be prepared from new vials. MEDI4736 does not contain preservatives and any unused portion must be discarded.

Reconstitution of investigational product

MEDI4736 requires reconstitution prior to use. The reconstitution should be performed with 4.0 mL sterile WFI for each vial with the liquid added gently to the side of the vial to minimize product foaming. The vial should be gently rotated or swirled for 5 minutes or until dissolution is complete. The vial should not be shaken or vigorously agitated. Reconstituted MEDI4736 should stand undisturbed at room temperature for a minimum of 5 minutes or until the solution clarifies. The reconstituted solution should appear clear or slightly opalescent. A thin layer of bubbles on the liquid surface is considered normal.

Doses will be administered using a 250 mL IV bag containing 0.9% (w/v) saline and delivered through an IV administration set. The volume of reconstituted MEDI4736 to add to the IV bag is calculated as follows:

Volume of MEDI4736 (mL) =

Dose (10 mg/kg) × Subject Weight (kg) ÷ MEDI4736 Concentration (nominal 50 mg/mL)

Subject weight at baseline should be used for dosing calculations unless there is a ≥ 10% change in weight. An additional volume of 0.9% (w/v) saline equal to the calculated volume of MEDI4736 to be added to the IV bag must be removed from the bag prior to addition of MEDI4736. The calculated volume of MEDI4736 is then added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag. Following preparation of the dose, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes, using a 0.2-µm in-line filter. Flush the IV line with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

Example: For a subject weighing 80 kg and dosed at 10 mg/kg, 16.0 mL [10 mg/kg × 80 kg divided by 50 mg/mL] of MEDI4736 is to be diluted in a 250 mL IV bag containing 0.9% (w/v) saline. First, 16.0 mL of saline is removed from the IV bag, and then 16.0 mL of MEDI4736 is added to the bag. The bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag and the diluted MEDI4736 is administered as described above.

5.3 Dosing Instructions and Schedule

The first day of dosing is considered Day 1. Subjects will receive MEDI4736 as an IV infusion over approximately 60 minutes. The IV line will be flushed with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered (unless prohibited by institutional practice).

Since the compatibility of MEDI4736 with other IV medications and solutions, other than normal saline (0.9% [w/v] Sodium Chloride for Injection), is not known, the MEDI4736 solution should not be infused through an IV line in which other solutions or medications are being administered. The date, start time, interruption, and completion time of MEDI4736 administration must be recorded in the source documents.

5.3.1 Monitoring of Dose Administration

Subjects will be monitored during and after infusion with assessment of vital signs per institutional practice.

In the event of Grade ≤ 2 infusion-related reaction, the infusion rate of MEDI4736 may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. In subjects experiencing ≤ Grade 2 infusion reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) and/or corticosteroids or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion reaction is Grade 3 or higher in severity, treatment with MEDI4736 will be discontinued.

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

5.5 Concomitant Medications

5.5.1 Permitted Concomitant Medication

Investigators may prescribe concomitant medications or treatments (e.g., acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as "excluded" as listed in Section 5.5.2.

Treatment of isolated lesions for palliative or curative intent is acceptable after discussion with the Principal Investigator (e.g., by local surgery, ablation or radiotherapy).

5.5.2 Excluded Concomitant Medications

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

The following medications are considered exclusionary during the study. The Principal Investigator must be notified if a subject receives any of these during the study.

- Any investigational anticancer therapy
- Any concurrent chemotherapy (except as permitted above), immunotherapy, or biologic therapy. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.
- Immunosuppressive medications including, but not limited to systemic corticosteroids (>10 mg/day prednisone or equivalent), methotrexate, azathioprine, and tumor necrosis factor alpha (TNF-α) blockers. Use of immunosuppressive medications for the management of investigational product-related AEs, in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted
- Live attenuated vaccines within 30 days of MEDI4736 dosing

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

1. Written informed consent obtained.
2. Histologically- or cytologically- confirmed CRC.
3. Pre-existing Tumor-Infiltrating Lymphocytes in an archived tumor specimen or fresh biopsy, defined as an average of ≥4 TILs/ High Power Field (HPF) in 5 consecutive HPFs, within the area with the highest TILs at low power; or, DNA mismatch repair deficiency, determined by immunohistochemistry or polymerase chain reaction per MSKCC institutional standard practice. DNA mismatch repair deficient tumors may be TIL positive or negative.

4. Locally advanced or metastatic CRC.
5. Subjects have received two or more standard available therapies known to prolong survival and for which they would be considered eligible. At a minimum, such therapies should include regimens containing oxaliplatin and irinotecan in combination with a fluoropyrimidine (e.g., FOLFOX and FOLFIRI or their variants).
6. Age ≥ 18 years at time of study entry.
7. Eastern Cooperative Oncology Group (ECOG) status of 0 or 1.
8. Adequate organ and marrow function as defined below:
    - Absolute neutrophil count ≥ 1,500/$mm^{3.}$
    - Platelet count ≥ 90,000/$mm^{3.}$
    - AST and ALT ≤ 3 × institutional upper limit of normal (ULN) or ≤ 5 × ULN for subjects with liver metastases.
    - Bilirubin ≤ 1.5 × ULN or ≤ 3 × ULN for subjects with documented/suspected Gilbert"s disease.
    - Serum creatinine ≤ 1.5 x ULN;
9. Radiographically measurable disease per RECIST 1.1.
10. Life expectancy ≥ 16 weeks.
11. Willingness to provide consent for use of archived tissue for research purposes.
12. Subjects will be required to agree to a biopsy performed at baseline and again at week 8 of the study in order to be eligible for enrollment in stage 1 of the study.
13. Females of childbearing potential who are sexually active with a nonsterilized male partner must use 2 methods of effective contraception from screening, and must agree to continue using such precautions for 90 days after the final dose of investigational product; cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.
    - Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause).
    - Subjects must use 2 acceptable methods of effective contraception as described in below.
14. Nonsterilized males who are sexually active with a female partner of childbearing potential must use 2 acceptable methods of effective contraception from Day 1 and for 90 days after receipt of the final dose of investigational product.

Table 6.1 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 • Progesterone T [a] • 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.

6.3 Subject Exclusion Criteria

1. Anticancer therapy, monoclonal antibody or major surgery within 4 weeks prior to the first dose of MEDI4736.
    - Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.

2. Any prior Grade ≥ 3 irAE while receiving immunotherapy (including anti-CTLA-4 or anti-CD137 MAb) or any unresolved irAE of any grade (controlled irAE endocrinopathies are allowed).

3. Prior exposure to any anti-PD-1 or anti-PD-L1 antibody.

4. Current or prior use of immunosuppressive medication within 28 days before the first dose of MEDI4736, 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.

5. Any unresolved toxicity CTCAE >Grade 2 from previous anti-cancer therapy.

6. Active autoimmune disease within the past 2 years, except for mild conditions not requiring systemic treatment, such as vitiligo.

7. Any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment. NOTE: Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable (e.g., by local ablation, surgery or radiotherapy).

8. Active or prior documented inflammatory bowel disease (e.g., Crohn"s disease, irritable bowel syndrome, ulcerative colitis).

9. Receipt of radiation therapy within 4 weeks prior to starting investigational product, or limited field of radiation for palliation within 2 weeks of the first dose of investigational product.

10. Known allergy or reaction to any component of the MEDI4736 formulation or its excipients.

11. Known central nervous system (CNS) metastases requiring treatment, such as surgery, radiation or steroids.

12. Known history of confirmed primary immunodeficiency.

13. History of organ transplant requiring therapeutic immunosuppression.

14. Other malignancy within 3 years, except for noninvasive malignancies such as cervical carcinoma in situ (CIS), non-melanomatous carcinoma of the skin or ductal carcinoma in situ (DCIS) of the breast that has/have been surgically cured, or prior malignancy considered by the investigator to be of low likelihood for recurrence.

15. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any patient known to have active hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the patient to give written informed consent.

16. Women who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control.

17. Any other condition(s) that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of subject safety or study results.

18. Subjects who are known to be HIV positive.

19. Receipt of live attenuated vaccination within 30 days prior to receiving MEDI4736.

7.1 RECRUITMENT PLAN

This study will be available to all patients seen at Memorial Hospital, who meet the eligibility criteria outlined in section 6.0.

Memorial Hospital is a referral center for CRC. In addition, the study may be placed on the institutional Website to maximize patient recruitment. Patients will be identified from medical oncology clinics for treatment of their disease.

The investigators take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. There will be no limitation to access with regard to race or gender. Patients will be required to read, agree to, and sign an IRB-approved informed consent form prior to registration on this trial. The registration procedure will be conducted as described in section 15.0. Patients will not receive payment for their participation on this study.

8.0 PRETREATMENT EVALUATION

To be completed within 28 days of starting therapy:

- CT scan with contrast (chest, abdomen and pelvis). If patient is unable to receive CT contrast, or the abdominal/pelvic target lesion is indeterminate on CT scan then MRI with contrast (abdomen and pelvis) plus CT chest may be perfromed. Non-contrast CT CAP may be used if the target lesion(s) do not require contrast for accurate measurements.

- 12-lead Electrocardiogram (EKG).

- Signed informed consent for study participation.
- History and physical examination, including height, weight, vital signs (temperature, pulse rate, respiration rate, blood pressure), and performance status (ECOG).
- Serum pregnancy test for all women of childbearing potential. If the test result is positive related to pregnancy, the patient will not be allowed to participate in this study.
- CBC with differential and platelet count, serum chemistries (Na, Cl, BUN, Creatinine, K, CO2, and glucose), LFTs (AST, ALT, alkaline phosphatase, total bilirubin), calcium, albumin, total protein, and CEA
- Serology for HepBsAg, HepBcAb and hepatitis C antibody (negative test acceptable prior to screening period)
- Blood test for research purposes (for patients enrolled in stage 1 only).
- Perform pre-treatment tumor biopsy for research purposes (for patients enrolled in stage 1 only).

9.1 TREATMENT/INTERVENTION PLAN

Eligible patients will receive the following treatment every two weeks

- MEDI4736 at 10 mg/kg i.v. over approximately 60 minutes.

A treatment may be moved ± 3 days for administrative reasons, including clinic closure for holidays. A cycle constitutes one completed administration of MEDI4736.

Patients will be seen the day of administration of MEDI4736. A medical history, with particular reference to toxicities, including medication review, and physical examination will be conducted at each treatment visit.

Laboratory parameters for treatment on Cycle #1, Day #1 are:

- Absolute Neutrophil Count $\geq$ 1500/mm^3
- Platelet Count $\geq$ 90,000/mm^3
- AST and ALT $\leq$ 3 × ULN or $\leq$ 5 × ULN for subjects with liver metastases
- Bilirubin $\leq$ 1.5 × ULN or $\leq$ 3 × ULN for subjects with Gilbert"s disease
- Serum creatinine $\leq$ 1.5 x ULN

Laboratory parameters for subsequent treatments are as follows:

- Absolute neutrophil count $\geq$ 1000/mm^3
- Platelet count $\geq$ 75,000/mm^3
- AST and ALT $\leq$ 3 × ULN or $\leq$ 5 × ULN for subjects with liver metastases
- Bilirubin $\leq$ 1.5 × ULN or $\leq$ 3 × ULN for subjects with Gilbert"s disease

- Serum creatinine ≤ 1.5 x ULN

If the above parameters are not met, then treatment should be delayed one week (± 3 days) until recovered, up to a maximum of 30 days delay. Re-treat as per section **10.1, Dose delay/ modification**.

9.2 RESEARCH BLOOD AND BIOPSY SPECIMENS

9.2.1 Research blood

For patients enrolled in stage 1, blood specimens will be obtained for research purposes within 28 days prior to treatment or on Day 1, then Week 2, Week 4, and week 8. An additional blood draw beyond week 8 is permitted based upon interesting clinic/immunological findings.

Specimens should be collected prior to drug administration. Four (4) tubes of blood are to be collected in BD Vacutainer® CPT™ Cell Preparation Tubes with Sodium Heparin. Each tube should contain approximately 10 cc of blood. Whole blood (PAXgene DNA) will be collected from all subjects at baseline only (appendix A). Peripheral blood mononuclear cells and plasma will then be isolated per institutional practice in the Immune Monitoring Facility (IMF).

9.2.2 Research biopsy

For patients enrolled in stage 1, a pre-treatment tumor biopsy will be obtained from an accessible metastatic or primary lesion within 28 days of starting treatment and then again at week 8 (± 1 wk). If this is done by an interventional radiology or surgical procedure, then informed consent for the will be required per standard institutional practice. Where applicable, the same tumor lesion should be biopsied at baseline and on-treatment.

Patients will be permitted to continue enrollment and treatment on protocol in the event that insufficient material was obtained from the biopsy. The on treatment biopsy will not be required if this is no longer considered appropriate at the time of the planned procedure, for example, if the tumor is no longer accessible, the procedure is deemed to be unsafe, or if the patient refuses.

Tumor lesion planned for biopsy may be an index lesion if ≥ 2 cm in at least one diameter.

If clinically practical, subjects will undergo 5 core biopsies. Two core biopsies will be placed in formalin and processed for FFPE, 2 core biopsies will be immediately frozen in liquid nitrogen and then stored at -80°C . The fifth core biopsy will be placed in culture medium to isolate tumor infiltrating lymphocytes or for cell culture (appendix B).

If the patient undergoes a routine procedure, tissue may be obtained for future correlative analyses. Up to 20 x 5μm slides (unstained) may be obtained from each routine procedure where tissue was extracted. Tissue from routine procedures may be sent directly to the IMF facility for immediate processing (e.g. isolation of Tumor Infiltrating Lymphocytes).

9.2 CORRELATIVE STUDIES

Pharmacodynamic changes may be evaluated for associations with clinical activity, and safety (adverse event) data. Tissue may be used for correlative studies such as IHC, tumor mutation analysis, proteomic analysis, and immunodiversity.

9.2.1 Whole Blood

Whole blood (PAXgene DNA) will be collected from all subjects enrolled in stage 1 at baseline and may be used to generate genomic DNA for SNP genotyping or genome sequencing. Genotyping analyses will focus on SNPs within genes associated with immunity (e.g. Fc gamma receptor genes) and with other immunoregulatory signaling pathways to explore the possibility that natural variation within those genes is associated with response to MEDI4736 therapy and/or with adverse events observed during treatment. HLA genotyping may be completed to support additional analyses described below.

Flow cytometry will be performed at baseline and during treatment to assess baseline and changes in composition/activation status of lymphocyte subsets present in peripheral blood mononuclear cell preparations (PBMCs). Lymphocyte subsets to be assayed may include, but are not limited to CD8+ and CD4+ T-cell subsets (activated; effector/memory; regulatory) and populations of those cells as defined by the expression of activation, exhaustion, or signaling markers such as ICOS, HLA-DR, PD-1, CTLA-4, and/or intracellular IFNγ. NK cell populations may be monitored in a similar fashion with a focus on characterizing subsets defined by the expression of activation markers (e.g. NKG2D; IL-21R) and/or by markers that are associated with the potential of NK cells to lyse target cells (e.g., CD107a, granzyme, perforin). Additional flow cytometry-based assays will focus on defining and monitoring the abundance of myeloid-derived suppressor cells (MDSCs), a cell type which appears to negatively impact anti-tumor activity and which has been shown to promote immune escape by limiting activated CD8 T-cell infiltration into the tumor microenvironment[36].

Immune cells may be evaluated using HLA-A2-restricted tetramer assays to detect and quantify the presence of T cells directed against specific antigens which are anticipated to be presented to the immune system due to study treatment. Detecting on-treatment increases in these T cell populations may be considered evidence of adaptive immune responses in CRC.

9.2.2 Plasma

To understand the prevalence of circulating proteins and the impact they may have on the clinical activity and/or safety of MEDI4736 treatment, the protein concentrations of a panel of cytokines, chemokines, and other relevant immunomodulatory, soluble factors may be investigated by ELISA and/or other relevant multiplex-based protein assay methods. Examples of analytes to be assessed may include but are not limited to factors induced by IFNγ signaling (e.g., T cell chemoattractants CXCL9; CXCL10) and other factors generally involved in inflammatory processes. Plasma may be used also to assess the presence and/or concentration of anti-tumor antibodies using a mulitplex platform such as Invitrogen"s Protoarray platform(c). Levels of sPD-L1 in peripheral blood may also be assessed.

9.2.3 Tissue Biopsies and/or archived tissue

The presence of TILs within tumors in response to MEDI4736 treatment will be evaluated baseline and on-treatment biopsies and, when feasible, tissue acquired from routine procedures. Archived tissue (up to 20 x 5 μm slides), tissue acquired from routine procedures (up to 20 x 5 μm slides per procedure), and biopsy tissue may be analyzed using immunohistochemistry for PD-L1 expression and other immune-related genes, and gene expression (microarray and/or RT- QPCR) research platforms. Laser Capture Microdissection may be utilized to enrich specific regions of tumor material for use in similar or additional downstream applications, which may include in-situ hybridization, flow cytometry, ELISA, and/or assessment of miRNA. In all cases, the goal may be to determine the abundance of a battery of immunoregulatory genes or proteins associated with cancer cells and/or

cancer-interacting lymphocytes derived from biopsied material. Other biomarkers may be evaluated as determined by additional data. Remaining specimens may be stored for future studies related to MEDI4736/ CRC immunity.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

STUDY CALENDAR

Period	Screening	Treatment							Monitoring[14]			End of study visit[13]
Cycle[1]	<28 days[2]	1	2	3	4	5	6	7+	Months <12		Month 12+	
Week		0	2	4	6	8	10	12+	1	Even	Q3M	
Informed consent	x											
Medical history	x											
EKG	x											
CT/MRI[3]	x					x				x	x	x
Height[4]	x											
Physical examination	x	x	x	x	x	x	x	x	x		x	x
Vital signs/[4]	x	x	x	x	x	x	x	x	x		x	x
Performance status	x	x	x	x	x	x	x	x	x			
Report medications	x	x	x	x	x	x	x	x	x			x
Report side effects			x	x	x	x	x	x	x	x[15]		x
CBC[5,6]	x	x	x	x	x	x	x	x	x			x
Comp[5,7]	x			x		x		odd cycle	x			x
Thyroid function (TSH, fT3,fT4)	x			x		x		odd cycle	x			
CEA[8]	x			x		x		x	x	x	x	x
Hepatitis B and C[9]	x											
Pregnancy test if female (Serum)	x											
Research blood tests [5,10]	x		x	x		x						
Research tumor biopsy[11]	x					x						
Obtain archived tissue[12]	x											
MEDI4736		x	x	x	x	x	x	x				

1. Each cycle is approximately 2 weeks in duration, corresponds to 1 completed treatment.
2. These procedures must be performed within 28 days prior to starting protocol treatment on Cycle 1/Day 1.
3. CT scan (chest, abdomen and pelvis) will be performed during screening, then at 8 week (±1 wk) intervals and at final visit if more than 4 weeks from prior imaging. If patient is unable to receive CT contrast or the abdominal/pelvic target lesion is indeterminate on CT then MRI with contrast (abdomen and pelvis) plus CT without contrast (chest) may be performed. Imaging may be delayed up to 2 weeks if patient is receiving local therapy, such as radiation. During the monitoring phase, CT scans will be performed every 8 weeks (±1wk) for the first 12 months then every 3 months (±2 wks). After 24 months in the monitoring phase, follow up visits and scans can be performed up to every 6 months or per investigator discretion.
4. Vital signs to include heart rate, respiratory rate, blood pressure, and weight.
5. Blood to be collected prior to dosing any study medications.
6. Hematology to include standard complete blood cell (CBC) panel.
7. Comprehensive metabolic panel included sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, total protein, albumin, bilirubin, alkaline phosphatase, AST, ALT, calcium.

8. CEA to be obtained at baseline, then approximately every 4 weeks during treatment. During the monitoring phase, CEA to be obtained every 8 weeks (±1wk) for the first 12 months then every 3 months (±2 wks). After 24 months in the monitoring phase, CEA can be obtained up to every 6 months or per investigator discretion.
9. Serology for HepBsAg, HepBcAb and hepatitis C antibody (unless previously tested negative).
10. Blood draws for research purposes will be performed during screening/ day 1, then weeks 2, 4, and 8 for patients in stage 1 only.
11. Tumor biopsy for research purposes will be performed at baseline and wk 8 (±1 wk) for patients in stage 1 only.
12. Up to 20 x 5 μm slides (unstained) of archived tissue will be requested on all patients for research purposes. For patients undergoing routine procedures during the study, additional tissue (up to 20 x 5 μm slides (unstained)) may be obtained from each routine procedure for research purposes
13. EOS visit occurs 2-4 weeks after last dose of MEDI4736. CT scan OR MRI to be done only if last imaging was conducted greater than four weeks prior to the date of the Final Visit.
14. Monitoring phase time points are based on time since last dose of MEDI4736. Evaluations will be performed every 2 months +/-1 week for the first 12 months then every 3 months +/-2 weeks. After 24 months in the monitoring phase, evaluations can be performed up to every 6 months or per investigator discretion.
15. After the end of treatment, each subject will be followed for 30days for adverse event monitoring. Serious adverse events will be collected for 90 days after the end of treatment.

10.1 Dose delay/ modification

Following the first dose of MEDI4736, subsequent administration of MEDI4736 should be modified based on toxicities observed as described in Table 10.1 (below). All toxicities will be graded according to NCI CTCAE v4.03. Dose reductions are not permitted. Dose modifications will not be required for AEs that are clearly not attributed to MEDI4736.

Based on the mechanism of action of MEDI4736, potential irAEs may be similar to those seen with the use of ipilimumab and MDX-1106 including immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies[22,37]. Subjects should be monitored for signs and symptoms of irAEs. In absence of alternate etiology (e.g., infection or PD) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune related. It is recommended that management of such irAEs follow table 10.2 and the guidelines outlined for ipilimumab[38].

Table 10.1 MEDI4736 Dose Modification Due to Toxicity

	Immune-related Adverse Events (irAEs) [a]	All Other Events
Grade 1	None required.	None required. Up to 2 sequential doses may be skipped at the discretion of the investigator **For infusion-related reactions:** Refer to section 5.3.1
Grade 2	**For endocrinopathy:** Hold MEDI4736 when endocrinopathy is controlled, resume MEDI4736 administration at next scheduled dose **For dermatologic irAEs:** MEDI4736 may be dosed at the next scheduled time point **For pneumonitis:** Hold MEDI4736 until resolution to ≤Grade 1. If resolution to ≤ Grade 1 occurs within 3 days of the initiation of maximal supportive care (including corticosteroids), resume MEDI4736 administration at next scheduled dose. Otherwise, discontinue MEDI4736 **For all other irAEs:** Hold MEDI4736 until resolution to ≤ Grade 1. If resolution to ≤ Grade 1 does not occur within 30 days, discontinue MEDI4736	**For infusion-related reactions:** Refer to section 5.3.1 **For all other AEs**: No dose adjustment is required. Up to 2 sequential doses may be skipped at the discretion of the investigator
Grade 3	**For endocrinopathy:** Hold MEDI4736 when endocrinopathy is controlled, resume MEDI4736 administration at next scheduled dose **For dermatologic irAEs:** Hold MEDI4736 until resolution to ≤ Grade 1 or baseline. • If resolution to ≤ Grade 1 or baseline does not occur within 30 days, discontinue MEDI4736 **For elevations in transaminases:** • For elevations in transaminases up to 8 × ULN, hold MEDI4736 until resolution to ≤ Grade 1 or baseline. If elevations downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume MEDI4736 administration at next scheduled dose. Otherwise, discontinue MEDI4736 • For elevations > 8 × ULN, discontinue MEDI4736 **For elevations in bilirubin:** • For elevations in bilirubin up to 5 × ULN, hold MEDI4736 until resolution to ≤ Grade 1 or baseline. If elevations downgrade to ≤ Grade 2 (< 3 × ULN) within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume MEDI4736 administration at next scheduled dose. Otherwise, discontinue MEDI4736 • For elevations in bilirubin > 5×ULN, discontinue MEDI4736 • **For all other irAEs:** Discontinue MEDI4736.	**For infusion-related reactions:** Discontinue MEDI4736 **For increase in GGT:** Hold MEDI4736 until resolution to ≤ Grade 1 or baseline. For decreases that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume MEDI4736 administration at next scheduled dose. Otherwise, discontinue MEDI4736 **For all other AEs:** • Hold MEDI4736 until resolution to ≤ Grade 1 or baseline. For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume MEDI4736 administration at next scheduled dose. • Otherwise, discontinue MEDI4736
Grade 4	Discontinue MEDI4736.	Discontinue MEDI4736

	Immune-related Adverse Events (irAEs) [a]	All Other Events
Grade 1	None required.	None required. Up to 2 sequential doses may be skipped at the discretion of the investigator **For infusion-related reactions:** Refer to section 5.3.1

Table 10.2 Management of Immune-related Adverse Events

1	Subject evaluation to identify any alternative etiology
2	In the absence of a clear alternative etiology, all events of inflammatory nature should be considered to be immune related
3	Symptomatic and topical therapy should be considered for low grade events
4	Systemic corticosteroids should be considered for a persistent low grade event or for a severe event
5	More potent immunosuppressives should be considered for events not responding to systemic steroids

11.0 TOXICITIES/SIDE EFFECTS

MEDI4736 has demonstrated reasonable safety. Based on the current phase I trial of MEDI4736, side effects that may occur include:

Likely
- Fatigue
- Diarrhea
- Vomiting
- Dizziness
- Rash

Less Likely
- Anemia
- Nausea
- Influenza-like illness
- Infusion-related reaction
- Dehydration
- Pruritus

In addition, potential irAEs may be similar to those seen with the use of ipilimumab and MDX-1106 including immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies

11.1 SAFETY MONITORING

Subjects will be evaluated for occurrence of AEs at each visit. Events will be characterized and reported as described below. Safety will also be monitored by performing physical exams and routine laboratory procedures.

11.1.1 Adverse Events and Serious Adverse Events

Definitions of AEs, non-serious AE, and serious adverse events (SAEs) are provided in this section. Additionally, provided in the sections below are reporting guidelines for any AE or SAE occurring during this study.

Definition of Adverse Event and Non-Serious Adverse Event

The following definition of AE will be used for the study: “Any untoward medical occurrence in a subject 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), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to medicinal (investigational) product.”

This definition includes any abnormalities or anomalies that were not seen at baseline or which worsened during the course of the study, if present at baseline.

A “non-serious” adverse event is any event that does not meet the definition of “serious adverse event” as presented, below.

Reporting and Treating Non-Serious Events

It is the responsibility of the investigator to perform regular assessments for AEs. Subjects will be regularly queried about the occurrence of any AEs and will be monitored throughout the study for reactions to study drug and/or study procedures. The investigator and clinical staff will record all AEs, whether volunteered by or elicited from the subject, at any time during a subject"s participation in the study. Abnormal laboratory findings (e.g., hematology, comprehensive metabolic panel) or other abnormal assessments (e.g., vital signs) will be recorded as AEs if they are judged as clinically significant by the investigator.

All subjects experiencing an AE will be evaluated by the investigator and monitored until resolution of the events or until the investigator deems the event clinically stable and/or at an acceptable level. Unless the event requires hospitalization (SAE), medical treatment will be provided to the subjects at the unit and treatment medication and/or medical procedures will be provided per the treating-investigator"s clinical discretion. All clinically significant AEs, including clinically significant laboratory abnormalities, will be followed until resolution. AEs meeting the definition of SAEs require special reporting in addition to documentation in the CRDB as described below.

All AEs, including clinically significant laboratory and assessment abnormalities will be recorded according to “Common Terminology Criteria for Adverse Events” V4.0 (CTCAE) must be recorded in the CRDB. Events occurring prior to initiation of first dose should be recorded on the Medical History page of the CRDB. Any AE occurring after initiation of first dose of study drug should be recorded on the Adverse Event page of the CRDB. AEs should be recorded in the CRDB using the medical terminology found in the source documentation. Whenever possible, diagnoses should be

given when signs and symptoms are due to a common etiology. It is the investigator‟s responsibility to provide his/her assessment of the relationship of the event to the study drug and the severity of the event using the following scales:

- Relationship

➢ *Unrelated*: The AE is clearly attributable to a concurrent illness, concurrent medication, clinical state, or environmental factor other than the investigative agent.

➢ *Unlikely*: The occurrence of the AE does not follow the study in a temporal sequence and/or based upon available subject information, e.g., medical history, disease process, known pharmacology of drug, a relationship between the drug and AE is unlikely.

➢ *Possible*: The AE follows a reasonable temporal sequence from the time of study drug administration, but it is possible that other factors; e.g., subject‟s clinical state or concomitant mediations, environmental factors, or the drug‟s pharmacology may have caused the AE.

➢ *Probable*: The AE follows a reasonable temporal sequence from the time of study drug administration, follows a known response pattern of the medication class, and cannot be reasonably explained by other factors.

- Severity

The severity of all adverse events should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) V4.0. For those adverse events not listed in the CTCAE, the following grading system should be employed:

➢ *Mild* (CTCAE Grade 1): Transient symptoms, awareness of sign/symptom, but easily tolerated and no interference with subject‟s daily activities

➢ *Moderate* (CTCAE Grade 2): Marked signs/symptoms that interfere with subject‟s usual activities, but still acceptable

➢ *Severe* (CTCAE Grade 3): Incapacitating signs/symptoms which cause considerable interference with the subject‟s daily activities, unacceptable

➢ *Life-threatening* (CTCAE Grade 4): Life-threatening of disabling AE

➢ *Death* (CTCAE Grade 5): Death-related AE. See CTCAE Guidelines for assigning Grade 5.

11.1.2 Serious Adverse Events

Definition of Serious Adverse Event

The following definition of SAE applies for the study: “A serious AE means any AE occurring at any dose that results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious AE when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. A life-

threatening AE is any AE that places the subject or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred (e.g., it does not include a reaction that, had it occurred in a more severe form, might have caused death)." Reporting and Treating Serious Adverse Events as per section 17.2.

Pregnancies

Any pregnancy occurring after the first dosing is considered an immediately reportable event. Such events must be reported within one (1) working day of the investigator becoming aware of the event. Subjects who become pregnant during the trial will be immediately discontinued from the study, but shall be followed for the duration of the pregnancy. It is the Principal investigator"s responsibility to provide to the sponsor follow-up information on the outcome of the pregnancy including information about any sequelae.

11.1.3 Other Events of Special Interest

Hepatic Function Abnormality

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in bilirubin to greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product.

Events of hepatic function abnormality (as defined above) should be recorded according to the definitions of AE and SAE:

- If an event of hepatic function abnormality is considered to be related to a pre-existing condition and does not represent a worsening of this condition and/or is considered to be within the range of normal physiological fluctuation for the subject, the event does not meet the definition of an AE and does not need to be recorded as such.
- If a definitive diagnosis for an underlying condition unrelated to the investigational product is established for an event of hepatic function abnormality, the diagnosis should be recorded as an AE/SAE.
- If no definitive diagnosis is determined for an event of hepatic function abnormality, the term "hepatic function abnormal" should be used to report the AE/SAE.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

For the purposes of this study, patients will be evaluated for response every 4 cycles (8 weeks), or as clincially indicated if interim toxicity occurs mandating cancer staging re-assessment. RECIST 1.1 criteria will be used.

CT scan with contrast of the chest, abdomen, and pelvis

- CT scans should be performed with contiguous cuts in slice thickness of 5 mm or less. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm.

MRI scans

- MRI of the abdomen and pelvis is acceptable for measurement of lesions provided that the same anatomical plane is used for serial assessments. If possible, the same imaging device should be used for serial evaluations. In case of MRI, measurements will be preferably performed in the axial (transverse) plane on contrast-enhanced T1-weighted images. However, there are no specific sequence recommendations.

Measurability of Tumor Lesions

Tumor lesions will be categorized as follows:

- **Measurable Lesions -** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm)
  - 10 mm caliper measurement by clinical exam (when superficial)
  - Malignant lymph nodes are considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).
- **Nonmeasurable Lesions -** Nonmeasurable lesions are defined as all other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis). Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
- **Target Lesions -** All lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions. 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.

- **Non-target Lesions -** It is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”)

Response Criteria

Evaluation of Target Lesions

- **Complete Response -** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm (the sum may not be “0” if there are target nodes).
- **Partial Response -** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease -** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression.)
- **Stable Disease -** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

Evaluation of Non-target Lesions

- **Complete Response -** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- **Non-complete response/Non-progressive disease -** Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease -** Unequivocal progression of existing non-target lesions will be defined as the overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. In the absence of measurable disease, change in non-measurable disease comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from „trace“ to „large,“ an increase in lymphangitic disease from localized to widespread.

Appearance of New Lesions

The appearance of new lesions is considered PD according to RECIST v 1.1 guidelines. Considering the unique response kinetics that have been observed with immunotherapy, new lesions may not represent true disease progression. In the absence of rapid clinical deterioration, subjects may continue to receive treatment with MEDI4736.

Evaluation of Overall Response

Table 12 provides overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions.

Table 12 Evaluation of Overall Response

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Complete response	Complete response	No	Complete response
Complete response	Not evaluable [a]	No	Partial response
Complete response	Non-complete response / non-progressive disease	No	Partial response
Partial response	Non-progressive disease and not evaluable [b]	No	Partial response
Stable disease	Non-progressive disease and not evaluable [b]	No	Stable disease
Not all evaluated	Non-progressive disease	No	Not evaluable
No target lesion [a]	Not all evaluated	No	Not evaluable
No target lesion [a]	Non-complete response / non-progressive disease	No	Non-complete response / non-progressive disease
Progressive disease	Any	Yes/No	Progressive disease
Any	Progressive disease	Yes/No	Progressive disease
Any	Any	Yes	Progressive disease
No target lesion [a]	Unequivocal progressive disease	Yes or No	Progressive disease
No target lesion [a]	Any	Yes	Progressive disease

[a] Defined as no target lesions at baseline.
[b] Not evaluable is defined as either when no or only a subset of lesion measurements are made at an assessment.

irRECIST

Due to the potential for tumors to appear larger, including new lesions, prior to response in immunotherapy trials, subjects are permitted to continue treatment beyond progression. In order to factor in the appearance of new measurable lesions, the immune-related RECIST (irRECIST) is a modified RECIST version 1.1 that includes new measurable lesions into the sum of the diameters when determining overall response.

13.1 CRITERIA FOR REMOVAL FROM STUDY

In the absence of serious toxicity or complications, all patients will continue treatment for up to 2 years. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression (unless the patient continues treatment beyond progression).
- Development of an intercurrent medical condition or need for concomitant treatment that precludes further participation in the trial.
- Unacceptable toxicity or any adverse event that precludes further participation in the trial.
- The investigator removes the patient from the trial in the best interests of the patient.
- Patient death.

- Study completion or discontinuation for any reason.
- Patient withdraws consent to continued participation in the trial or is lost to follow up.

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). Subjects who are permanently discontinued from receiving investigational product will return for end of study visit, unless consent is withdrawn, the subject is lost to follow-up or begins another treatment. All subjects will be followed for survival by telephone (unless not otherwise following up at Memorial Hospital) every 3 months for up to 2 years.

If consent is withdrawn, the subject will not receive any further investigational product or further study observation.

14.0 BIOSTATISTICS

The primary endpoint of this trial is the best response rate in dMMR CRC (cohort 1) and TIL+ CRC (cohort 2) patients according to RECIST 1.1. Currently there is no standard of care for this patient population and there is currently no known drug for which the response rate would be expected to be greater than about 5% in patients that have failed current regimes. A two-stage Simon"s optimal design will be employed to test the null hypothesis that the true response rate is ≤5% versus the alternative hypothesis that the true response rate is at least 25% with type I and II error rates of 10% each. Each cohort will be evaluated separately for this purpose. In the first stage, we will accrue 9 patients in each cohort. If 0 objective tumor responses (PR or CR) are observed among the 9 subjects treated in a cohort, then subject enrollment will be terminated in that cohort. If at least 1 response is observed among the 9 subjects treated in a cohort, then the study will be expanded to enroll a total of 24 treated subjects in that cohort. At the end of the study, if 2 or fewer objective tumor responses are observed in a cohort, then the study will be considered not worthy of further investigation in that particular cohort. If at the end of the study ≥3 tumor responses per RECIST1.1 are observed in a cohort, then further investigation of MEDI4736 in that patient population will be considered worthwhile. This study requires accrual of a minimum of 18 subjects and up to a maximum of 48 subjects if both cohorts are expanded to the second stage. The accrual time is estimated to be 2 years.

Antitumor Activity

Assessments of antitumor activity will be based on the ORR, PFS, and OS. Response Evaluation Criteria in Solid Tumors guidelines (v1.1)[39] with modifications to account for the unique response patterns observed with immunotherapy will be used to determine tumor response.

The ORR is defined as the proportion of subjects CR or PR based on RECIST criteria. The exact 95% CI of ORR will be estimated using the binomial distribution. The ORR defined based on irRECIST criteria will also be estimated using the binomial distribution and exact 95%CI will be provided. Progression-free survival will be measured from the start of treatment with MEDI4736 until the documentation of disease progression or death due to any cause, whichever occurs first. Progression-free survival will be censored on the date of last tumor assessment documenting absence of tumor progression for subjects who are still alive

prior to data cutoff, dropout, or the initiation of alternate anticancer treatment. Subjects having no tumor assessments after the start of treatment with MEDI4736 will have PFS censored on the first date of treatment with MEDI4736. Progression-free survival will be evaluated using the Kaplan-Meier method(Kaplan and Meier, 1958). Overall survival will be determined as the time from the start of treatment with MEDI4736 until death. For subjects who are alive at the end of study or lost to follow-up, OS will be censored on the last date when subjects are known to be alive. The OS will be evaluated using the Kaplan-Meier method.

Safety and Tolerability Analyses

All recorded adverse events will be listed and tabulated by system organ class, preferred term and treatment. Any significant vital signs and clinical laboratory test results will be listed and summarized. Any significant physical examination findings, and clinical laboratory results will be listed.

Biomarker Analysis

Exploratory research studies will be done only on the 1st stage patients to evaluate the effect of this therapy will be performed using research blood draws and tumor biopsies at baseline and at week 8. Cohorts 1 and 2 will be combined for this analysis given the small sample size.

The pharmacodynamic effect of MEDI4736 on Tumor Infiltrating Lymphocytes (TILs), such as CD4+ and CD8+ T-cells, and expression of tumor markers, such as PD-L1, will be assessed by summary statistics, and investigated graphically to explore patterns of change from pre-treatment to post-treatment specimens.

The pharmacodynamic effect of MEDI4736 on markers in peripheral blood, such as ICOS, HLA-DR, PD-1, CTLA-4; and, serum proteins, such as CXCL9; CXCL10, will be assessed by summary statistics, and investigated graphically to explore patterns of change over time, i.e.: pretreatment, then week 2, week 4, and week 8.

In addition, the relationship of TIL changes and tumor marker expression with measures of peripheral blood markers will be summarized descriptively. Fisher"s exact test will be employed to assess associations between categorical variables while Spearman's rank correlation will be used for continuous variables. Wilcoxon signed rank test will be used to test for differences in continuous expression tumor markers between pre- and post-treatment specimens while McNemar"s test will be used to assess these relationships for binary markers. Fisher"s exact test will be employed to assess associations between categorical variables

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.3 Randomization

n/a

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secured database (Clinical Research Database, CRDB) at Memorial Sloan-Kettering Cancer Center. Source documentation will be available to support the computerized patient record.

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits may be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials”, which can be found at http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC DSM Plans can be found on the MSKCC Intranet at http://mskweb5.mskcc.org/intranet/_assets/_tables/content/359689/Data_safety%20Monitoring07.pdf

17.1 PROTECTION OF HUMAN SUBJECTS

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines.

Inclusion of Women and Minorities: Memorial Sloan-Kettering Cancer Center has filed forms HHS 441 (civil rights), HHS (handicapped individual), 639-A (sex discrimination), and 680 (age discrimination); we also take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. Patients of all races, both male and female, will be accepted into the protocol. The proposed study population is as described in section 7.0.

Exclusion of Lactating or Pregnant Women: Children have been excluded from this study. Colorectal adenocarcinoma is an adult cancer. Thus, the relevance of these drug to the pediatric population has not been established. Lactating and pregnant women are also excluded because of potential anti-proliferative effects of chemotherapy that may be harmful to the developing fetus or nursing infant.

Benefits: It is possible that this treatment will result in shrinkage of colorectal cancer or in a stabilization of an otherwise progressing disease. It is not known, of course, whether these or any other favorable events will occur. It is not known whether this treatment will affect the overall survival of the patients.

Costs: The patient will be responsible for the costs of standard medical care, including, CT scans, all drug administration fees and all hospitalizations, even for complications of treatment. MEDI4736 will be supplied to patients by MedImmune at no cost. Patients will not be responsible for the costs of blood procurement obtained for research purposes, the cost of special testing of any tissue for research purposes, or the cost for obtaining the tumor biopsy for research purposes.

Incentives: No incentives will be offered to patients/subjects for participation in the study.

Alternatives: Patients may be eligible for other investigational studies, or focus on palliative care options.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patient"s name or any other personally identifying information will not be used in reports or publications resulting from this study. The Food and Drug Administration or other authorized agencies (e.g., qualified monitors) may review patients records and pathology slides, as required.

17.2 Privacy

MSKCC"s Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.3 Serious Adverse Event (SAE) Reporting

The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 90 days after the last dose of MEDI4736 or until the initiation of alternative anticancer therapy. The investigator and/or Sponsor are responsible

for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- Subject"s name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject"s condition
    - Indication if the subject remains on the study
    - If an amendment will need to be made to the protocol and/or consent form.

The PI"s signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB AE report should be completed as above and the FDA assigned IND/IDE number written at the top of the report. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

17.2.1 SAFETY REPORTING The Institution will be responsible for: 1) reporting all suspected, unexpected serious adverse reactions (SUSARs) where subject has received MedImmune Development Product and provided to MedImmune Patient Safety at the same time the report(s) are sent to the local Regulatory Authority; and 2) as the Sponsor, meeting regulatory and ethics committee safety reporting requirements and obligations in all participating countries.

In accordance with local Regulatory FDA requirements, Institution, as the IND Sponsor, will establish and maintain records and submit Safety Reports to the FDA as required by 21 CFR 312.32 or as required by other applicable regulations. In the conduct of research under this Agreement, the Parties will comply with specific guidelines and policies for reporting adverse

events, as well as procedures specified in the Protocol(s). Collaborator must provide MedImmune Patient Safety with a copy of all initial and follow-up Safety Reports CIOMS concurrently with their submission to the local Regulatory Authority to drugsafety@medimmune.com and AEMailboxClinicalTrialTCS@astrazeneca.com. The Developmental Core Safety Information (DCSI) included in the current Investigator"s Brochure will be used to determine expectedness for regulatory reporting purposes.

When assessing causality, MedImmune Patient Safety uses a binary causality scale ("related" or "not related"). SAEs assessed by the Institution as "definitely, possibly, or probably related" will be considered "related" by MedImmune Patient Safety. SAEs assessed as "not related, remotely, or unlikely", are considered "not related" by MedImmune Patient Safety.

Monthly, and not later than 15 calendar days after the end of each calendar month, Institution shall provide a copy of all other SAEs (e.g., SAEs assessed as not related, or subject received placebo or active comparator), to MedImmune Patient Safety in the form of a CIOMS [or CIOMS II line listing] to: AEMailboxClinicalTrialTCS@astrazeneca.com.

MedImmune will forward SUSARs for a MedImmune Development Product to Investigators who are participating in sponsored studies in accordance with local requirements.

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

APPENDIX A: Requisition For Blood Specimens
APPENDIX B: Requisition For Biopsy Specimens

APPENDIX A: REQUISITION FOR BLOOD SPECIMENS

Phase II Study to Evaluate the Efficacy of MEDI4736 in Immunological Subsets of Advanced Colorectal Cancer

A) Section A: Patient information (To be completed by RSA) Patient initials: _____ Patient study ID#:_____ Site: _____	**B) Section B: Sample information** (To be checked off by RSA) **4 CPT tubes (10 cc) will be collected at the following time points** **[ ]**Baseline **[ ]**Week 2 **[ ]**Week 4 **[ ]**Week 8 **[ ]**Week ____ **PAXgene Blood DNA Tubes (8.5 cc)** **[ ]**Baseline
C) Section C: Sample Collection information (To be completed by phlebotomy) Drawn By:_____ Date/ Time:_____	Sample Collection Instructions: 1. Gently invert all tubes 8-10 times at room temperature immediately after collection 2. Write patient initials, date, and time of collection on each tube 3. Place all collected tubes in biohazard ziplock bag 4. Send all specimens at room temperature via Stat Messengers to _____
D) Section D: Sample Processing information (To be completed by laboratory personnel) Lab ID#: _____ Received by: _____ Date/Time: _____	
E) **Section E: Sample shipping information** (To be completed by laboratory personnel) Sent by: _____ Date/Time: _____ Received by: _____ Date/Time: _____	Sample shipping Instructions Ship samples on dry ice to: Dr. Jianda Yuan Memorial Sloan-Kettering Cancer Center Zuckerman Research Building 425 East 66th street, Z1545 New York, NY 10065

APPENDIX B: REQUISITION FOR BIOPSY SPECIMENS OR LEFT OVER TISSUE OBTAINED DURING A ROUTINE PROCEDURE

Phase II Study to Evaluate the Efficacy of MEDI4736 in Immunological Subsets of Advanced Colorectal Cancer

A) Section A: Patient information (To be completed by RSA) Patient initials: _____ Patient study ID#: _____ Site: _____	**B) Section B: Sample information** (To be checked off by RSA) **[ ]** Baseline: **5 Core Biopsies** **[ ]** Week 8: **5 Core Biopsies** **[ ]** Routine Procedure: **5 Cores or divided tumor**
C) Section C: Sample Collection information (To be completed by physician or designee) Obtained By: _____ Procedure: _____ Date/ Time: _____	Sample Collection Instructions: 1. Cores # 1, 2: Place into formalin (3-5 cc) 2. Cores # 3, 4: Place in sterile Nunc tube and snap freeze in liquid nitrogen 3. Core # 5: Place into 3-5 cc RPMI under sterile conditions
D) Section D: Storage/Processing information (To be completed by laboratory personnel) Lab ID#: _____ Received by: _____ Date/Time: _____	Sample Storage/ Processing Instructions 1. Cores # 1, 2: Store at 4-8°C 2. Cores # 3, 4: Store at -70 to -80°C 3. Core # 5: Process immediately for TIL isolation and/ or tissue culture
E) **Section E: Sample shipping information** (To be completed by laboratory personnel) Sent by: _____ Date/Time: _____ Received by: _____ Date/Time: _____	Sample shipping Instructions Ship samples 1, 2, and 5 at room temperature; samples 3 and 4 on dry ice, attention: Dr. Jianda Yuan Memorial Sloan-Kettering Cancer Center Zuckerman Research Building 425 East 66th street, Z154 New York, NY 10065