SUMMARY OF CHANGES

For Protocol Amendment # to: 07

NCI Protocol#: 10021
Local Protocol #: 17-719

NCI Version date: 08/30/2019
Protocol Date: 08/30/2019

#	Page(s)	Change
1	Throughout Document	Incorporated CIMAC biomarker network for biomarker analyses

For Protocol Amendment # to:

NCI Protocol #: *10021*

Local Protocol #: *17-719*

ClinicalTrials.gov Identifier: NCT02888743

TITLE: A Phase 2 Study of MEDI4736(durvalumab) and Tremelimumab Alone or in Combination with High or Low-Dose Radiation in Metastatic Colorectal and NSCLC

Study disease:
1. Non-small cell lung cancer 10029514
2. Colorectal cancer 10010029

Corresponding Organization: LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO

Principal Investigator: *Jonathan Schoenfeld*
Dana-Farber Cancer Institute
450 Brookline Ave. DA L257
Boston, MA 02115
Phone: 617-632-3591
Fax: 617-632-4247
jdschoenfeld@partners.org

Participating Organizations

LAO-11030 / University Health Network Princess Margaret Cancer Center LAO
LAO-CA043 / City of Hope Comprehensive Cancer Center LAO
LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
LAO-MN026 / Mayo Clinic Cancer Center LAO
LAO-NC010 / Duke University - Duke Cancer Institute LAO
LAO-NJ066 / Rutgers University - Cancer Institute of New Jersey LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / University of Pittsburgh Cancer Institute LAO
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO
LAO-NCI / National Cancer Institute LAO

Statistician:
Anita Giobbie-Hurder
Institute
450 Brookline Ave (CLSB 11007)
Boston, MA 02215
*p*617-632-2193
*f*617-632-5444
agiohur@jimmy.harvard.edu

Study Coordinator:
Amanda Stroiney Dana-Farber Cancer
Dana Farber Cancer Institute
450 Brookline Ave.
Boston, MA 02215
p617-632-3289
f617-632-7227
amanda_stroinry@dfci.harvard.edu

Responsible Research Nurse:
Rose Baylies, R.N.
Dana-Farber Cancer Institute
450 Brookline Ave
Boston, MA 02215
p617-632-6278
f617-632-6949
RosemarieKristinaM_baylieskelley@dfci.harvard.edu
janiceamanda_stroineyrussell@dfci.harvard.edu

Responsible Data Manager:
Amanda Stroiney
Dana Farber Cancer Institute
450 Brookline Ave.
Boston, MA 02215
p*617-632-3289*
f*617-632-7227*

NCI-Supplied Agent(s):
MEDI4736(NSC 778709)
Tremelimumab (NSC 744483)

IND Sponsor: DCTD, NCI

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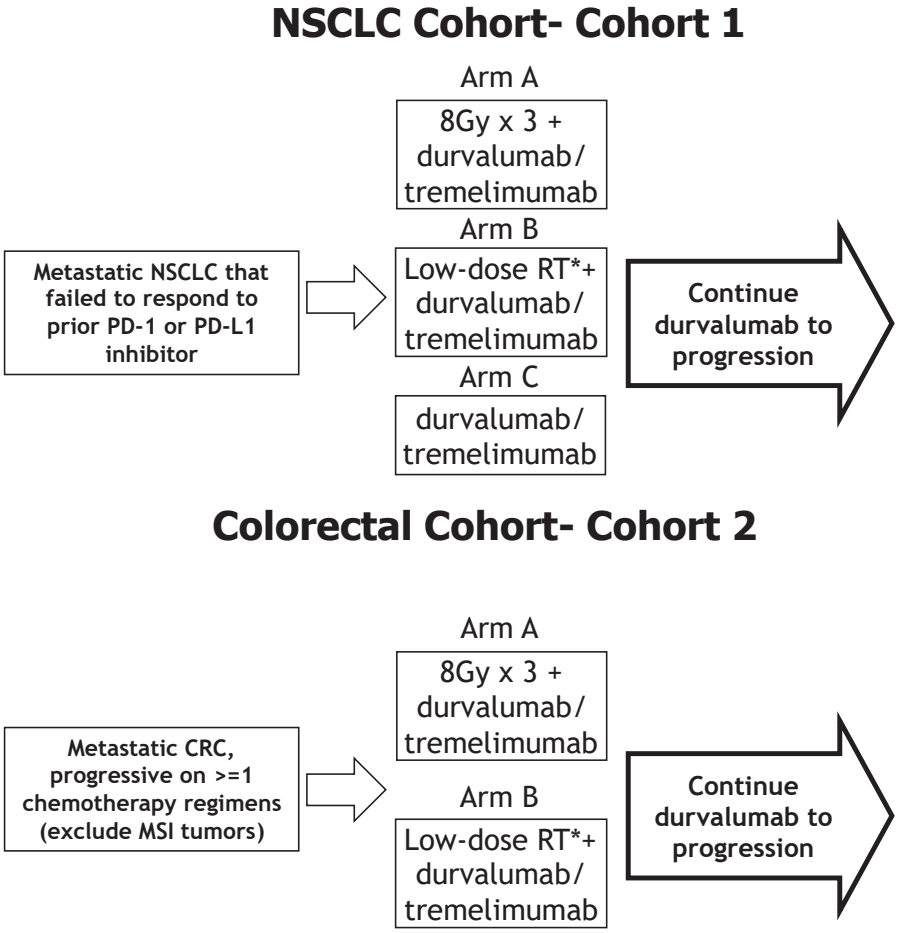
SCHEMA


NSCLC Cohort- Cohort 1
Arm A
8Gy x 3 + durvalumab/ tremelimumab
Arm B
Low-dose RT*+ durvalumab/ tremelimumab
Arm C
durvalumab/ tremelimumab
Metastatic NSCLC that failed to respond to prior PD-1 or PD-L1 inhibitor
Continue durvalumab to progression
Colorectal Cohort- Cohort 2
Arm A
8Gy x 3 + durvalumab/ tremelimumab
Arm B
Low-dose RT*+ durvalumab/ tremelimumab
Metastatic CRC, progressive on >=1 chemotherapy regimens (exclude MSI tumors)
Continue durvalumab to progression
*0.5 Gy BID x2 days repeated q4weeks with durvalumab / tremelimumab

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1. OBJECTIVES

1.1 Primary Objectives

NSCLC Cohort:

1. To assess safety and tolerability of combined checkpoint blockade with MEDI4736(durvalumab) and tremelimumab alone or with high or low-dose radiation in NSCLC
2. To compare the overall response (excluding the irradiated lesion(s)) between combined checkpoint blockade with MEDI4736 and tremelimumab alone or combined checkpoint blockade with low or high dose radiation.

Colorectal Cohort:

1. To assess safety and tolerability of combined checkpoint blockade with MEDI4736 and tremelimumab with high or low-dose radiation
2. To determine the overall response rate (excluding the irradiated lesion(s)) with combined checkpoint blockade with MEDI473 6and tremelimumab with either low or high dose radiation.

1.2 Secondary Objectives

NSCLC Cohort

- To estimate median progression-free survival and overall survival
- To determine local control within the irradiated field(s) and abscopal response rates
- To evaluate associations between PD-L1 expression as well as levels of infiltrating CD3+, CD8+ T-cells and overall response
- To explore changes in changes in PD-L1 expression, circulating T-cell populations, T-cell infiltration, RNA expression, spatial relationship of immune markers, and mutational burden as a result of low or high dose radiation

Colorectal Cohort

- To estimate median progression-free survival and overall survival
- To determine local control within the irradiated field and abscopal response rates
- To evaluate associations between PD-L1 expression as well as levels of infiltrating CD3+ CD8+ T-cells and overall response
- To evaluate changes between PD-L1 expression as well as levels of infiltrating CD3+, CD8+ T-cells induced by targeted low or high dose radiation
- To explore changes in changes in circulating T-cell populations, T-cell infiltration, RNA expression, spatial relationship of immune markers, and mutational burden as a result of low or high dose radiation

1.3. Exploratory Endpoints

1. To explore the inclusion of patient reported symptomatic adverse events

2. BACKGROUND

2.1 *Study Disease(s)*

Metastatic non-small cell lung cancer

Over 225,000 people are diagnosed per year with non-small cell lung cancer in the United States, and this disease is responsible for over 150,000 deaths per year, making it the leading cause of cancer deaths and representing a clear unmet need [1]. In patients without a targetable driver mutation, first-line chemotherapy with two cytotoxic agents is generally superior to single agent therapy and is associated with an approximate 25% response rate and 1-year survival between 30 and 40%[2]. Responses to additional lines of chemotherapy following progression are significantly reduced and generally less than 10%, with median survival of approximately 6 months in this setting[3]. In comparison, PD-1 checkpoint blockade has been associated with an approximate 20% response rate and improved survival as compared to chemotherapy in the second line setting in both squamous and non-squamous cancers[4, 5]. For these reasons, PD-1 inhibition is actively being investigated in the first line setting, with promising initial results [6]. CTLA-4 therapy alone has not demonstrated impressive response rates[7]; however, an intriguing case report demonstrated the combination of CTLA-4 and radiation led to a complete radiologic response[8]. The combination of CTLA-4 and PD-1 inhibition is also being investigated in this disease; however, preliminary reports suggest that the majority of metastatic non-small cell lung cancer patients may not respond to the combination of these two agents alone[9]. Therefore, we propose to evaluate whether low or high dose radiation will increase response rates as compared to combined checkpoint blockade of CTLA-4 and PD-L1 alone in patients that have previously failed to respond to either PD-1 or PD-L1 inhibitors.

Metastatic colorectal cancer

Approximately 130,000 people are diagnosed with colorectal cancer annually in the United States, and this disease is responsible for over 45,000 deaths per year[10]. First-line chemotherapy with multi-agent regimens can have response rates approaching 50%[11, 12]. In the second line setting, there is a significantly decreased response rate that is generally less than 20%, and many patients are not candidates for many of the potential second-line regimens because of prior treatment and/or concerns regarding toxicity and quality of life[13].

Previous studies have suggested that treatment with immune checkpoint blockade alone does not generally lead to response in most colorectal cancer patients, except for patients with microsatellite instable tumors[14]. Therefore, we propose to attempt to induce a significant number of responding patients in microsatellite stable patients by combining either low or high dose radiation with CTLA-4 and PD-1 blockade in patients that have progressed after first line chemotherapy.

2.2 CTEP Agent(s)

2.2.1 MEDI4736(durvalumab)

Immune responses directed against tumors are one of the body's natural defenses against the growth and proliferation of cancer cells. However, over time and under pressure from immune

attack, cancers develop strategies to evade immune-mediated killing allowing them to develop unchecked. One such mechanism involves upregulation of surface proteins that deliver inhibitory signals to cytotoxic T cells. PD-L1 is one such protein, and is upregulated in a broad range of cancers with a high frequency, with up to 88% expression in some indications. In a number of these cancers, including lung[15], renal [16-18], pancreatic [19-21], and ovarian cancer [22], tumor cell expression of PD-L1 is associated with reduced survival and an unfavorable prognosis. For example, in ovarian cancer, the 5-year survival rate in patients with low expression of PD-L1 was 80.2% compared to 52.6% in patients with high expression levels of PD-L1 [22]. In lung cancer, only 20% of patients with tumors expressing PD-L1 survived more than 3 years compared to 49% of patients with tumors lacking PD-L1 expression[15]. Along with PD-L1 expression data generated internally, these data suggest that an antibody targeting PD-L1 has the potential to affect multiple solid tumor types. PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 acts at multiple sites in the body to help regulate normal immune responses and is utilized by tumors to help evade detection and elimination by the host immune system tumor response. In the lymph nodes, PD-L1 on antigen-presenting cells binds to PD-1 or CD80 on activated T cells and delivers an inhibitory signal to the T cell [23, 24]. This results in reduced T-cell activation and fewer activated T cells in circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 and CD80 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T cells, preventing them from killing target cancer cells and protecting the tumor from immune elimination[25]. Based on in vitro studies, 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]. The levels of tumor-infiltrating lymphocytes, and more specifically cytotoxic T cells, have been correlated with improved prognosis in a number of cancers including colorectal, melanoma, and lung [27], suggesting that an antitumor immune response is beneficial to patients. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of several preclinical studies using mouse tumor models support this hypothesis [28-30]. In these studies, antibodies directed against PD-L1 or its receptor, PD-1, demonstrated antitumor activity.

MEDI4736is a human mAb of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1 and is being developed by AstraZeneca/MedImmune for use in the treatment of cancer. (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) The proposed mechanism of action for MEDI4736 is interference of the interaction of PD-L1, expressed on cancer cells and a subset of leukocytes, with the PD-1 (cluster of differentiation [CD] 279) and B7-1 (CD80) molecules on antigen-presenting cells and T-cells. By binding to PD-L1 on tumor cells, the mechanism of action of MEDI4736 includes stimulation of the patient's antitumor immune response.

The non-clinical experience is fully described in the current version of the MEDI4736Investigator's Brochure. In vitro studies demonstrate that MEDI4736 antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFN-γ). Additionally, MEDI4736 demonstrated a lack of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) in

cell-based functional assays. In vivo studies show that MEDI4736 inhibits tumor growth in a xenograft model via a T-lymphocyte (T-cell) dependent mechanism. Moreover, an anti-mouse (m)PD-L1 antibody demonstrated improved survival in a syngeneic tumor model when given as monotherapy.

To date MEDI4736has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. Details on the safety profile of MEDI4736monotherapy are summarized below. Refer to the current MEDI4736Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

The majority of the safety data currently available for MEDI4736 are based on the first-time-in-human, single-agent study (Study CD-ON-MEDI4736-1108; hereafter referred to as Study 1108) and are summarized in the IB. Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W, durvalumab exhibited non-linear (dose‑dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg Q2W, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half‑life with doses ≥3 mg/kg Q2W is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab (For further information on immunogenicity, please see the current IB). [1]

Data from Study D4190C00006 (Phase I trial in NSCLC patients using the combination of durvalumab and tremelimumab) also show an approximately dose-proportional increase in PK exposure for durvalumab over the dose range of 3 to 20 mg/kg durvalumab Q4W or Q2W. (For further information on PK observations in Study 006, please see the current IB).

The observed durvalumab PK data from the combination study were well in line with the predicted monotherapy PK data (5th median and 95th percentiles) for a Q4W regimen. Monoclonal antibodies directed against immune checkpoint proteins, such as programmed cell death ligand 1 (PD-L1) as well as those directed against programmed cell death-1 (PD-1) or cytotoxic T-lymphocyte antigen-4 (CTLA-4), aim to boost endogenous immune responses directed against tumor cells. By stimulating the immune system however, there is the potential for adverse effects on other tissues.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune mediated mechanism and which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. These risks can include gastrointestinal AEs such as colitis and diarrhoea, pancreatitis, pneumonitis/interstitial lung disease (ILD), renal AEs such as nephritis and increases in creatinine, hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis, endocrinopathies such as hypo- and hyper-thyroidism,

hyophysitis,adrenal insufficiency, diabetes mellitus type I and diabetes insipidus, and neurotoxicities such as myasthenia gravis and Guillain-Barre syndrome.

Risks with durvalumab include, but are not limited to, diarrhea/colitis and intestinal perforation, pneumonitis/ILD, endocrinopathies (hypo- and hyper-thyroidism, type I diabetes mellitus, hypophysitis and adrenal insufficiency) hepatitisincreases in transaminases, nephritis/increases in creatinine, pancreatitis increases in amylase and lipase, rash/pruritus/dermatitis, myocarditis, myositis/polymyositis, other rare or less frequent inflammatory events including neurotoxicities, infusion-related reactions, hypersensitivity reactions, and infections/serious infections. Further information on all identified and potential risks with durvalumab please always refer to the current version of the durvalumab IB.

In monotherapy clinical studies AEs (all grades) reported very commonly (≥ 10% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, asthenia, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 9% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 6% of patients experienced an SAE that was considered to be related to durvalumab by the study investigator.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (see the Dosing Modification and Toxicity Management Guidelines in Section 6).

A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB.

The safety of durvalumab + tremelimumab combination therapy was initially evaluated in the ongoing dose escalation and dose expansion Study 006, in patients with NSCLC, and is being studies in a number of other ongoing clinical trials in a number of different indications, and has to date shown a manageable safety and tolerability profile.

The potential risks with the combination of durvalumab + tremelimumab are similar to those for durvalumab and tremelimumab monotherapy. Emerging data from study 006, other studies evaluating the combination, and from combinations of other agents in the same class indicate an increased frequency and/or severity of some of these potential immune-mediated toxicities. In durvalumab+tremelimumab combination studies at the dose of durvalumab 20mg/kg and tremelimumab 1mg/kg AEs (all grades) reported very commonly (≥ 10% of patients) are fatigue, diarrhoea,nausea, dyspnea, decreased appetite, pruritus, vomiting, anaemia, constipation, cough, abdominal pain, pyrexia, back pain, hyponatraemia and rash.

Approximately 13% of patients experienced an AE that resulted in permanent discontinuation of study drug and approximately 13% of patients experienced an SAE that was considered to be related to durvalumab and tremelimumab by the study investigator.

A detailed summary of durvalumab + tremelimumab combination AE data can be found in the

current version of the durvalumab IB.

Information on durvalumab efficacy data can be found in the current version of the durvalumab IB

2.2.2 Tremelimumab

Tremelimumab, a CTLA-4 mAb of the IgG 2 kappa isotype, is an immunomodulatory therapy (IMT) that is being developed by AstraZeneca for use in the treatment of cancer. Tremelimumab is a human IgG2 mAb directed against CTLA-4. CTLA-4 is a critical regulatory signal for T-cell expansion and activation following an immune response, and it serves as a natural braking mechanism that maintains T-cell homeostasis. During T-cell activation, T cells upregulate CTLA-4, which binds to B7 ligands on antigen-presenting cells, sending an inhibitory signal that limits T-cell activation. Tremelimumab blocks the inhibitory signal resulting from CTLA-4 binding to B7, leading to indirect prolongation and enhancement of T-cell activation and expansion. An extensive program of non-clinical and clinical studies has been conducted for tremelimumab both as monotherapy and combination therapy with conventional anticancer agents to support various cancer indications using different dose schedules. Refer to the tremelimumab IB for a complete summary of non-clinical and clinical information; see Section 5.3 for guidance on management of tremelimumab-related toxicities.

To date tremelimumab has been given to more than 1500 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of tremelimumab monotherapy are summarized in this Section. A detailed summary tremelimumab exposure data can be found in the current version of the tremelimumab IB.

In clinical subjects, tremelimumab exhibits linear (dose-proportional) PK following IV infusion. The estimate of clearance (CL), volume of distribution at steady state (Vss), and terminal-phase half-life is 0.132 mL/h/kg, 81.2 mL/kg and 22.1 days, respectively. These values are consistent with those of natural IgG2.

Risks with tremelimumab monotherapy include, but are not limited to, GI effects (colitis, diarrhoea, enterocolitis and intestinal perforation), endocrine disorders (hypo and hyperthyroidism, hypophysitis and adrenal insufficiency), skin effects (rash, and pruritus), elevations in lipase and amylase and clinical manifestations of pancreatitis, other gastrointestinal events e.g. ulcerative colitis, dehydration, nausea and vomiting; hepatic events including hepatitis, and liver enzyme elevations; pneumonitis and ILD; nervous system events including encephalitis, peripheral motor and sensory neuropathies, Guillain-Barre and proximal muscle weakness; cytopenias including thrombocytopenia, anemia and neutropenia; infusion-related reactions, anaphylaxis, and allergic reactions; renal events including renal failure, acute kidney injury, nephritis, nephrotic syndrome, autoimmune nephritis and electrolyte abnormalities such as hypokalemia; autoimmune diseases including autoimmune arthritis, Sjogren's syndrome and giant cell temporal arteritis; hyperglycemia and diabetes mellitus; and pyrexia.

Further information on the identified and potential risks with tremelimumab please always refer to the current version of the tremelimumab IB.

Using pooled data from monotherapy clinical studies AEs (all grades) reported very commonly (≥ 10% of patients) were diarrhea, nausea, fatigue, pruritus, decreased appetite, rash, vomiting, dyspnoea, constipation, cough, pyrexia, abdominal pain, decreased weight, headache, asthenia, and anaemia. Approximately 16% of patients experienced an AE that resulted in permanent discontinuation of tremelimumab and approximately 45% of patients experienced an SAE.

A detailed summary of tremelimumab monotherapy AE data can be found in the current version of the tremelimumab IB.

Please also refer to the tremelimumab IB for a complete summary of non-clinical and clinical information; see Section 5.3 for guidance on management of tremelimumab-related toxicities. Information about safety of combined tremelimumab / MEDI4736is provided in section 2.1, below, and also the MEDI4736IB.

2.2.2.1 MEDI4736/ tremelimumab combination

A population PK model was developed for durvalumab using monotherapy data from the Phase 1 study, CD-ON-MEDI4736-1108 (N = 292; doses of 0.1 to 10 mg/kg Q2W or15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight on PK of durvalumab (coefficient of ≤ 0.5). The impact of body weight-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady-state PK concentrations (5th, median and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body weight of ~75 kg). A total of 1000 subjects were simulated using body weight distribution of 40 to 120 kg. Simulation results demonstrate that body weight- based and fixed dosing regimens yield similar median steady-state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen. Similarly, a population PK model was developed for tremelimumab using data from Phase 1 through Phase 3 (N = 654; doses of 0.01 to 15 mg/kg Q4W or every 90 days; metastatic melanoma; Wang et al, 2014). The population PK model indicated minor impact of body weight on PK of tremelimumab (coefficient of ≤ 0.5). The weight-based (1 mg/kg Q4W) and fixed dosing (75 mg/kg Q4W; based on median body weight of ~75 kg) regimens were compared using predicted PK concentrations (5th, median and 95th percentiles) using population PK model in a simulated population of 1,000 subjects with body weight distribution of 40 to 120 kg. Similar to durvalumab, simulations indicated that both body weight-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-subject variability with fixed dosing regimen. Similar findings have been reported by others (Ng et al, 2006; Wang et al, 2009;[1SEP]Zhang et al, 2012; Narwal et al, 2013). Wang and colleagues investigated 12 mAbs and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al, 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in PK/pharmacodynamics parameters[1SEP](Zhang et al, 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on an average body weight of 75 kg, a fixed dose of 750 mg Q2W durvalumab is equivalent to 10 mg/kg Q2W, 1500 mg Q4W durvalumab is equivalent to 20 mg/kg Q4W, and 75 mg Q4W tremelimumab is equivalent to 1 mg/kg Q4W.

The safety of durvalumab + tremelimumab combination therapy was initially evaluated in the ongoing dose escalation and dose expansion Study 006, in patients with NSCLC, and is being studied in a number of other ongoing clinical trials, in a number of different indications, and has to date shown a manageable safety and tolerability profile.

The types of risks with the combination of durvalumab + tremelimumab (based on an equivalent durvalumab dose of 20m/kg and a tremelimumab dose of 1mg/kg) are similar to those for durvalumab and tremelimumab monotherapy. Emerging data from study 006, other studies evaluating the combination, and from combinations of other agents in the same class indicate an increased frequency and/or severity of some of these immune-mediated toxicities.

For information on all identified and potential risks with the durvalumab+tremelimumab combination please always refer to the current version of the durvalumab IB

In durvalumab+tremelimumab combination studies at the dose of durvalumab 20mg/kg and tremelimumab 1mg/kg AEs (all grades) reported very commonly (≥ 10% of patients) are fatigue, diarrhoea,nausea, dyspnea, decreased appetite, pruritus, vomiting, anaemia, constipation, cough, abdominal pain, pyrexia, back pain, arthralgia, hypothyroidism, asthenia, oedema peripheral, weight, decreased hyponatraemia and rash.

Approximately 15% of patients experienced an AE that resulted in permanent discontinuation of study drug and approximately 15% of patients experienced an SAE that was considered to be related to durvalumab and tremelimumab by the study investigator.

A detailed summary of durvalumab + tremelimumab combination AE data can be found in the current version of the durvalumab IB.

2.3 Other Agent(s) - Radiotherapy

Radiotherapy is a mainstay of cancer management, with approximately 50% of cancer patients receiving radiation during their course of illness[31]. Advances in technology have allowed for more precise radiation treatments delivered with such techniques as intensity modulated radiotherapy (IMRT) or stereotactic radiosurgery (SRS). These targeted forms of radiation therapy have become more widely adapted over recent years[32]. Although large field radiation has historically been appreciated for its immunosuppressive ability, targeted radiation can induce substantial changes in the tumor microenvironment beyond cellular cytotoxicity that evoke innate and adaptive immune responses.

Radiation directly damages DNA or more commonly indirectly induces the formation of free radicals that cause tumor cell apoptosis[33]. Following DNA damage, mechanisms of radiation-mediated tumor cell death include apoptosis, necrosis, mitotic catastrophe, or autophagy[31]. It is

now increasingly appreciated that under the proper circumstances these mechanisms of cellular damage and death induced by focal radiation can enhance anti-tumor immune responses, although inhibitory effects may also be present[34]. More specifically, previous studies have highlighted radiation-induced changes in costimulatory immune signals, proinflammatory cytokines, chemokines, effector, and immunosuppressive T cell subsets, as well as in immune receptors on tumor cells. Some of these changes in localized and systemic immune mediators have been linked to expansion of tumor-reactive T cells, as well as improved clinical responses in preclinical models[35].

The potential immunologic effects of radiation therapy include radiation-induced increases in epitope diversity, antigen presentation, and T-cell trafficking [36, 37] that may compliment the immune effects of both CTLA-4 and PD-1 pathway inhibition [38]. Indeed, preclinical studies have demonstrated synergies with both classes of agents[36] in terms of improved local and distant control, including "abscopal" regression of established tumors outside of the radiation treatment field. Preclinical results of radiation combined with PD-1 inhibitors have been particularly impressive in recent studies summarized below in table 1. Of note, the combination of radiation, CTLA-4 and PD-1 inhibition led to 60-80% response rates across tumor models[38], significantly greater than any single component or the combination of dual checkpoint blockade without radiation.

Table 1 – Studies demonstrating synergy between radiation and PD-1 pathway inhibition[38-42]

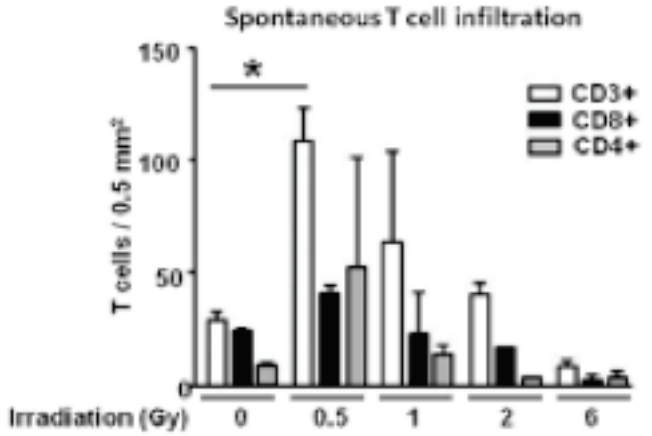
Study	Model	Benefit
Deng et al. JCI 2014	TUBO (breast) MC38 (colon)	- Tumor growth - Rechallenge - Contralateral tumor growth
Dovedi et al. Can Res 2014	4T1 (breast) CT26 (colon) 4434 (melanoma)	- Tumor growth - Survival - Rechallenge
Sherabi et al. CIR 2014	B16 (melanoma) 4T1 (breast)	- Tumor growth - Rechallenge
Tywman-Saint Victor et al. Nature 2015	B16 (melanoma) TSA (breast) PDA (pancreatic)	- Tumor growth - Survival - Contralateral tumor growth
Zeng et al. IJROBP 2013	GL261 (glioma)	- Tumor growth - Survival - Rechallenge

There is mixed evidence about the most appropriate dose of radiation to use in combination with immune therapy. For a variety of reasons, extrapolation of radiation dose effects from animal to human studies is not straightforward[43], not the least of which being the absolute differences in numbers of irradiated cells. However, these limitations notwithstanding, various animal studies have demonstrated potential synergy with hypofractionated and high dose radiation[36]. Specifically, 8 Gy x 3 was compared with other fractionated and single fraction regimens in combination with CTLA-4 inhibition and provided the most enhanced response of primary and abscopal lesions[36]. 8 Gy fractions administered to a total dose of 16 or 24Gy have also been specifically tested in combination with CTLA-4 [38]. In this study, increased numbers of circulating PD1+ CD8+ T-cells were associated with poor responders, suggesting a potential benefit to the addition of PD1 pathway inhibition to the 8 Gy per fraction / CTLA-4 blockade

combination. Finally the feasibility of delivering 8 Gy fractions for palliative benefit at sites throughout the body has been confirmed by a study conducting in patients with oligometastatic disease [44].

There are also animal models that suggest that low dose per fraction radiation may be more effective at recruiting T-cells to the tumor microenvironment than higher doses [45]. Specifically, in a preclinical study performed by Klug et al., a dose of 0.5 Gy was the most significant inducer of T-cell infiltration into tumor deposits 7 days following the receipt of treatment (Figure 1)[45]. Given increased T-cell infiltration has been associated with improved response to immune checkpoint blockade, this may indicate potential synergy.

Figure 1 – Adapted from Klug et al.



Low dose fractionated radiotherapy (LDFRT) is particularly appealing as a potential treatment strategy given potential immune effects, tolerability and favorable side effect profile, as well as the phenomenon of low dose hyper-radiosensitivity whereby cell killing is more effective than might be expected extrapolating from higher dose effects[46, 47]. Indeed, previous data suggests that LDFRT causes clonogenic inhibition with corresponding in vitro response data in addition to in vivo response data. Specifically, LDFRT was shown to potentiate the effects of cisplatin independent of the hyper-radiation sensitivity in human lung cancer cells [48]. In this study, to improve the understanding of HRS in a setting of low dose fractions versus clinically relevant dose fractionation settings, the cells were subjected to 12 fractions of 0.5 Gy or 6 fractions of 1 Gy or 3 fractions of 2 Gy. The decrease in surviving fractions was directly proportional to the number of fractions in all the cell lines for all fractionating schemes and the differences were statistically significant. Overall, all the fractionation schemes were statistically significant and 2 Gy dose per fraction had the highest surviving fraction in both H-157 and UKY-29 lines except at a total dose of 4 Gy and 6 Gy for UKY-29. For UKY-29, the mean estimates (of surviving fractions) at a total dose of 4 Gy for 0.5 Gy, 1 Gy and 2 Gy dose per fraction were very close to each other and resulted in no statistically significant difference at all possible pairwise comparisons (p-values ranges from 0.0331 to 0.5561). However, at a total dose of 6 Gy, the mean differences between all possible pairwise comparisons were statistically significant (p-

value<0.0003, see table and figure pasted below).

Figure 2 – Adapted from Gupta et al.

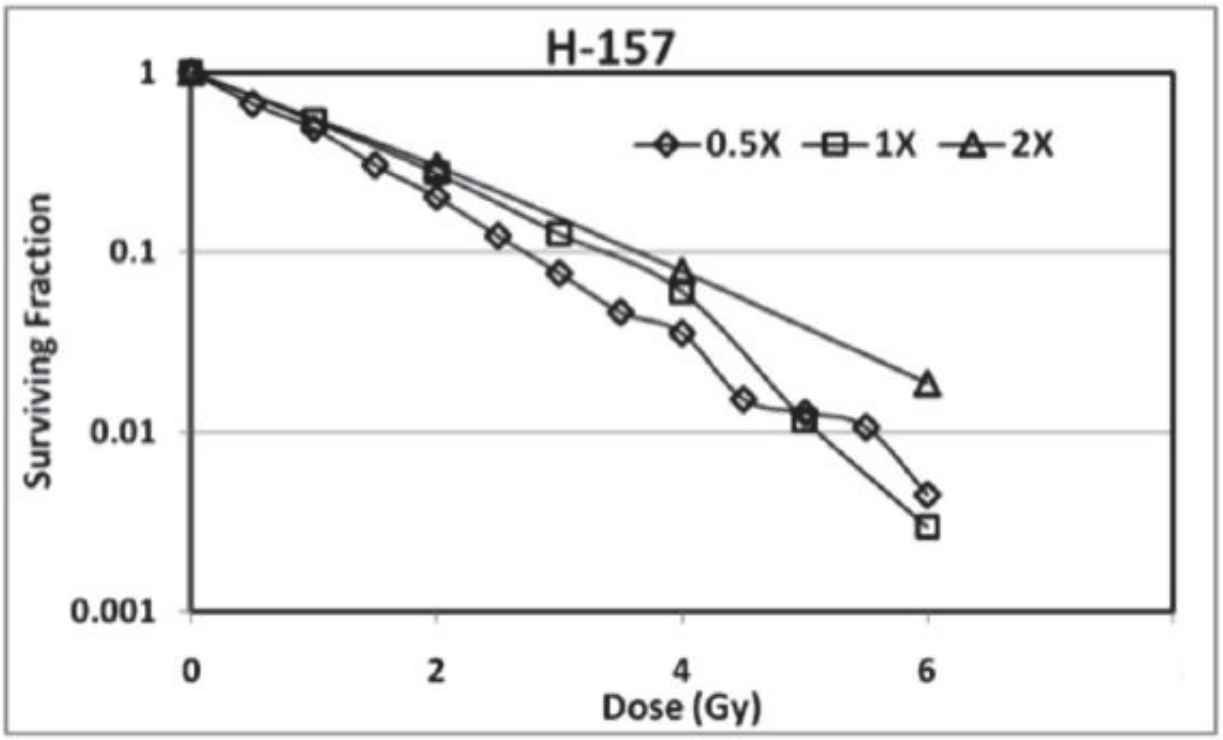


Table 2 – Adapted from Gupta et al. The following hypothesis was tested for surviving fraction as an outcome of measure for two cell lines at a given specific dose level. Hypothesis: There are no differences in means surviving fractions among different fractionations at a given cell line.

Cell***	Dose (Gy)*	Fractionation (dose per fraction)	Estimate**	Standard Error**	P-value**¥
H-157					
	2	0.5Gy	0.203	0.018	0.0001
		1Gy	0.275	0.018	0.0001
		2Gy	0.301	0.018	0.0001
		0.5Gy *vs.* 1Gy	-0.072	0.026	**0.0196**
		0.5Gy *vs.* 2Gy	-0.099	0.026	0.0037
		1Gy *vs.* 2Gy	-0.027	0.026	**0.3169**
	4	0.5Gy	0.035	0.003	0.0001
		1Gy	0.060	0.003	0.0001
		2Gy	0.078	0.003	0.0001
		0.5Gy *vs.* 1Gy	-0.025	0.004	0.0001
		0.5Gy *vs.* 2Gy	-0.043	0.004	0.0001
		1Gy *vs.* 2Gy	-0.018	0.004	0.0011
	6	0.5Gy	0.004	0.001	0.0001
		1Gy	0.003	0.001	0.0023
		2Gy	0.019	0.001	0.0001
		0.5Gy *vs.* 1Gy	0.002	0.001	**0.1584**
		0.5Gy *vs.* 2Gy	-0.014	0.001	0.0001
		1Gy *vs.* 2Gy	-0.016	0.001	0.0001

* Note that only 0Gy, 2Gy, 4Gy, 6Gy dose levels are common to all different fractionation groups i.e. 0.5Gy, 1Gy and 2Gy dose per fraction. Therefore, the analysis was restricted only to 0Gy, 2Gy, 4Gy, 6Gy dose levels. Since there is no variation in surviving fraction at dose=0Gy (i.e. SF=1 for all fractionation schemes) no test can be done.
** Estimate, its standard error and p-value for a given cell and the dose level were calculated from fitting one-way analysis of variance (one-way ANOVA) to surviving fractions with different fractionation schemes
¥ Type-I error was set to 5%. The p-values for pairwise group comparisons i.e. 0.5Gy vs. 1Gy dose per fraction, 0.5Gy vs. 2Gy dose per fraction and 1Gy vs. 2Gy dose per fraction should be compared to 1.66% due to Bonferroni correction to multiple comparison. Bold p-values are the one that are NOT statistically significant.
***Overall, all the fractionation schemes were statistically significant and 2Gy dose per fraction scheme had the higher surviving fraction in both cells for all doses but not for UKY-29 at a total dose of 4Gy and 6Gy. Notice that the mean estimate for UKY-29 at a total dose of 4Gy for 2Gy dose per fraction and at dose=0.5Gy were very close to each other. There were statistically significant differences between different fractionation schemes when we performed pairwise comparisons such as 0.5Gy vs. 1Gy dose per fraction, 0.5Gy vs. 2Gy dose per fraction and 1Gy vs. 2Gy dose per fraction at a given dose level for each of the cell lines. The bold p-values listed in the table are the ones that are NOT statistically significant i.e. there is no significant differences between the mean surviving fraction for given two groups for that particular cell line and the dose level.

In addition to this study, a number of other preclinical studies have demonstrated potential efficacy and immunologic effects of LDFRT [46]. Additionally, in systematic human studies of patients treated with radiation and ipilimumab, two studies have interestingly found that systemic responses tended to improve most following lower fractional doses of radiation[49, 50]. In addition, Golden et al. recently report a promising 28% abscopal response rate in patients treated with fractionated radiation at a dose of 3.5 Gy per fraction in combination with systemic GM-

CSF[51]. Clinically, the use of LDFRT has been explored as a palliative treatment option in prior and ongoing clinical trials [52, 53]. Twice a day radiation regimens have a proven track record of feasibility and efficacy in squamous cell carcinoma of the head and neck as well as small cell lung cancer and have been investigated in non small cell lung cancer and [54-56], as does the use of palliative radiation regimens administered at set intervals that can be tailored to response and toxicities, such as the QUAD-SHOT regimen [57, 58].

2.4 Rationale

Clinical and nonclinical data suggest that combining immunotherapy agents that target 2 non-overlapping pathways such as MEDI4736 and tremelimumab may result in improved response rates relative to monotherapy with either agent alone [59]. Support for this is seen in mouse syngeneic models of transplantable solid tumors demonstrating superior anticancer activity of the combination therapy compared with monotherapy. Refer to the MEDI4736 IB for a full description of these results. Furthermore, clinical data from the combination of CTLA-4 and PD-1 blockades in melanoma have resulted in higher 1-year survival and an ORR of 40% compared to either agent alone, with rapid, deep and durable responses [59]. The combination of these agents has also demonstrated improved response as compared to single agent immune checkpoint blockade in a randomized controlled trial [60]. Additional support has been observed in sponsored studies with the preliminary efficacy and safety data available for Study D4190C00006 (see above).

Study D4190C00006 is a Phase Ib dose-escalation study to establish safety, PK/pharmacodynamics, and preliminary antitumor activity of MEDI4736 + tremelimumab combination therapy in patients with advanced NSCLC. The dosing schedule utilized is MEDI4736 (every 4 weeks [q4w]) up to Week 48 (12 months), combined with tremelimumab q4w up to Week 24 for 7 doses, then tremelimumab every 12 weeks (q12w) for 2 additional doses for up to 12 months. Preliminary efficacy, safety and clinical data summarized above demonstrate that the combination can be safely combined with evidence of clinical activity.

Despite the improved response rates seen with the combination of CTLA-4 and PD-L1 inhibitors across multiple disease types, there is still a need to improve response rates further to increase the potential for long term clinical benefit. In lung cancer, preliminary data indicate that there will be an increasing population of patients who have failed to respond to PD-1 directed therapies. Although response rates may be increased with combined checkpoint blockade, the majority of patients will likely not respond. In patients with microsatellite stable colorectal cancer, few responses have been observed with single or combination checkpoint blockade. These data highlight the need for further potentiation of the immune system.

Specifically, by increasing antigen presentation, anti-tumor immune responses, and immune infiltration, targeted radiation has the potential to increase response rates to combined checkpoint blockade in these diseases, as evidenced by preclinical studies that have elucidated mechanisms of synergy that extend across multiple disease types [38]. This immune potentiating effect of radiation will be evaluated in the context of this trial. We further explore whether LDFRT may serve as an efficient means of immune potentiation in the setting of combined checkpoint blockade.The use of LDFRT in this study will allow for repeated cycles of radiation to be

delivered with checkpoint blockade, which is not usually feasible with higher dose regimens and may have additional immune stimulating effects extrapolating from the preclinical data that demonstrated superiority of multiple fraction radiation regiments as compared to single dose regimens [61]. Similar to vaccination in infectious disease, repeated administration of radiation could potentially help generate a more robust and durable anti-tumor immune response.

Specifically, this trial will enroll two cohorts of patients. The first cohort will include patients with non-small cell lung cancer that have previously progressed on prior PD-1pathway directed therapy. This randomized phase 2 cohort will test the hypothesis that either low or high dose radiation will improve response rates in this setting. The second cohort will include patients with metastatic colorectal cancer (excluding patients with known microsatellite instability), in which checkpoint blockade alone is expected to have little effect. Here, a two-stage Simon design will evaluate whether the addition of low or high dose radiation to this regimen will result in promising response rates. The combination of radiation and concurrent immune checkpoint blockade is relatively novel; therefore, we will also carefully monitor safety and toxicity on this protocol. The potential overlapping toxicity should be limited to the local effects of radiation including pneumonitis, skin inflammation and swelling, lymphopenia and general symptoms such as fatigue. However, initial analyses conducted by our group and others have not suggested significant increases in toxicity with the combination of radiation and immune checkpoint blockade [62, 63], including aptients whom received combined concurrent CTLA-4/PD-1 blockade [64]. Of note, several of these patients received radiation dose to the lung or colon, without any evidence of grade-3 or higher pneumonitis or colitis within the radiation treatment field, a reasuring deature that was also observed in our recently published multicenter analysis [65]. These are two potential theoretic concerns with the combination of radiation and immune checkpoint blockade, although the risk of these radiation induced side effects are likely reduced with the use of targeted radiation fields mandated in this protocol.

2.5 Correlative Studies Background

We plan a series of in-depth correlative studies to help identify the mechanism of action of combined checkpoint blockade in combination with radiation, identify biomarkers of response, and explain the mechanisms governing treatment response or failure. This study incorporates serial tissues samples pre- treatment, during therapy and at progression. These studies will also help us evaluate the immunomodulatory effects of different doses of radiotherapy in combination with dual checkpoint blockade of PD-1 and CTLA-4. Finally, by incorporating a tumor type in which anti-tumor activity with PD-1 and combined PD-1 plus CTLA-4 inhibition has been demonstrated (NSCLC) [4, 5, 9] and a cohort in which response is unproven (MSS CRC) we can evaluate for varying mechanisms of treatment resistance.

<u>Integrated biomarkers - PD-L1 expression, CD3+, CD8+ T-cell infiltration</u>

Data from ongoing studies with MEDI4736 and other agents targeting the PD-1/PD-L1 pathway suggest, as shown in a number of tumor types (e.g., NSCLC, renal cell carcinoma, and melanoma), that monotherapy may be more efficacious for tumors with PD-L1-expression. For example, data presented by Roche at the Annual Meeting of the American Society of Clinical Oncology 2013 [66] suggested that PD-L1 expression in NSCLC, melanoma, and renal

cell carcinoma patient cohorts is associated with greater clinical benefit from anti-PD-L1 treatment. Using a proprietary assay for PD-L1 immunohistochemistry (IHC), a 36% ORR was observed in patients who had PD-L1-positive tumors, 33% with PR and 50% with SD. In contrast, in patients with PD-L1-negative tumors, only a 13% ORR was observed, 33% with PR and 28% with SD. Similarly, in data presented by Bristol-Myers Squibb at the Annual Meeting of the American Society of Clinical Oncology 2013 [67], PD-L1 staining, when assessed using a different method and scoring algorithm, appeared to be associated with greater clinical benefit in patients treated with nivolumab (anti-PD-1). A 44% ORR was observed in patients with PD-L1–positive tumors versus a 17% ORR in patients with PD-L1–negative tumors, with patients with PD-L1–positive tumors having a higher PFS (9.1 versus 2.0 months) and OS than patients with PD-L1-negative tumors (21 versus 12 months). Similar patterns were seen in a data set presented by Merck & Co at the World Conference on Lung Cancer [68] and in a prospective trial evaluating PD-L1 expression in patients treated with pembrolizumab [68]. Therefore, it appears that the selection of patients based on PD-L1 expression levels within the tumor microenvironment may improve the probability and/or quality of responses to PD-1 pathway-targeting agents and may have merit as a patient enrichment tool.

Response to dual blockade of the PD-1 and CTLA-4 checkpoint may be less dependent on PD-L1 expression[60]. Pre-clinical data suggest that radiotherapy may upregulate intratumoral PD-L1 expression[40] but little is known about the dose response of these effects. Additionally little is known about how the pattern of expression (i.e., tumor cells vs. infiltrating immune cells) affects response. According to a recent publication[69] roughly 50% of NSCLCs express PD-L1 in tumor cells and 50% in tumor infiltrating immune cells. About 15% of CRCs express PD-L1 in tumor cells but about 50% in tumor infiltrating immune cells. Data presented at ASCO and SITC indicate that MEDI4736monotherapy response rates in NSCLC are 27% in PD-L1 positive tumors and 5% in PD-L1 negative tumors. In patients with dual checkpoint blockade (MEDI4736+ tremelimumab) the response rate was 35% in PD-L1 positive tumors and 22% in PD-L1 negative tumors; however, preliminary data suggests that PD-L1 expression could potentially serve as a predictive biomarker in this setting (Hellman et al. ASCO 2016).

In this study, we will examine PD-1 expression as a predictor of response in all patient cohorts and treatment arms, investigating if PD-L1 expression as a biomarker of response in patients treated with dual checkpoint inhibition in NSCLC or colorectal cancer in the setting of low or high dose radiation. Additionally, sequential biopsies, when feasible, will allow us to evaluate the impact of radiotherapy + dual checkpoint inhibition on PD-L1 expression. When available, we will also collect data in regards to prior PD-L1 testing performed (date, type of testing, result).

In addition to PD-L1 expression, increased numbers of tumor infiltrating lymphocytes have also been associated with benefit following treatment with PD-1 pathway blockade. CD8+ T-cells present at the invasive front margin between tumor and stroma was associated with favorable response in patients with metastatic melanoma treated with the PD-1 inhibitor pembrolizumab [70]. Similarly, in patients with mismatch repair deficient tumors, CD8+ T-cells, particularly at the invasive front margins, were associated with a trend towards response or stable disease [14]. Radiation has also been demonstrated to impact levels of tumor infiltrating T-cells in animal models and clinical series [71, 72]. Interestingly, this effect may extend outside of the radiation

treatment field in patients treated with checkpoint blockade [8]. Therefore, we will also evaluate T cell infiltration in the tumor microenvironment as a predictor of outcome and also determine changes in this parameter induced by low and high dose radiation.

Multiplex Immunofluorescence – Spatial Analysis of the Immunologic Tumor Microenvironment

As mentioned above, TILs and a T-cell inflamed phenotype have been linked with response to CTLA-4 checkpoint blockade in melanoma[73, 74]. Exclusion of T-cells in the tumor microenvironment has also been linked with lack of response to checkpoint inhibition[75] with down-regulation of CCL4 mediated dendritic cell recruitment as one potential mechanism[75]. RT has been demonstrated to induce TILs[45] and may potentially overcome this mechanism of resistance to checkpoint blockade. Our unpublished data suggests that RT can induce CCL4 expression and increase TILs. These studies will examine the density and subtype of TILs using markers such as CD3, CD4, CD8, CD56, FoxP3, and PD-1 and integrate spatial proximity data to determine whether a combined analyses of features of the tumor microenvironment such as PD-L1 expressing tumor cells in proximity to CD8+, PD-1 expressing T-cells is a better predictor of response to combined checkpoint blockade than single markers in isolation. We will also examine changes in the tumor microenvironment that occur as a result of if high or low dose radiotherapy in combination with dual checkpoint blockade.

Mutational Burden

Mutational burden and antigenic load are thought to represent a surrogate for tumor antigenicity and have been linked with response to checkpoint blockade in NSCLC[76]. The purpose of these studies is to perform whole exome sequencing to examine mutational load as a biomarker of response to radiotherapy + dual checkpoint inhibition in patients with NSCLC and to define potential tumor antigens.

RNA seq

The purpose of these studies will be to examine the intratumoral and peripheral gene signatures and correlate with treatment outcomes in a hypothesis generating manner. Genes examined will include cytokines, chemokines, markers of T-cell exhaustion, and canonical pathways of immune activation or suppression including indolamine 2,3 dioxygenase. RNAseq will be used to identify infiltrating immune cell populations using deconvolution techniques and also confirm expression of predicted neoantigens.

CyTOF

The purpose of these studies will be a detailed examination of immune cell subsets and functionality in the periphery and in the tumor and to correlate these readouts with treatment response in a hypothesis-generating manner.

Luminex

The purpose of these studies will be to examine systemic cytokine and chemokine signatures pre-therapy and during therapy and to correlate these readouts with treatment response in a hypothesis generating manner.

2.6 Exploratory Patient Reported Outcomes

The Patient-Reported Outcomes version of the CTCAE was designed for patients to report their symptomatic AEs in a complementary manner to clinician graded CTCAE AE items. https://healthcaredelivery.cancer.gov/pro-ctcae) While the measurement system has been validated, the current use of PRO-CTCAE in clinical trials remains exploratory. Clinician reported AE items remains the safety standard. There is no real-time review of the patients' responses. Patients are encouraged to report their concerning symptoms to their physicians and/or nurses.

In this study, the Comprehensive Adverse Event and Potential Risk list (CAEPR) has identified multiple symptomatic AEs to be monitored through clinician reporting. These symptomatic AE items can be reported by patients through the PRO-CTCAE. Patients will be asked to respond to 24 questions that represent 13 AE items (**diarrhea, nausea, abdominal pain, vomiting, fatigue, decreased appetite, headache, shortness of breath, fever, night sweats, general pain, cough, itching and rash**). For each AE item, the patient may be asked 1-3 questions for the presence, frequency, severity and level of interference (see Appendix C). Patients will score their responses 0 to 5 at baseline and every 2 weeks for the first two cycles (8 weeks) and the once every 4 weeks at the beginning of each subsequent cycle for a total of 8 cycles.

The patient scores do not correspond to clinician grading, particularly as clinicians use medical judgement to grade based upon a safety concern. Patients are providing their assessment of the severity, frequency and level of interference. The collection of both patient and clinician offers the opportunity to explore levels of severity and interference that correspond with protocol specific events. PRO-CTCAE scores are not to be used for protocol specific dose modifications. Patients are to be instructed to contact their clinical team for any concerning symptoms.

The PRO-CTCAE data will be evaluated for data quality, to characterize baseline symptom status of patients on study, to explore the development of symptomatic AEs and their change over time. Feasibility of the electronic collection as well compliance of patients with the reporting will be captured. In addition, patient reported symptomatic AE scores will be analyzed in an exploratory way with other relevant clinical information including, but not limited to, collections of symptomatic AEs, clinician graded AEs, and laboratory information.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed non-small cell lung cancer (cohort 1) or colorectal cancer (cohort 2)

3.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm (≥2 cm) with conventional techniques or as ≥10 mm (≥1.5 cm) with spiral CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease. See also 3.1.7 as all measurable/target lesions must not be located with in the planned radiation field.

3.1.3 Patients in both cohorts must have progressive disease following prior therapy. Specifically:

- Cohort 1 (NSCLC): Patients must have evidence of radiologic or clinical disease progression during previous treatment with systemic PD-1 directed therapy and/or have been deemed not to derive clinical benefit from PD-1 directed treatment. This includes patients who demonstrated an initial response and subsequent progression. No prior treatment with chemotherapy or targeted agents are required. Intervening therapy is allowed between previous PD-1 directed treatment and there is no required interval from prior PD-1 treatment required. PD-1 directed treatment includes treatment with antibodies targeting the PD-1 receptor such as pembrolizumab or nivolumab, as well as PD-L1 targeted antibodies such as MEDI4736(durvalumab), atezolizumab and avelumab. These agents may have been administered as part of a clinical trial.
- Cohort 2 (Colorectal cancer): Patients must have progressed on ≥ one -line chemotherapy.

At least 21 days must have elapsed from prior systemic therapy(chemotherapy or radiation).

3.1.4 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of MEDI4736in combination with tremelimumab and radiation in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.5 ECOG performance status ≤1 (Karnofsky ≥60%, see Appendix A) and life expectancy greater than 6 months. Furthermore, enrollment of patients with greater than 10 measurable lesions is discouraged.

3.1.6 Patients must have normal organ and marrow function independent of transfusion for at least 7 days prior to screening and independent of growth factor support for at least 14 days prior to screening as defined below:

– Hgb	>=9g/dl
– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– total bilirubin	<=1.5 x normal institutional limits. This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent

		hyperbilirubinemia[predominantly unconjugated bilirubin] in the absence of evidence of hemolysis or hepatic pathology), who will be allowed in consultation with their physician.
–	AST(SGOT)/ALT(SGPT)	≤2.5 × institutional upper limit of normal; for patients with hepatic metastases, ALT and AST <=5x ULT
–	creatinine clearance	Measured creatinine clearance (CL) >40 mL/min OR Calculated creatinine clearance (CL) >40 mL/min as determined by Cockcroft-Gault (using actual body weight) Males: Creatinine CL = Weight (kg) × (140 - Age) (mL/min) 72 × serum creatinine (mg/dL) Females: Creatinine CL = Weight (kg) × (140 - Age) × 0.85 (mL/min) 72 × serum creatinine (mg/dL)

3.1.7 Patients must have at least one lesion that has not previously been irradiated (and is not within a previously radiated field) and for which palliative radiation is potentially indicated and could be safely delivered at the radiation doses specified in this protocol. This lesion must not be the only measurable lesion (as defined in 3.1.2) so that it is still possible to determine the response rate outside of the radiation treatment field. This lesion must not be within the CNS (brain or spinal cord) or requiring urgent or emergent palliative radiation given the timing of radiation specified on this protocol. Furthermore, this lesion:

- For cohort 1 (NSCLC cohort) – the lesion to be irradiated must be in the lung, lymph nodes, adrenal gland or liver
- For cohort 2 (colorectal cohort) – the lesion to be irradiated must be in the liver

3.1.8 The effects of MEDI4736and tremelimumab on the developing human fetus are unknown. For this reason and because radiation is known to be teratogenic, evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients is required. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced oophorectomy with last menses >1 year ago, had

chemotherapy-induced menopause with >1 year interval since last menses, or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).

Female patient of child-bearing potential

- Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception (see table) from the time of screening and must agree to continue using such precautions for 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy. Non-sterilised male partners of a female patient must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

Male patients with a female partner of childbearing potential

- Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from screening through 180 days after receipt of the final dose of durvalumab + tremelimumab combination therapy or 90 days after receipt of the final dose of durvalumab monotherapy. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.

- Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (see table).

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly are described inthe tab;e below. Note that some contraception methods are not considered highly effective (e.g. male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Highly Effective methods of contraception (<1% failure rate)

Barrier/Intrauterine methods	Hormonal Methods
• Copper T intrauterine device • Levonorgesterel-releasing intrauterine system (eg, Mirena®)[a]	• Implants: Etonogestrel-releasing implants: e.g. Implanon® or Norplan® • Intravaginal Devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g. NuvaRing® • Injection: Medroxyprogesterone injection: e.g. Depo-Provera® • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: e.g. Ortho Evra® • Minipillc: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone based pill

[a] This is also considered a hormonal method

Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

3.1.9 Ability of a patient or a Legally Authorized Representative (LAR) to understand and the willingness to sign a written informed consent document.

3.1.10 Body weight > 30 kg.

3.1.11 Must have a life expectancy of at least 12 weeks

3.1.12 **Cohort specific eligibility requirements:**

3.1.12.1 Cohort 1 (NSCLC cohort)

3.1.12.1.1. Ability to undergo a fresh tumor biopsy for the purpose of screening for this clinical trial (including able and willing to give valid written consent) to ability or to provide an available archival tumor sample taken less than 3 months prior to study enrollment (and not obtained prior to progression on a PD-1/PD-L1 inhibitor) if a fresh tumor biopsy is not feasible with an acceptable clinical risk. Tumor lesions used for fresh biopsies should be the same lesions to be irradiated when possible and should not be the same lesions used as RECIST target lesions, unless there are no other lesions accessible. Additional, optional archival tumor tissue is also requested from before the prior PD-1 directed therapy.

3.1.12.2 Cohort 2 (Colorectal cohort)

3.1.12.2.1. Ability to undergo a fresh tumor biopsy for the purpose of screening for this clinical trial (including able and willing to give valid written consent) to ability or to provide an available archival tumor sample taken less than 3 months prior to study enrollment if a fresh tumor biopsy is not feasible with an acceptable clinical risk. Tumor lesions used for fresh biopsies should be the same lesions to be irradiated when possible and should not be the same lesions used as RECIST target lesions, unless there are no other lesions accessible.

3.1.12.2.2. MSS tumor as documented by either:
- IHC testing that does not suggest loss of MLH-1, MSH-2, PMS2 or MSH6.
- PCR testing that does not suggest MSI

3.2 Exclusion Criteria

3.2.1 Patients who have had systemic(chemotherapy, biologic therapy or radiotherapy) within 3 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study

3.2.2 Receipt of prior radiotherapy or condition for any reason that would contribute radiation dose that would exceed tolerance of normal tissues, at the discretion of the treating physician.

3.2.3 Patients who have not recovered from adverse events due to prior anti-cancer therapy (*i.e.*, have residual toxicities > Grade 1)

3.2.4 Patients who are receiving any other investigational agents.

3.2.5 Patients with untreated brain metastases, spinal cord compression, or leptomeningeal carcinomatosis should be excluded from this clinical trial because of their poor prognosis, because of symptoms that may arise from inflammatory reactions, and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. Patients whose brain metastases have been treated may participate provided they show radiographic stability (defined as 2 brain images, both of which are obtained after treatment to the brain metastases. These imaging scans should both be obtained at least four weeks apart and show no evidence of intracranial progression). In addition, any neurologic symptoms that developed either as a result of the brain metastases or their treatment must have resolved or be stable either, without the use of steroids, or are stable on a steroid dose of ≤10mg/day of prednisone or its equivalent <<and anti-convulsants>> for at least 14 days prior to the start of treatment

3.2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to tremelimumab and MEDI4736or previous toxicity attributed to MEDI4736or other PD-1 or PD-L1 directed therapy that led to drug discontinuation.

3.2.7 Prior exposure to immune-mediated therapy, including durvalumab and tremelimumab, except for anti-PD-1 or anti_PD-L1 therapy (including durvalumab) in NSCLC patients. This includes anti-CTLA-4 agents (prior treatment with these agents is NOT allowed in either cohort) and, excludes therapeutic anticancer vaccines. Exposure to other investigational agents may be permitted after discussion with the Study PI.

3.2.8 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, uncontrolled hypertension, pneumonitis, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.9 Pregnant women are excluded from this study because MEDI4736(durvalumab), tremelimumab are immune checkpoint inhibitors with the potential for teratogenic or abortifacient effects, as is radiation therapy. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with MEDI4736(durvalumab), tremelimumab and radiation, breastfeeding should be discontinued if the mother is treated with MEDI4736(durvalumab), tremelimumab and radiation.

3.2.10 Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab + tremelimumab combination therapy, whichever is later.

3.2.11 HIV-positive patients are ineligible due to the risks associated with immune checkpoint blockade. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.2.12 Any concurrent chemotherapy, immune therapy, biologic, hormonal therapy for cancer treatment.

3.2.13 Current or prior use of immunosuppressive medication within 14 days before the first dose of their assigned IP. The following are exceptions to this criterion:
- Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection)
- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
- Steroids as pre-medication for hypersensitivity reactions (eg, CT scan pre-medication)

3.2.14 Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.

3.2.15 History of allogeneic organ transplantation

3.2.16 Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease, diverticulitis (with the exception of diverticulosis). sarcoidosis syndrome, or other serious GI chronic conditions associated with diarrhea; systemic lupus erythematosus; Wegener syndrome[granulomatosis with polyangiitis]; Graves' disease; rheumatoid arthritis; hypophysitis; uveitis; sarcoidosis syndrome, etc.) within the past 3 years prior to the start of treatment. The following are exceptions to this criterion:
- Patients with vitiligo or alopecia
- Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement or psoriasis not requiring systemic treatment
- Any chronic skin condition that does not require systemic therapy
- Patients without active disease in the last 5 years may be included but only after consultation with the study physician
- Patients with celiac disease controlled by diet alone

3.2.17 History of another primary malignancy except for
- Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of study drug and of low potential risk for recurrence [SEP]
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated carcinoma in situ without evidence of disease (eg, cervical cancer in situ)

3.2.18 Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from electrocardiograms (ECGs) using Fridericia's Correction. Abnormal ECGs should be repeated.

3.2.19 History of active primary immunodeficiency

3.2.20 Known history of previous clinical diagnosis of tuberculosis

3.2.21 Active infection including hepatitis B (known positive HBV surface antigen (HBsAg) result or, hepatitis C. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA. Negative serologies documented over the past year are sufficient evidence of this.

3.2.22 Receipt of live, attenuated vaccine within 30 days prior to the first dose of investigational treatment. Note: Patients, if enrolled, should not receive live vaccine during the study and up to 30 days after the last dose of investigational treatment.

3.2.23 Any condition that, in the opinion of the Investigator, would interfere with evaluation of the investigational treatment or interpretation of patient safety or study results

3.2.24 Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria

-Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab may be included only after consultation with the Study Physician.

3.2.25 **Cohort specific exclusion criteria:**

3.2.25.1 Cohort 1 (NSCLC cohort)

3.2.25.1.1. In regards to administration of prior anti-PD-1 or anti PD-L1 antibodies, a patients:

Must not have experienced a toxicity that led to permanent discontinuation of prior immunotherapy.

All AEs while receiving prior immunotherapy must have completely resolved or resolved to baseline prior to screening for this study.

Must not have experienced a ≥ Grade 3 immune related AE or an immune related neurologic or ocular AE of any grade while receiving prior immunotherapy. NOTE: Subjects with endocrine AE of ≤ Grade 2 are permitted to enroll if they are stably maintained on appropriate replacement therapy and are asymptomatic.

Must not have required the use of additional immunosuppression other than corticosteroids for the management of an AE, not have experienced recurrence of an AE if re-challenged, and not currently require maintenance doses of > 10 mg prednisone or equivalent per day.

3.2.25.1.2. Eligibility for FDA-approved agents targeting the EGFR, ROS1 or ALK pathway, which should be evaluated as per standard of care. Exceptions to this requirement may be considered on a case-by-case basis by the principal investigator if the patient was previously treated with another targeted agent.

3.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research.

Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

4.1.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN or RAVE or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	**IVR**	**NPIVR**		**AP**	**A**
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔		✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔		✔	
HSP/GCP training	✔	✔		✔	
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔		✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval.

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572

An active status on a participating roster at the registering site

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the 10021 protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP-IAM username and password.

- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select LAO-MA036 and protocol #10021.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Requirements For 10021 Site Registration:

-
- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

4.2.3 Requirements for Protocol #10021 Site Registration for Sites Participating in the Medidata Patient Cloud ePRO to collect PRO-CTCAE Items

a. Medidata Patient Cloud ePRO

This study includes the use of Medidata Patient Cloud ePRO (electronic patient-reported outcomes). After the patient is registered to the trial via OPEN, and if the patient is willing to participate in electronic data collection, the site staff will then complete a registration for the patient to the Patient Cloud ePRO through iMedidata. Note: Site staff must have already completed required eLearning for the Patient Cloud ePRO application to register a patient and information about the training is in the ePRO Appendix. The registration to the Patient Cloud ePRO will create a unique patient registration code that the site staff will provide to the patient. The patient (with assistance from the site staff) should be instructed to download the Patient Cloud ePRO app onto his/her own device (IOS, Android, phone or tablet) and use the unique patient registration code to create an account. Once the patient's account is set up, the patient will be able to complete the submission of patient reported outcomes electronically for the trial.

For sites providing a shared institutional device for use by multiple patients on site:

- The site staff should assist the patient with access and registration to the Patient Cloud ePRO app, and the patient can then complete the electronic data submission independently. Site staff may need to assist patients with logging on to the device at each visit.

b. CRA Patient Registration Instructions for ePRO

Please visit the Medidata Learning Tool for reference information on Patient Cloud ePRO for CRAs.

i. The subject registration process starts in iMedidata. Begin by selecting the Patient Cloud ePRO Registration link for your study

ii. The patient management app will display, select your STUDY and SITE from the drop downs and click Launch.
iii. Now you can register your first patient. Create a subject ID and select a Country / Language from the drop down, (these are the only required data fields). The subject initials are optional, but are helpful in identifying which subject ID maps with which activation code. When finished, click Add.
iv. The subject added and will include the date the patient was added, the subject ID, subject initials, (if included) and a unique auto-generated activation code. The activation code is unique for each patient and linked to the subject ID, it is not interchangeable. In addition, there is a status section, which indicates if the patient has registered. When the patient has registered the status will change from "invited" to "registered".

REMINDER- SITE STAFF MUST HAVE ALREADY COMPLETED THE MEDIDATA PATIENT CLOUD TRAINING IN ORDER TO REGISTER STUDY PARTICIPANTS .PLEASE VISIT THE MEDIDATA LEARNING TOOL FOR REFERENCE INFORMATION ON PATIENT CLOUD EPRO FOR CRAS. HTTPS://LEARN.MDSOL.COM/PATIENT-CLOUD/EN/VIDEO-LIBRARY-FOR-PROVIDERS-102101952.HTML

4.2.4 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission
When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

4.2.5 Checking **Site** Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-

IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks..

4.3 Patient Registration

4.3.1 OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:
- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
    - To approve slot reservations or access cohort management: Be identified to Theradex as the "Client Admin" for the studySlot enrollment will be used for the first 10 patients in each arm for the colorectal cancer cohort to allow for the parallel Simon two-stage designs. For the NSCLC cohorts, slot enrollment will be used for the first 20 patient in each arm to allow for an early safety look after 10 patients per arm, and for an interim evaluation of efficacy at 20 patients per arm.
- Have regulatory approval for the conduct of the study at their site.

Prior to accessing OPEN/IWRS, site staff should verify the following:
- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all patients have signed an appropriate consent form and HIPAA

authorization form.

4.3.3 Patient Enrollment Instructions

Patients within the NSCLC cohort will be randomly assigned in a 1:1:1 allocation to MEDI4736(durvalumab)/tremelimumab alone
or to
MEDI4736(durvalumab)/tremelimumab with either high- or low-dose radiation.

Patients enrolled to the colorectal cancer cohort will be randomized in a 1:1 allocation to MEDI4736(durvalumab)/tremelimumab with either high- or low-dose radiation.

The randomization schemes will be developed and conducted separately.
Within each cohort, the randomization will be based on the permuted block method.

4.3.4 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.3.5 Digital RT Submission Using Triad

Patients will have their treatment plans submitted to IROC Rhode Island via TRIAD. See section 5.1 Radiation therapy 9) Compliance criteria for details of the data to be submitted.

TRIAD is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit DICOM, DICOM RT and other objects. TRIAD anonymizes and validates images as they are transferred.

TRIAD Access Requirements

Site radiation therapy staff who will submit data images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account, and be registered as an AP, NPIVR or IVR. Please refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.

To submit data via TRIAD, the site user must be on the site's roster and be assigned the 'TRIAD site user' role in RSS.. Users should contact their site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role.

TRIAD Installations

When a user applies for a CTEP-IAM account with the proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit data. TRIAD installation documentation can be found by following this link https://triadinstall.acr.org/triadclient/

This process can be done in parallel with obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

4.3.6 Patient Registration for ePRO (Medidata Patient Cloud)

This study includes the use of Medidata Patient Cloud ePRO, (electronic patient-reported outcomes). After the patient is registered to the trial, the CRA (Clinical Research Associate) will complete a second registration to the Patient Cloud ePRO. The CRA will create a unique patient registration code by accessing the Patient Cloud ePRO through iMedidata. Patients (with assistance from CRAs) will need to download the Patient Cloud ePRO app onto their own device and use the unique registration code given by the CRA to create an account. Once completed, the patient will be able to complete the submission of patient reported outcomes electronically.

If sites intend to use a shared institutional device, the CRA can assist the patient with access and registration to the Patient Cloud ePRO app, with the patient completing the electronic data submission independently. Detailed instructions are included in Appendix D. If patients will be using devices supplied by the institution, CRAs will need to help the patient log into the device registration to the Patient Cloud are included in Appendix D.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 28 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. All weight-based dosing will be calculated according to the treating institution's standard dosing policy. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Radiation therapy:
In addition to providing palliative benefit, this study attempts to use radiation to engender a systemic immune response in the context of combined checkpoint inhibition. Prior to radiation simulation, initial staging scans will be analyzed in detail. Lesions will be prioritized for treatment as follows (in order of priority): 1) Lesions must be safe to irradiate at the dose prescribed by the protocol as deemed by the treating radiation oncologist and able to meet standardly accepted radiation dose constraints and as specified below; 2) Lesions must be

irradiated for potential palliative benefit as determined by the treating physicians but must not require urgent palliation (e.g. cord compression, pain crisis). Additionally, the following cohort specific rules will be applied when choosing a radiation target.

Cohort 1 (NSCLC patients): Irradiation of 1-2 lesions within the lung, lymph nodes, liver or adrenal glands are allowed. In order of priority, irradiation of: 1) lesions progressing on prior PD-1 directed therapy; 2) liver > lung > adrenals > lymph nodes; and 3) the largest feasibly treated lesion that may provide palliative benefit, is preferred.

Cohort 2 (Colorectal patients): Only irradiation of 1-2 lesions within the liver / porta hepatis are allowed. Irradiation of the largest feasibly treated lesion within the liver complex that may provide palliative benefit is preferred.

The radiation treatment and planning process will proceed as follows:

1) Localization, Simulation and Immobilization:
    a. Immobilization
        i. Patients will be positioned in a stable and comfortable position allowing accurate reproducibility of the target position from treatment to treatment.
        ii. A variety of immobilization systems may be used, including full-body stereotactic frames that surround the patient on three sides and/or full-body, patient-customized rigid pillows (conforming to patients' external contours) . Patient immobilization must be reliable enough to insure that the gross tumor volume (GTV) does not deviate beyond the confines of the planning treatment volume (PTV) with any significant probability (i.e., < 5%).

    b. Radiation CT simulation
        i. The treatment planning process will include CT based simulation with axial imaging every 1.25- 2.5-mm to cover the area(s) of interest.
        ii. Intravenous (i.v.) contrast during the planning CT is optional, but recommended for tumors adjacent to blood vessels and for liver tumors.
        iii. Average phase CT (from 4D CT) is recommended as the baseline CT for radiation therapy planning, but free-breathing and exhale breath-hold CT may also be used.

    c. Internal Motion Management
        i. Internal tumor and organ motion (e.g. due to breathing) must be accounted for during the simulation and planning process.
        ii. Deep inspiration or expiration breath hold is not allowed for initial tumor motion assessment as such assessment generally overestimates free breathing tumor motion. Options for motion assessment included real time fluoroscopy, 4-D CT scanning,
        iii. For targets (e.g. lung, liver, adrenal and thoracic/upper abdominal lymph node targets), that have significant motion 4D-CT planning is mandatory for patients randomized to receive 24 Gy in 3 fractions, and other motion management gating/compression systems may be used.
        iv. In some tumor locations, the assessed tumor motion measurement

indicates that tumor motion (e.g. > 1 cm) would increase the likelihood of resulting in marginal miss or excessive volume of irradiation unless a motion management strategy is employed.

v. Acceptable motion management include reliable abdominal compression, linear accelerator beam gating with the respiratory cycle, tumor tracking, and active breath-holding techniques. Internal organ management maneuvers must be reliable enough to insure that the GTV does not deviate beyond the confines of the PTV with any significant probability (i.e., < 5%).

d. Daily Target Localization

i. Image-guided raidaiton therapy (IGRT) is mandatory for patients randomized to receive 24 Gy in 3 fractions.

ii. Isocenter or reference point port localization images should be obtained on the treatment unit immediately before each treatment to ensure proper alignment of the geometric center (i.e., isocenter) of the simulated fields. These IGRT images can be obtained with planar kV imaging devices, an in-room helical CT device, tomotherapy helical CT, cone-beam CT equipment, of standard EPID imaging.
For SBRT treatments, all IGRT systems must be checked daily to guarantee coincidence between the imaging coordinate system and the treatment coordinate system. This test is required by the AAPM Task Group 142 report and is described in detail in both the ASTRO/ACR practice guideline on SBRT available at:http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/ro/stereo_body_radiation and the ACR Technical Standard on IGRT available at:http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/med_phys/monitor_IGRT.
This test is particularly important when the treatment equipment is not equipped with any device that allows direct visualization of anatomical structures using the treatment beam. For example, this test must be performed routinely for the CyberKnife, Tomotherapy units as well as any BrainLab equipment that does not include an electronic portal imaging device (EPID) that intercepts the treatment beam.

iii. Fiducial markers may be placed for localization of soft tissue targets depending on institutional practice, but should be considered for targets in the liver and adrenal for participants on Arm A.

2) Contours: Tumor contours will be defined by the physician and radiation oncology staff:

- Gross tumor volume (GTV): These volumes include gross disease and further details regarding contouring technique are shown in the Table below. Elective irradiation to other areas is not permitted. For targets that have significant motion (e.g. lung or liver targets), 4D-CT planning with is mandatory for patients randomized to receive 24 Gy in 3 fractions, and other motion management (e.g. gating/compression systems) may be used. Delineation of an internal target volume (ITV) in these cases

is mandatory using the 4D-CT data set or maximum intensity projections (MIP) for lung tumors and minimum intensity projection (MinIP) for liver metastases as appropriate. Sites should be aware that the (MIP/MinIP) should be used with caution because the MIP reconstruction for lung or MinIP reconstruction for liver may erroneously define an ITV in cases of significant irregular breathing or when tumors abut soft tissue structures (e.g., the diaphragm for MIP) or fat (for the MinIP). The exact margins are patient- specific. Additional imaging modalities (e.g. PET, MRI, diagnostic CT with contrast) may be fused with the planning CT to guide GTV-delineation.

- CTV: Clinical tumor volume. An optional 0-1 cm margin on GTV is allowed when determining the CTVs at the treating radiation oncologist's discretion to account for any uncertainty or microscopic disease. This margin may be expanded based on clinical judgment with permission of the principal investigator.
- PTV: A 5mm planning tumor volume (PTV) margin will be uniformly added to the CTV will also be included to account for set up variation, as appropriate to each individual lesion.

Planning Parameter	**Lung**	**Liver**	**Adrenals**	**Mediastinal/ Cervical Lymph Nodes**
CT window/level	Pulmonary/ mediastinal	Hepatic	Soft Tissue	Pulmonary/ mediastinal
Additional Optional Studies	PET/CT	PET/CT MRI	PET/CT	PET/CT
Anatomy of focus for multi modality fusion	Bony Anatomy	Liver	Bony Anatomy	Bony anatomy
4DCT	Mandatory	Mandatory	Mandatory	Mandatory for mediastinal LN
OARs	Spinal Cord Brachial Plexus Chest Wall/Rib Esophagus Great Vessels Heart Lung Skin Trachea/Bronchial Tree	Spinal Cord Chest Wall/Rib Dudoenum Esophagus Jejunum/Ileum Large Bowel Heart Kidneys Liver Great Vessels (IVC) Lungs Stomach Skin	Spinal Cord Chest Wall/Rib Dudoenum Esophagus Jejunum/Ileum Large Bowel Kidneys Liver Great Vessels Renal Hilum/vascular trunk Stomach Skin	Spinal Cord Brachial Plexus Esophagus Great Vessels Heart Lung Skin Trachea/Bronchial Tree

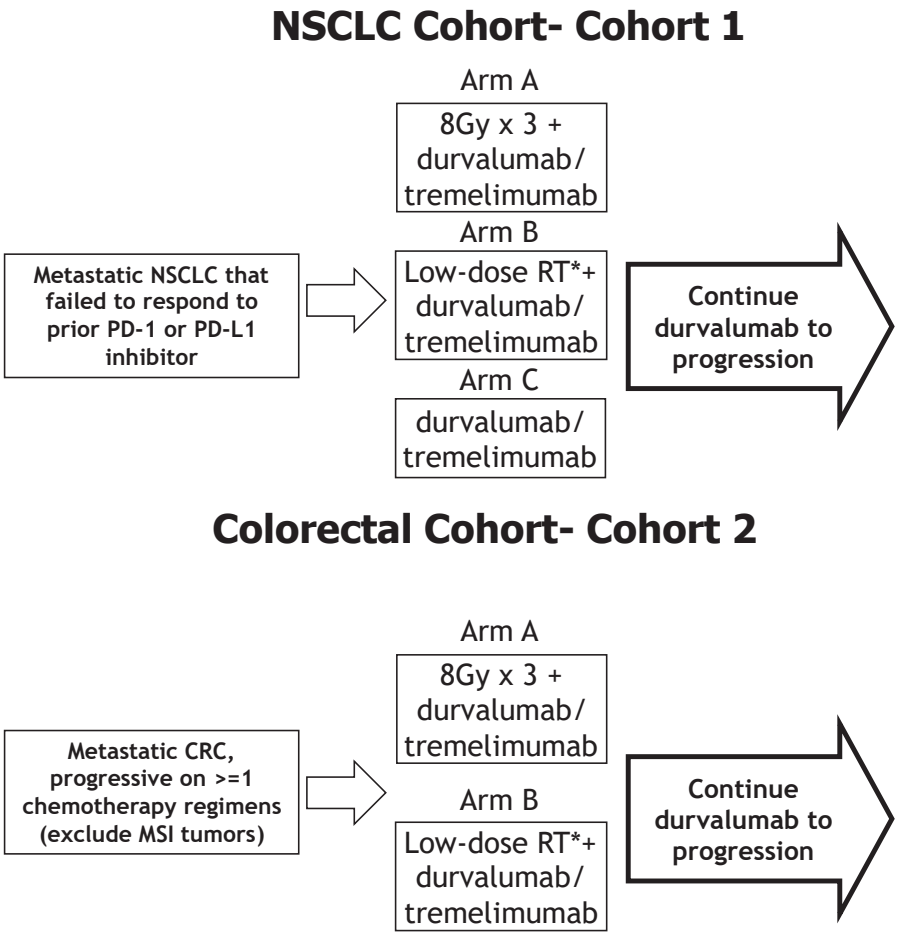
- Several contours of the organs at risk will be defined by the physician and/or treatment planner if visible within the axial slices covered by the PTV using existing guidelines as described below. These contours should be labeled according Standard Naming Conventions listed below in parentheses as per
    - Spinal cord (SpinalCord)
        - The spinal cord will be contoured based on the bony limits of the spinal canal. The spinal cord should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV.
    - Brachial plexus (BrachialPlex_L and BrachialPlex_R)
        - The defined ipsilateral brachial plexus originates from the spinal nerves exiting the neuroforamina on the involved side from around C5 to T2. However, for the purposes of this protocol, only the major trunks of the brachial plexus will be contoured using the subclavian and axillary vessels as a surrogate for identifying the location of the brachial plexus. This neurovascular complex will be contoured starting proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries) and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the second rib.
    - Esophagus (Esophagus)
        - The esophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia. The esophagus should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV and ideally from the post-cricoid space to the GE junction.
    - Great Vessels (GreatVes)
        - The great vessels (aorta and vena cava, not the pulmonary artery or vein) will be contoured using mediastinal windowing on CT to correspond to the vascular wall and all muscular layers out to the fatty adventitia. The great vessel should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 cm below the inferior extent of the PTV. For right sided tumors, the vena cava will be

      contoured, and for left sided tumors, the aorta will be contoured
    - Heart/pericardium (Heart)
        - The heart will be contoured along with the pericardial sac. The superior aspect (or base) for
        - purposes of contouring will begin at the level of the inferior aspect of the aortic arch (aortopulmonary
        - window) and extend inferiorly to the apex of the heart.
    - Trachea and proximal bronchial tree (Trachea, Bronchus)
        - The trachea and proximal bronchial tree including the mainstem and

lobar bronchi including trachea, the carina, the right and left mainstem bronchi, the right and left upper lobe bronchi, the intermedius bronchus, the right middle lobe bronchus, the lingular bronchus,
    - and the right and left lower lobe bronchito the bifurcation of the first segmental airways will be contoured using mediastinal windows on CT to correspond to the mucosal, submucosa and cartilage rings and airway channels associated with these structures.
- Skin (Skin)
    - The skin will be defined as the outer 0.5 cm of the body surface. As such it is a rind of uniform thickness (0.5 cm) which envelopes the entire body in the axial planes. The cranial and caudal surface of the superior and inferior limits of the planning CT should not be contoured as skin unless skin is actually present in these locations (e.g., the scalp on the top of the head).
- Stomach (Stomach)
    - The entire stomach and its contents should be contoured as a single structure as a continuation of the esophagus and ending at the first part of the duodenum.
- Duodenum (Duodenum)
    - The wall and contents of the 1st, 2nd, and 3rd parts of the duodenum will be contoured as one structure beginning where the stomach ends and finishing as the superior mesenteric artery crosses over the third part of the duodenum
- Jejunum/ilieum (Bowel small)
    - Small bowel from end of duodenum to the ileocecal area.
- Large Bowel (Bowel large)
    - From the ileocecal area to include the ascending, transverse, descending and sigmoid colon as one structure.
- Renal hilum/vascular trunk (Kidney Hilums)
    - The renal artery and vein from the renal cortex to the great vessels.
- Liver (Liver)
    - The entire live minus the GTV
- Kidneys (Kidney_L and Kidney_R)
    - Both the right and left kidney, excluding renal pelvis/collecting system, should be contoured in their entirety (the renal cortex)
- Lung (Lungs)
    - Both the right and left lungs should be contoured as one structure. Contouring should be carried out using pulmonary windows. All inflated and collapsed lung should be contoured; however, gross tumor (GTV) and trachea/ipsilateral bronchus as defined above should not be included in this structure.

3) Prescriptions: Patients randomized to higher dose radiation arm (Arm A) will be prescribed a total dose of 24 Gy in 3 fractions. Patients randomized to the lower dose radiation (Arm B) will be prescribed a total dose of 2 Gy in 4 fractions to be repeated with each of the first 4 cycles (total overall dose 8 Gy). In cohort 1 (NSCLC), patients randomized to the no radiation arm (Arm C) will not receive any radiation. Please also

refer to schema below:



Only photons treatments are allowed, and volumetric treatment planning is mandated. Planning may be 3D conformal, IMRT or SBRT, as appropriate to each individual case / lesion to achieve coverage of the PTV target and maintain normal tissue tolerance. The percentage PTV covered to 100% of the prescription dose will be reported along with the maximum hotspot; reasonable effort should be made to keep this greater than 95% while maintaining normal tissue dose constraints as indicated below. Bolus may be used as appropriate. Note that for patients prescribed 24 Gy in 3 fractions, maximum hotspot should not exceed 115% in any case.

4) Timing of radiation treatment:
   - Arm A: Higher dose radiation. Radiation will start on week 2. Three treatments of 8 Gy will generally be delivered every other day. They must not be delivered on consecutive calendar days and more than one fraction may not be delivered on the same day. The total treatment time must not extend over more than 10 calendar days. Shorter treatment courses (approximately 5 days) are favored, but no specific

treatment schedule is mandated to account for weekends, holidays, machine maintenance, etc.

- Arm B: Lower dose radiation: Radiation will start on week 2. Four treatments of 0.5 Gy will be delivered no more frequently than every 6 hours and will be scheduled to occur twice per day over a period of two days. Although treatment is allowed to extend over three calendar days in the case of machine maintenance or patient illness, this is strongly discouraged.
    - Note: Patients enrolled on Arm B should continue to receive lower dose radiation (2 Gy delivered in 4 fractions) with each of the first 4 cycles of treatment (weeks 2, 6, 10, 14). The radiation target and treatment plan need not change between treatment courses; however, if there is clinical or radiographic evidence of complete resolution of the irradiated lesion, this lesion should not be treated with additional radiation. If this occurs and there is another lesion appropriate for palliative radiation that satisfies the above criteria, additional lower dose radiation may be considered after discussion with the study PI. This irradiation of a new lesion will not be counted as tumor progression.

5) Dosimetry:
    a. Only photons treatments are allowed, and volumetric treatment planning is mandated.
    b. Planning may include 3D conformal, IMRT or SBRT, as appropriate to each individual case / lesion to achieve coverage of the PTV target and maintain normal tissue tolerance. IROC credentialing is required for the most complex modality (IMRT>3D) used by each center as well as for IGRT (see section 4.2.2).
    c. PTV coverage should ideally be 95% of PTV conformally covered by the prescription isodose surface (D95=100%), , while maintaining normal tissue dose constraints as indicated below. Bolus may be used as appropriate
    d. The percentage PTV covered to 100% of the prescription dose will be reported along with the maximum hotspot;.
    e. Doses higher than the prescription isodose (i.e., hotspots) should be manipulated to occur within the planning target volume.
    f. Note:For patients prescribed 24 Gy in 3 fractions, maximum hotspot should not exceed 115% in any case.
    g. For purposes of dose planning and calculation of monitor units for actual treatment, this protocol requires tissue density heterogeneity corrections approved by IROC. Examples of appropriate tissue density heterogeneity correction algorithms include properly commissioned superposition/convolution (collapsed cone), AAA, and Monte Carlo. Simple pencil beam and Clarkson algorithms that account for attenuation but not scatter will not be allowed.
    h. For 3D conformal cases, coplanar or non-coplanar beam arrangements will be custom designed for each case to deliver conformal prescription dose distributions.
    i. For IMRT cases, the treatment dose plan may be made up of multiple static beams or arcs, and the apertures are determined by inverse treatment planning
    j. For SBRT cases, either conformal or IMRT techniques are allowed.

i. 3D-conformal SBRT: Three-dimensional coplanar or non-coplanar beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. Non-opposing, non-coplanar beams are preferable. Typically, ≥ 10 beams of radiation will be used with roughly equal weighting. Generally, more beams are used for larger lesion sizes. When static beams are used, a minimum of seven non-opposing beams should be used. For arc rotation techniques, a minimum of 340 degrees (cumulative for all beams) should be utilized. For this protocol, when using a gantry mounted linear accelerator, the isocenter is defined as the common point of gantry and couch rotation for the treatment unit. For other types of treatment units (e.g., tomotherapy or CyberKnife), a reference point in space that is typically positioned at the center of the target is used instead of a mechanical isocenter. For non-IMRT or dose painting techniques, the conformal field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam‟s eye view (i.e., no additional "margin" for dose buildup at the edges of the blocks or MLC jaws beyond the PTV). The only exception will be when observing the minimum field dimension of 3 cm when treating small lesions (see above). As such, prescription lines covering the PTV will typically be the 60-90% line (rather than 95-100% as is common with conventional radiotherapy); however, higher isodoses (hotspots) must be manipulated to occur within the target and limited to 115% per protocol and should not be in normal tissue. The stereotactic reference point (corresponding to the mechanical isocenter for gantry mounted treatment units) will be determined from system fiducials (or directly from the tumor) and translated to the treatment record.

ii. IMRT SBRT: The treatment dose plan will be made up of multiple static beams or arcs and , the apertures are determined by inverse treatment planning.

6) Organs at risk (OAR). Treating radiation oncologists will abide by accepted radiation dose constraints, especially in regards to 24 Gy delivered in 3 fractions. For patients in Arm B, a cumulative dose calculation is also recommended to record dose delivered to OAR. Additionally, for patients prescribed 24 Gy in 3 fractions, maximum hotspot should not exceed 115% in any case.

The following table lists maximum dose limits to a maximum point or to a critical volume for critical organs at risk. Except for the rib, these are absolute limits, and treatment delivery that exceeds these limits will constitute a protocol violation). The dose is listed as total delivered. PTV coverage may be compromised to ensure an acceptable plan. Please use the indicated planning system names for the structures in your treatment planning system.

Note: Maximum point dose will be defined as the maximum dose to a 0.035 cc volume.

Table 5.1: Critical Organ Dose-Volume Limits for Arm A.

Structure Description	Planning System Name	Volume (cc)	Volume Max (Gy)	Max Point Dose (Gy)	Volumetric Constraint	Avoidance Endpoint
Spinal cord	SpinalCord	<0.25	18	19.5		Myelitis
Brachial plexus	BrachialPlexs = BrachialPlex_L + BrachialPlex_R	<3	22.5	24		Plexopathy
Cauda equina	CaudaEquina	<5	21.9	24		Neuritis
Esophagus	Esophagus	<5	21	27		Stenosis/Fistula
Great Vessels	GreatVes	-<5	-21	25.2 (105% of Rx dose)		
Heart/pericardium	Heart	<15-	24-	25.2 (105% of Rx dose)		Pericarditis
Trachea and ipsilateral bronchus	Trachea, Bronchus	<4	15	25.2 (105% of Rx dose)		Stenosis/Fistula
Sacral Plexus	SacralPlex	<5	22.5	24		Plexopathy
Skin s	Skin	<10	22.5	24		Ulceration
Stomach	Stomach	<10	21	24		Ulceration/Fistula
Duodenum	Duodenum	<5	15	24		Ulceration/Fistula
Jejunum/ileium	Bowel_Small	<5	16.2	25.2 (105% of Rx dose)		Ulceration/Fistula
Large Bowel	Bowel_Large	<20	24	25.2 (105% of Rx dose)		Ulceration/Fistula
Renal Hilum	Kidney_Hilums	<15	19.5	-25.2 (105% of Rx dose)		Malignant hypertension
Liver	Liver	700cc spared from volume max	17.1	-		
Kidneys	Kidneys = Kidney_L + Kidney_R	200cc spared from volume max	14.4			
Lung (left and right)	Lungs	1000mL spared from volume max	11.4		V20<10%	
Lung (left and right)	Lungs	1500mL spared	10.5		V20<10%	

		from volume max				
Lung (left and right)		1500mL spared from volume max	10.5			

Rib/Chest wall Dose Constraints
Recent studies have shown that the rib and chest wall in proximity to the treated lesion may represent an organ at risk for complication such as chest wall pain and rib fracture. While target coverage should not be compromised to limit dose to the rib/chest wall, every effort should be made to minimize dose and hostpots to this OAR.

7) Planning Priorities
    a. Successful treatment planning goals are listed above. In general, attempts should be made to successfully satisfy all of the goals without deviation. In some circumstances, improvements can be made to the dosimetry plan beyond simply meeting the specified goals. In other circumstances, clinicians are faced with the prospect of not ideally meeting one or more of the goals (i.e., accepting an acceptable deviation). In this section, we provide priorities in which a most ideal plan for protocol purposes is realized. Suggested priority of planning goals in order of importance is:

        i. Respect spinal cord dose constraints.
        ii. Meet organ constraints other than spinal cord.
        iii. Achieve PTV coverage

8) Technical Factors:
    a. <u>Physical Factors:</u>
        i. Only photon (x-ray) beams produced by linear accelerators,with photon energies of at least 6MVwill be allowed.
        ii. Cobalt-60 and charged particle beams (including electrons, protons, and heavier ions) are not allowed.
        iii. For lung tumor cases, > 10 MV may be used but not > 15 MV, and should be used sparingly only for a limited number (≤ 2) beams that must travel more than a cumulative distance of 10 cm through soft tissue

(not lung) to reach the target .

b. Treatment Platforms
    i. The trial allows most commercially available photon producing treatment units except the exclusion of units described above (e.g., cobalt units and charge particle accelerators). As such, conventional linear accelerators, specialized linear accelerators with image guidance (e.g., TrueBeam, Agility, Novalis, Trilogy, Synergy, Artiste) are allowed. These units can be used with conformal dose delivery or IMRT. Other specialized accelerators (e.g., the CyberKnife® or Tomotherapy) are allowed as long as they meet the technical specifications of the protocol
c. Minimum Field Size
    i. For SBRT treatments, because of uncertainties in beam commissioning resulting from electronic disequilibrium within small beam apertures, an equivalent square field dimension of 3.0 cm is required for any field used for treatment delivery for sites using standard 3-D conformal techniques where nearly all of the PTV is encompassed for each beam.
d. **Dose Verification at Treatment**
    i. Personal dosimeter measurements (e.g., diode, TLD) are not required, but may be obtained for surface dose verification for accessible beams as per institutional preference.
e. Use of Intensity Modulated Radiation Therapy (IMRT) Using Multileaf Collimation
    i. The protocol allows for IMRT, but caution should be utilized when tumor motion is significant since IMRT can result in dosimetric inaccuracies especially in circumstances where tumor motion is either unknown or not properly accounted. Thus, IMRT should only be utilized if tumor motion is less than 5 mm, OR if motion management inherently diminishes motion effects (e.g., gating, breath hold, or tracking).

9) Compliance Criteria
    a. Digital RT Data Submission Requirements

Submission of treatment plans in digital format as DICOM RT is required. Digital data must include CT scans, structures, plan, and dose files. This study uses TRIAD for RT data submission. Use of TRIAD requires several preliminary steps. See section 4.3.5 for details. Additional information can be found at https://www.irocqa.org/Resources/TRIAD for guidelines regarding digital submission using TRIAD. Use of SFTP will also be accepted as an alternate method of data submission on this study. See the instructions for submission of data via SFTP on the IROC Rhode Island website (www.irocri.qarc.org) under Digital Data.

Any items on the list below that are not part of the digital submission may be included with the transmission of the digital RT data.

On-treatment review is NOT required for this study. Within one week of the completion of radiation therapy, detailed treatment data shall be submitted as follows:

i. Treatment Planning System Output

a. RT treatment plans including CT, structures, dose and plan files. These items are included in the digital plan.

b. Dose volume histograms (DVH) for the composite treatment plan for all target volumes and required organs at risk. For all IMRT plans, a DVH shall be submitted for a category of tissue called "unspecified tissue." This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure. DVHs are included in the digital plan.

c. Digitally reconstructed radiographs (DRR) for each treatment field, showing the collimator and beam aperture. Submission of DRR's is not required for IMRT.

d. Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.

i. Supportive data

a. All diagnostic imaging used to plan the target volume. This includes CT, MRI and/or PET. Digital format is required.
b. If the recommended doses to the organs at risk are exceeded, an explanation should be included for review by the IROC and the radiation oncology reviewers.

ii. Forms

a. RT-1 Dosimetry Summary Form

b. Motion Management Reporting Form (if applicable)

c. The RT-2 Radiotherapy Total Dose Record Form

d. A copy of the patient's radiotherapy record including the prescription, and the daily and cumulative doses to all required areas.

Supportive data and forms may be included with the transmission of the digital RT data or submitted separately via e-mail (DataSubmission@qarc.org) or mailed to:

IROC Rhode Island QA Center
640 George Washington Highway, Building B, Suite 201
Lincoln, Rhode Island 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601

Questions regarding the dose calculations or documentation should be directed to:

Protocol Dosimetrist
IROC Rhode Island QA Center
640 George Washington Highway, Building B, Suite 201
Lincoln, Rhode Island 02865-4207

Phone: (401) 753-7600

Fax: (401) 753-7601

b. Dosimetry Compliance

	Per Protocol	**Variation Acceptable**	**Deviation Unacceptable**
Prescription Dose	Delivered daily or total dose to the PTV is within 5% of the protocol dose.	Delivered daily or total dose to the PTV differs from the protocol specified dose by 6-10%	Delivered daily or total dose to the PTV differs from the protocol specified dose by >10%
Dose Uniformity	More than 95% of the PTV receives the prescribed dose.	95% of the PTV receives between 95 and 100% of the prescribed dose	95% of the PTV receives <95% of the prescribed dose. For Arm A maximum dose >115% of the prescribed dose.
Volume	Volumes follow protocol guidelines	CTV or PTV margins are less than the protocol specified margins or excessively large	GTV does not encompass gross disease resulting in inadequate tumor coverage.
Organs at Risk	Dose to all OAR's meets the criteria in Table 5.1 for Arm A.	For Arm A dose to any OAR (except spinal cord and brachial plexus) exceeds the maximum point dose limits in Table 5.1 by more than 2.5%.	For Arm A dose to any OAR (except spinal cord and brachial plexus) exceeds the maximum point dose limits in Table 5.1 by more than 5%. **Dose to spinal cord or brachial plexus may not exceed the limits in Table 5.1.**
Interruptions	Treatment is completed within 10 calendar days for Arm A and 2 calendar days for Arm B.	Treatment is completed within 3 calendar days for Arm B.	Treatment is completed in >10 calendar days for Arm A and >3 calendar days for Arm B.

5.1.1 Tremelimumab and MEDI4736(durvalumab)

1.1.1.1 Regimen Description					
Agent	Premedication; Precautions	Dose	Route	Schedule	Cycle Length
Tremelimumab	Mot routinely	75mg	IV over 1 hour before	Day 1	28 days

	necessary unless prior infusion reaction	Max of 4 doses	MEDI4736/durvalumab; refer to section 8.1.2 for compatible infusion set materials		(4 weeks)
MEDI4736(durvalumab)	Not routinely necessary unless prior infusion reaction	1500mg Max of 13 doses	IV over 1 hour; refer to section 8.1.1 for compatible infusion set materials	Day 1	
Patients will receive tremelimumab 75 mg q4w for 4 doses in combination with MEDI4736, 1500 mg for 4 doses, followed by MEDI4736monotherapy 1500 mg q4w initiated 4 weeks after the last combined dose and administered for up to 9 additional doses. Observation period for post MEDI4736 will be 60 minutes. MEDI4736 infusion will start approximately 1 hour after the end of tremelimumab infusion for the first infusion only. Infusions may be administered consecutively at subsequent infusions at the Investigator's discretion. A window of +/-10 minutes is allowed for infusion of study treatment. A window of +/- 2 days is allowed between cycles.					

5.1.2 Radiation therapy

The individual medical / radiation oncologist may deliver supportive care as indicated. The use of prophylactic steroids before or after the radiation treatments is not allowed. In patients who receive radiation twice per day, at least 6 hours must elapse between treatments.

5.2 Definition of Dose-Limiting Toxicity

Although there is significant safety data for the MEDI4736/ tremelimumab treatment and palliative radiation, the combination is relatively untested, although emerging safety data suggests the combination of the two treatments (specifically in regards to limited palliative radiation treatment fields) do not increase the rates of irAE or radiation toxicity [64]. Although this retrospective data compares favorably to previous studies testing combined checkpoint inhibition, to provide greater confidence in the safety of radiation and combined checkpoint inhibition, DLT's will be monitored in a step-wise fashion and over time. As part of the safety assessment for the NSCLC cohort, complete review of the adverse event data for the first 10 patients assigned to MEDI4736(durvalumab)/tremelimumab/high-dose RT and for the first 10 patients assigned to treatment with MEDI4736(durvalumab)/tremelimumab/low-dose RT will occur after completion of two cycles of therapy. If three of more patients within a therapy arm experience one or more pre-specified dose-limiting toxicities the addition of RT will be considered too toxic and enrollment to that arm will stop. If this occurs in the high-dose radiation arm, all safety data from that arm will be reviewed and a protocol amendment may be considered.

Concurrent with the end of the first stage of each Simon design for the colorectal cohort, a complete safety review of adverse event data will be conducted for each treatment. If three of more patients within a therapy experience one or more pre-specified dose-limiting toxicities, enrollment to that arm will stop.

Dose-limiting toxicity (DLT) is based on the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE). Although we will continue to monitor toxicity over time, the DLT period in this study refers to toxicities experienced during the first 4 weeks of treatment.

DLTs will be graded according to the National Cancer Institute's CTCAE v5.0 https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (http://ctep.cancer.gov/forms/CTCAEv45.pdf).

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

- Any Grade 4 irAE
- Any ≥ Grade 3 colitis
- Any Grade 3 or 4 noninfectious pneumonitis irrespective of duration
- Any Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care
- Any Grade 3 irAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤ Grade 1 or baseline within 14 days
- Liver transaminase elevation > 8 × ULN or total bilirubin > 5 × ULN
- Any grade 3 or 4 febrile neutropenia
- Any grade 3 or 4 thrombocytopenia with significant bleeding
- Any ≥ Grade 3 non-irAE, except for the exclusions listed below

The definition excludes the following conditions:

- Grade 3 fatigue lasting ≤ 7 days
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic
- Grade 3 inflammatory reaction attributed to a local antitumor response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes, etc)
- Concurrent vitiligo or alopecia of any AE grade

- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
- Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days. Grade 3 or Grade 4 febrile neutropenia will be a DLT regardless of duration or reversibility
- Grade 3 or 4 lymphopenia
- Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention, and improves by at least 1 grade within 3 days
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days
- Grade 3 fever lasting ≤ 24 hours with or without medical therapy and is not considered an SAE

Immune-related AEs (irAEs) are defined as AEs of immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. In the absence of clinical abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT.

While rules for adjudicating DLTs are specified above, an AE that is Grade < 3 or listed as exempt above may also be defined as a DLT after consultation with the sponsor and Investigators, based on the emerging safety profiles of MEDI4736and tremelimumab. Likewise, subjects who become not evaluable for DLT because they discontinued or interrupted treatment due to toxicities other than DLTs will be counted as DLT subjects using the same criteria as other DLTs (Grade 3 or higher toxicity that occurs during the DLT evaluation period and excluding toxicity that is clearly and directly related to the primary disease or to another etiology.)

Management and dose modifications associated with the above adverse events are outlined in Section 6.

5.3 General Concomitant Medication and Supportive Care Guidelines

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

Acceptable Concomitant Medications

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

fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

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

Prohibited Concomitant Medications

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

- Anti-cancer systemic chemotherapy or biological therapy or any other investigational cancer therapy other than those being investigated in this study.
- Immunotherapy not specified in this protocol.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial until 30 days after last dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids for any purpose other than to modulate symptoms from an event of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
- Additional radiation therapy non-specified in the protocol.
    - Note: If the patient develops indication for urgent palliative radiation such as brain metastases or spinal cord compression (either within the previously irradiated field or outside), the patient will be considered to have progressed (see below) and will be removed from the trial.
- Drugs with laxative properties and herbal or natural remedies for constipation should be used with caution through to 90 days after the last dose of tremelimumab during the study
- Sunitinib should not be given concomitantly or through 90 days after the last dose of tremelimumab (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib)
- EGFR tyrosine kinase inhibitors should not be given concomitantly, and should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
- Herbal and natural remedies which may have immune-modulating effects should not be given concomitantly unless agreed by the sponsor

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

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

5.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for 12 months or until one of the following criteria applies which would prompt permanent discontinuation of study treatment:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s), as defined in Section 6.
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient non-compliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

5.5 Duration of Follow Up

Patients will be followed for at least 12 weeks after removal from study treatment or until death, whichever occurs first. Patients removed from study treatment for unacceptable adverse event(s) will be followed until progression. All patients will be followed for at least a year from the time of initiation of treatment.

5.6 Criteria for Removal from Study

When study treatment is terminated per the criteria in Section 5.4 patients will remain on study follow-up.Study follow-up will be terminated at death or for at least one year from the time of treatment initiation and at least 12 weeks afer removal from study treatment, whichever occurs first. Patients removed from study treatment for unacceptable adverse event(s) will continue on study follow-up until the preceeding criteria are met or disease progression, whichever occurs later. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

5.7 Criteria to Resume Treatment

For non-autoimmune or inflammatory events, patients may resume treatment with study drug according to section 6.

If the criteria to resume treatment are met, the patient should restart treatment no sooner than the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol, the treatment should resume at the earliest convenient point that is within the 12 week delay period.

If treatment is delayed >12 weeks, the patient must be permanently discontinued from study therapy, except as specified in Section 5.4 (Duration of Therapy).

5.8 Treatment Beyond Progression

Immunotherapeutic agents such as MEDI4736and tremelimumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

If radiologic imaging shows progressive disease (PD), tumor assessment may be repeated by the site approximately 4-8 weeks later in order to confirm continued PD (as compared to the intial scan) with the option of continuing treatment per below while awaiting radiologic confirmation of progression, provided there are less than 5 new lesions, and the total tumor burden demonstrates less than 40% increased growth as compared to the initial scan. Additionally, any new CNS lesions must be treated prior to resuming therapy. If repeat imaging shows a reduction or stabilization in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued as per treatment calendar. If repeat imaging confirms continued PD, patients will be discontinued from study therapy. If reimaging is no worse than the prior scan 4 weeks prior, patients may continue therapy and be reimaged in another 8 weeks. If evidence for continued, increasing progression with subsequent imaging, the patient will be discontinued. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions. The decision to continue study treatment after the first evidence of disease progression determined by radiologic imaging is at the Investigator’s discretion based on the clinical status of the patient as described in the table below.

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD	Repeat imaging at approximately 4 weeks to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory scan	Repeat imaging at approximately 4 weeks to confirm PD if possible	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment	No additional imaging required	N/A
Repeat scan shows SD, PR, or CR	Continue regularly scheduled imaging assessments every 6 weeks	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments every 6 weeks	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion
Tumor imaging will be assessed every 12 weeks (84 ±7 days).				

Patients may receive study treatment while waiting for confirmation of continued PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention
- No urgent need for radiation therapy other than as specified by the protocol

5.9 Discontinuation of Treatment Following Complete Response

Discontinuation of treatment may be considered for patients who have attained a confirmed complete response (CR) that have been treated for at least 52 weeks on protocol and had at least two treatments with MEDI4736beyond the date when the initial CR was declared.

6. DOSING DELAYS/DOSE MODIFICATIONS- Dosing Modification And Toxicity Management Guidelines For Immune-Mediated, Infusion Related, And Non-Immune–Mediated Reactions (Medi4736 Monotherapy Or Combination Therapy With Tremelimumab Or Tremelimumab Monotherapy) 1 November 2017 Version

<table>
<tr><th colspan="3">General Considerations</th></tr>
<tr><th></th><th>Dose Modifications</th><th>Toxicity Management</th></tr>
<tr><td>Immune-related Adverse Events (Overall Management For toxicities not noted below)</td><td>Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v5.0.
In addition to the criteria for permanent discontinuation of study drug/regimen based on CTC grade/severity (table below) , permanently discontinue study drug/study regimen for the following conditions:
• Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) within 12 weeks after last dose of study drug/study regimen
• Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing.

Grade 1 — No dose modification

Grade 2 — Hold study drug/study regimen dose until grade 2 resolution to ≤ Grade 1**
• If toxicity worsens then treat as Grade 3 or Grade 4
•
Study drug/study treatment can be resumed once event stabilizes to grade ≤1 after completion of steroid taper
Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled , 2) the patient is clinically stable as per Investigator or treating physician’s clinical judgement, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent.

Grade 3 — Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below</td><td>It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table
– It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines.
– Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections.) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow.
– Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events
– For persistent (greater than 3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events promptly start prednisone PO 1-2mg/kg/day or IV equivalent
– Some events with high likelihood for morbidity and/or mortality – e.g., myo-carditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation.
– If symptoms recur or worsen during corticosteroid tapering 28 days of taper), increase the corticosteroid dose (prednisone dose [e.g. up to 2-4mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (≥ 28 days of taper)

– More potent immunosuppressives such as TNF inhibitors (e.g. infliximab) – (also refer to the individual sections of the immune related adverse event for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more</td></tr>
</table>

	Grade 4 Permanently discontinue study drug/study regimen Note: For Grade ≥3 asymptomatic amylase or lipase levels, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus). ** Note: If AE's develop in an interval where the next scheduled treatment is radiation (either low or high dose), radiation may be continued at the treating physician's discretion if the radiation treatment field is clearly unrelated to the AE (e.g. liver radiation in a patient who develops pneumonitis), provided the patient is clinically stable and willing to proceed with radiation treatment.	rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids. – With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. – Discontinuation of study drug is not mandated for Grade 3 / Grade 4 inflammatory reactions attributed to local tumour response (e.g. inflammatory reaction at sites of metastatic disease, lymph nodes etc.). Continuation of study drug in this situation should be based upon a benefit/risk analysis for that patient

Specific Immune -Mediated Reactions

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
Pneumonitis/ **Interstitial Lung Disease** (ILD)	Any Grade	General Guidance	For Any Grade – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests including other diagnostic procedures as described below – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan.
	Grade 1 (Asymptomatic, clinical or diagnostic observations only, intervention not indicated)	No dose modification required. However, consider holding study drug/study regimen dosing as clinically appropriate and during diagnostic work-up for other etiologies	For Grade 1 (Radiographic Changes Only) - Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated - Consider Pulmonary and Infectious disease consult
	Grade 2 (Symptomatic, medical intervention indicated, limiting instrumental ADL)	Hold study drug/study regimen dose until grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/regimen at next scheduled treatment date will be	For Grade 2 (Mild to Moderate New Symptoms) – Monitor symptoms daily and consider hospitalization – Promptly start systemic steroids (e.g., prednisone 1-2mg/kg/day PO or IV equivalent) – Reimaging as clinically indicated – If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started – If still no improvement within 3-5 days despite IV

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		based upon treating physician's clinical judgment. and after completion of steroid taper	methylprednisolone at 2-4/g/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab - Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungal or anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[123] - Consider pulmonary and infectious disease consult - Consider as necessary discussing with study physician
	Grade 3 or 4 (Grade 3: Severe symptoms; limiting self-care ADL; oxygen indicated; Grade 4: life threatening respiratory compromise, urgent intervention indicated [e.g. tracheostomy or intubation])	Permanently discontinue study drug/study regimen	For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life threatening - Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent - Obtain Pulmonary and Infectious disease consult; consider, as necessary, discussing with study physician. - Hospitalize the patient - Supportive Care (oxygen, etc.) - If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab - Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and in particular, anti PJP treatment (please refer to current NCCN

[1] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD
[2] NCI CTCAE version 4.03
[3] ASCO Educational Book 2015. Michael Postow MD. "Managing Immune Checkpoint Blocking Antibody Side Effects"

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
			guidelines for treatment of cancer-related infections (Category 2B recommendation)[4]
Diarrhea/ Colitis	Grade of Diarrhea (CTCAE version 4.03)	Any Grade	- Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs and ileus) - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, infections including testing for clostridium difficile toxin, etc.) - Steroids should be considered in the absence of clear alternative etiology, even for low grade events, in order to prevent potential progression to higher grade event - Use analgesics carefully; they can mask symptoms of perforation and peritonitis
	Grade 1 (Diarrhea:stool frequency of <4 over baseline per	No dose modification	For Grade 1 diarrhea : - Close monitoring for worsening symptoms - Consider symptomatic treatment including hydration, electrolyte

[4] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	day) (Colitis: asymptomatic; clinical or diagnostic observations only)		replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use of probiotics as per treating physician's clinical judgment.
	Grade 2 (Diarrhea:stool frequency of 4-6 over baseline per day) (Colitis: abdominal pain; mucus or blood in stool)	Hold study drug/study regimen until resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper	For Grade 2 diarrhea: – Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup such as imaging and/or colonoscopy to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. – If still no improvement within 3-5 days despite 2-4mg/kg IV methylprednisolone, promptly start immunosuppressives such as (infliximab at 5mg/kg once every 2 weeks[5]). . **Caution**: It is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab – Consider, as necessary, discussing with study physician if no resolution to ≤ Grade 1 in 3-4 days – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])

[5] ASCO Educational Book 2015 Michael Postow MD "Managing Immune Checkpoint Blocking Antibody Side Effects

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 3 or 4 diarrhea (Grade 3 diarrhea: stool frequency of ≥7 over baseline per day; Grade 4 diarrhea: life threatening consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medi-cal intervention indi-cated, peritoneal signs; Grade 4 colitis: life-threatening consequences, urgent intervention indicated)	Grade 3 Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. **Grade 4** Permanently discontinue study drug/study regimen.	For Grade 3 or 4 diarrhea: - Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent - Monitor stool frequency and volume and maintain hydration - Urgent GI consult and imaging and/or colonoscopy as appropriate - If still no improvement within 3-5 days of IV methylprednisolone 2 to 4mg/kg/day or equivalent, promptly start further immunosuppressives (e.g. infliximab at 5mg/kg once every 2 weeks). - Caution: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. - Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
Hepatitis (Elevated LFTs) **Infliximab should not be used for**	Grade of Liver Function Test Elevation (CTCAE version 5.0) Any Grade		- Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin - Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications)

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
management of Immune Related Hepatitis **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in HCC patients**	Grade 1 (Based on ULN regardless of baseline LFT) (AST or ALT >ULN and ≤3.0×ULN and/or TB > ULN and ≤1.5×ULN)	No dose modifications If it worsens, then treat as Grade 2 event	For Grade 1 AST or ALT and/or TB elevation - Continue LFT monitoring per protocol
	Grade 2 (Based on ULN regardless of baseline LFT)AST or ALT >3.0×ULN and ≤5.0×ULN and/or TB >1.5×ULN and ≤3.0×ULN)	Hold Study drug/study regimen dose until grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper	For Grade 2 AST or ALT and or TB elevation : – Regular and frequent checking of LFTs (e.g. every 1-2 days) until elevations of these are improving or resolved. – If no resolution to ≤ Grade 1 in 1-2 days, consider, as necessary, discussing with study physician. – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2mg/kg/day PO or IV equivalent. – If still no improvement within 3-5 days despite 1-2mg/kg/day of prednisone PO or IV equivalent, consider additional work up and start prompt treatment with IV methylprednisolone 2-4mg/kg/day. – If still no improvement within 3-5 days despite 2-4mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e.,mycophenolate mofetil)[6] . Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used**. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for

[6] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" , by Michael Postow MD

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
			treatment of cancer-related infections [Category 2B recommendation])
	Grade 3 (Based on ULN regardless of baseline LFT) (Grade 3: AST or ALT >5.0×ULN and ≤20.0×ULN and/or TB >3.0×ULN and ≤10.0×ULN)	For elevations in transaminases ≤ 8 × ULN, or elevations in bilirubin ≤ 5 × ULN -Hold study drug/study regimen dose until resolution to ≤ Grade 1 or baseline -Resume study drug/study regimen if elevations downgrade ≤ Grade 1 or baseline within 14 days and after completion of steroid taper. Permanently discontinue study drug/study regimen if the elevations do not downgrade to ≤ Grade 1 or baseline within 14 days For elevations in transaminases > 8 × ULN or elevations in bilirubin > 5 × ULN, discontinue study drug/study regimen Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT > 3x ULN +	For Grade 3 or 4 AST or ALT and/or TB elevation: – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent – If still no improvement within 3-5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent , promptly start treatment with immunosuppressive therapy (i.e.,mycophenolate mofetil) Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Perform hepatology consult, abdominal workup, and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
		bilirubin > 2x ULN without initial findings of cholestasis (i.e. elevated alkaline P04) and in the absence of any alternative cause[7]	
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC** See instructions at	Grade 4 (Grade 4: AST or ALT >20×ULN and/or TB >10×ULN) Any Grade	Permanently discontinue study drug/study regimen General Guidance	For any grade: -Monitor and evaluate liver function test: AST, ALT, ALP, and TB. -Evaluate for alternative etiologies {e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis (e.g., portal vein thrombosis).} -For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg

[7] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**			-For HCV+ patients: evaluate quantitative HCV viral load -Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load >2000 IU/ml -Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral HCV medications if HCV viral load increased by >2 -fold -For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above
	Grade 1 (Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline)	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as Grade 2 event. For all grades, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 2 (Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline) (Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline)	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or Grade 4. If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and treatment with IV methylprednisolone 2 to 4 mg/kg/day. If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 3 (Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline) (Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)	• Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	**For Grade 3:** – Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider, as necessary, discussing with study physician. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 4 (Isolated AST or ALT >20×ULN, whether normal or elevated at baseline)	Permanently discontinue study drug/study regimen.	**For Grade 4:** **Same as above** **(except would recommend obtaining liver biopsy early)**

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
Nephritis or Renal Dysfunction (Elevated Serum Creatinine)	Grade of Elevated Serum Creatinine (CTCAE version 4.03) Any Grade		– Consult with Nephrologist – Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc.) – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections etc.) – Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2) , in order to prevent potential progression to higher grade event

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 1 [Serum Creatinine > 1-1.5X baseline; > ULN to 1.5X ULN]	No dose modification	For Grade 1 elevated creatinine: - Monitor serum creatinine weekly and any accompanying symptom • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If it worsens, depending on the severity , treat as Grade 2 or Grade 3 or 4 - Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc.
	Grade 2 [Serum Creatinine>1.5-3.0X baseline; >1.5X-3.0XULN]	Hold study drug/study regimen until resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	For Grade 2 elevated creatinine: – Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc. – Carefully monitor serum creatinine every 2-3 days and as clinically warranted – Consult Nephrologist and consider renal biopsy if clinically indicated – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4mg/kg/day started. – Once the patient isimproving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]). – When event returns to baseline, resume study drug/study regimen

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
			and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: Serum Creatinine > 3.0 X baseline; >3.0-6.0 X ULN Grade 4: Serum Creatinine > 6.0 X ULN)	Permanently discontinue study drug/study regimen	- Carefully monitor serum creatinine on daily basis - Consult Nephrologist and consider renal biopsy if clinically indicated - Promptly start prednisone 1 to 2 mg/kg/day or IV equivalent - If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. - Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]
Rash (excluding Bullous skin formations)	Grade of Skin Rash (Please refer to NCICTCAE version 4.03 for	Any Grade	Monitor for signs and symptoms of dermatitis (rash and pruritus) **IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED****

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	definition of severity/grade depending on type of skin rash)		
	Grade 1	No dose modification	For Grade 1: – Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream)
	Grade 2	For persistent (> 1- 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to ≤ Grade 1 or baseline • If toxicity worsens then treat as Grade 3 • If toxicity improves Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	For Grade 2 : – Obtain dermatology consult – Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream) – Consider moderate-strength topical steroid – If no improvement of rash/skin lesions occurs within 3-5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids prednisone 1-2 mg/kg/day PO or IV equivalent – Consider skin biopsy if the event is persistent for >1-2 weeks or recurs
	Grade 3	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to ≤ Grade 1 or baseline within 30 days, then permanently discontinue Study drug/study regimen	For Grade 3 or 4: – Consult dermatology – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent – Consider hospitalization – Monitor extent of rash [Rule of Nines] – Consider skin biopsy (preferably more than 1) as clinically feasible.

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 4	Permanently discontinue study drug/study regimen	– Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) – Consider, as necessary, discussing with study physician
Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, adrenal insufficiency, etc: exocrine event of amylase/lipase increased also included in this section).	Any Grade (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity)		– Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infections, etc.) – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T_3 and free T_4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 1	No dose modification	For Grade 1: (including those with asymptomatic TSH elevation) – Monitor patient with appropriate endocrine function tests – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5X LLN, or TSH >2X ULN or consistently out of range in 2 subsequent measurements, include Free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until subject is clinically stable • If toxicity worsens then treat as Grade 3 or Grade 4 • Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled ,2) the patient is clinically stable as per Investigator or treating	For Grade 2: (including those with symptomatic endocrinopathy) – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy, and as clinically indicated, consider pituitary scan – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term, corticosteroids (e.g., 1-2mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g. hydrocortisone, sex hormones). – – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
		physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent.	endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) – For patients with normal endocrine work up (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	For Grade 3 or 4: – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
			endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) –
Neurotoxicity (to include but not limited to limbic encephalitis . autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	Grade of Neurotoxicity Depending on the type of neurotoxicity , refer to NCI CTCAE version 4.03 for defining the CTC grade/severity		
	Any Grade		– Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.) – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness) – Consider appropriate diagnostic testing (e.g. electromyogram and nerve conduction investigations) – Perform symptomatic treatment with neurological consult as appropriate
	Grade 1	No dose modifications	See "Any Grade" recommendations above.
	Grade 2	• For acute motor	– Consider, as necessary, discussing with the study physician

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
		neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to ≤ Grade 1 • For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to ≤ Grade 1. o If toxicity worsens then treat as Grade 3 or Grade 4 • Study drug/study regimen can be resumed once event stabilizes to grade ≤1 and after completion of steroid taper	– Obtain Neurology Consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine) – Promptly start systemic steroids prednisone 1-2mg/kg/day PO or IV equivalent – If no improvement within 3-5 days despite 1-2mg/kg/day prednisone PO or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (e.g. IVIG)
	Grade 3	• Hold Study drug/study regimen dose until resolution to ≤ Grade 1 • Permanently discontinue Study drug/study regimen if Grade 3 imAE does not resolve to ≤ Grade 1 within 30 days.	For Grade 3 or 4: – Consider, as necessary, discussing with study physician – Obtain Neurology Consult – Consider hospitalization – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g. IVIG) – Once stable, gradually taper steroids over ≥28 days
	Grade 4	• Permanently discontinue study drug/study regimen	
Peripheral neuromotor syndromes (such		Any Grade	– The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations which can result in substantial

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
as Guillain-Barre and Myasthenia Gravis)			morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation Important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG
	Grade 1	No dose modification	– Consider, as necessary, discussing with the study physician – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above – Obtain a neurology consult
	Grade 2	Hold study drug/study regimen dose until resolution to ≤ Grade 1 Permanently discontinue study drug/study regimen if it does not resolve to ≤ Grade 1 within 30 days or if there are signs of	Grade 2 – Consider, as necessary, discussing with the study physician – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above – Obtain a Neurology Consult

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
		respiratory insufficiency or autonomic instability	– Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine) *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If Myasthenia Gravis-like neurotoxicity is present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.
	Grade 3	Hold study drug/study regimen dose until resolution to ≤ Grade 1 Permanently discontinue Study drug/study regimen if Grade 3 imAE does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	For severe or life threatening (Grade 3 or 4) events: – Consider, as necessary, discussing with study physician – Recommend hospitalization – Monitor symptoms and obtain neurological consult *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 4	Permanently discontinue study drug/study regimen	neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE*: It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Cardiac toxicities (including arrhythmia, conduction disorder heart failure, lV dysfunction, Myocarditis)	**Any Grade**	**General Guidance** Discontinue drug permanently upon diagnosis of myocarditis, regardless of grade.	**For Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider, as necessary, discussing with the study physician. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections) -

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 1 (asymptomatic with laboratory (e.g., BNP, EKG, Troponin) and etiology is unclear)	No dose modifications required unless clinical suspicion for myocarditis is high, in which case suspected hold durvalumab-tremelimumab during workup. -If myocarditis is excluded, resume after complete resolution to Grade 0. - <u>If myocarditis is diagnosed, permanently discontinue durvalumab or tremelimumab</u>	**For Grade 1 (no definitive findings):** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. Consider using steroids if clinical suspicion is high.
	Grade 2, 3 or 4 (Grade 2: Symptoms with mild to moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support))	- If Grade 2 -- Hold study drug/study regimen If toxicity rapidly improves to Grade 0 AND myocarditis is excluded, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. -If myocarditis is diagnosed, permanently discontinue durvalumab or tremelimumab -If Grade 3-4, permanently discontinue study drug/study regimen.	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. - Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Myositis/Polymyositis ("Poly/myositis")	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
	Grade 1 (mild pain)	- No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
	Grade 2 (moderate pain	Hold study drug/study regimen dose until resolution to Grade ≤1.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization.

associated with weakness; pain limiting instrumental activities of daily living [ADLs])	- Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	– Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Grade 3 or 4 (pain associated with severe weakness; limiting self-care ADLs)	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** - Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether patient may require IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for

	treatment of cancer-related infections [Category 2B recommendation]).[a]

Additional Information:

- If drugs are given and then patient develops AE before or during radiation, radiation is also held, stopped, unless the treatment field is clearly unrelated to the AE (e.g. liver radiation in a patient who develops pneumonitis), provided the patient is clinically stable for radiation treatment.

- If either drugs are held then radiation is also held. If all radiation has not been delivered as per protocol, radiation would resume the week following the next drug administration, do not skip.

- If drugs are held, then any remaining radiation is also held until a week after the next cycle begins, per protocol.

- If patient experiences an AE, requiring drug hold/discontinuation, both drugs will be held.

- If drug or radiation is permanently discontinued for toxicity before completion of protocol treatment, the subject would need to come off treatment.

Infusion-Related Reactions		
Severity Grade	**Dose Modifications**	**Toxicity Management**
Any Grade		– Management per institutional standard at the discretion of investigator – Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes etc.) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, tachycardia, etc.)
Grade 1	The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event	For Grade 1 or Grade 2: – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator – Consider premedication per institutional standard prior to subsequent doses - Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 2	The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event Subsequent infusions may be given at 50% of the initial infusion rate	
Grade 3/4	Permanently discontinue study drug/study regimen	For Grade 3 or 4: Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid)

Non-immune Mediated Reactions **(Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician"**		
CTC Grade/Severity	**Dose Modification**	**Toxicity Management**
Any Grade	Note: dose modifications are not required for adverse events not deemed to be related to study treatment (i.e. events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly as per institutional standard
1	No dose modifications	Treat accordingly as per institutional standard

Non-immune Mediated Reactions **(Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician"**		
CTC Grade/Severity	**Dose Modification**	**Toxicity Management**
2	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline	Treat accordingly as per institutional standard
3	Hold study drug/study regimen 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 study drug/study regimen administration. Otherwise, discontinue study drug/study regimen	Treat accordingly as per institutional standard
4	Discontinue Study drug/study regimen (Note for Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, Investigator's clinical judgment and in consultation with the sponsor)	Treat accordingly as per institutional standard

Abbreviations:
AChE = acetylcholine esterase; ADA = American Dietetic Association; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; GI = gastrointestinal; IDS=Infectious Disease Service; ILD = interstitial lung disease; IM = intramuscular; irAE = immune-related adverse event; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PO = by mouth; TNF = tumor necrosis factor; TSH = thyroid stimulating hormone; ULN = upper limit of normal.

[i] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD
[ii] NCI CTCAE version 5.0
[iii] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD
[iv] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset of AEs, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. The SPEER is a list of events that are protocol-specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm for further clarification.

NOTE: The highest grade currently reported is noted in parentheses next to the AE in the SPEER. Report **ONLY** AEs higher than this grade expeditiously. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

7.1.1 CAEPRs for CTEP IND Agent(s)

7.1.1.1 CAEPR for MEDI4736

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
MEDI4736 (durvalumab, NSC 778709)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2833 patients.* Below is the CAEPR for MEDI4736 (durvalumab).

> **NOTE**: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4,

April 17, 2019[1]

Adverse Events with Possible Relationship to MEDI4736 (durvalumab) (CTCAE 5.0 Term) [n= 2833]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Blood and lymphatic system disorders - Other (idiopathic thrombocytopenic purpura)[2]	
		Thrombotic thrombocytopenic purpura[2]	
CARDIAC DISORDERS			
		Myocarditis[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
		Adrenal insufficiency[2]	
		Endocrine disorders - Other (diabetes insipidus)	
		Endocrine disorders - Other (diabetes mellitus type 1)[2]	
	Hyperthyroidism[2]		
		Hypopituitarism[2]	
	Hypothyroidism[2]		
EYE DISORDERS			
		Keratitis[2]	
		Uveitis[2]	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colitis[2]	
	Diarrhea		***Diarrhea (Gr 2)***
		Gastrointestinal disorders - Other - (gastrointestinal perforation)[2,3]	
	Nausea		***Nausea (Gr 2)***
		Pancreatitis[2]	
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
	Fatigue		***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (autoimmune hepatitis)[2]	
IMMUNE SYSTEM DISORDERS			
		Immune system disorders - Other (immune related adverse events)[2]	
		Immune system disorders - Other (sarcoidosis)	
INFECTIONS AND INFESTATIONS			
	Infection[4]		***Infection[4] (Gr 2)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			

Adverse Events with Possible Relationship to MEDI4736 (durvalumab) (CTCAE 5.0 Term) [n= 2833]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Infusion related reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		***Alanine aminotransferase increased[2] (Gr 2)***
	Aspartate aminotransferase increased[2]		***Aspartate aminotransferase increased[2] (Gr 2)***
	Creatinine increased		***Creatinine increased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthritis[2]		
		Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]	
	Myalgia		***Myalgia (Gr 2)***
		Myositis[2]	
NERVOUS SYSTEM DISORDERS			
		Guillain-Barre syndrome[2,5]	
		Myasthenia gravis[2]	
		Nervous system disorders - Other (aseptic meningitis)[2]	
		Peripheral sensory neuropathy	
RENAL AND URINARY DISORDERS			
	Dysuria		***Dysuria (Gr 2)***
		Renal and urinary disorders - Other (autoimmune nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Cough			***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
	Pneumonitis[2]		
	Respiratory, thoracic and mediastinal disorders - Other (dysphonia)		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Hyperhidrosis		
	Pruritus		***Pruritus (Gr 2)***
	Rash[2,6]		***Rash[2,6] (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (scleroderma)	
		Skin and subcutaneous tissue disorders - Other (severe dermatitis)[2,7]	
	Skin hypopigmentation		***Skin hypopigmentation (Gr 2)***

NOTE: Cardiomyopathy, and graft versus host disease, while not observed on clinical trials of MEDI4736 (durvalumab) at this time, are known events with this class of agent (PD-L1 antagonist).

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Immune-mediated adverse reactions (irAEs) have been reported in patients receiving MEDI4736 (durvalumab). irAEs can involve any of the organs or systems in the body. Most irAEs were reversible and managed with interruptions of MEDI4736 (durvalumab), administration of corticosteroids and supportive care, however, these events can be serious and fatal.

[3]Gastrointestinal perforations have been observed only in patients receiving MEDI4736 (durvalumab) in combination with tremelimumab (CP-675,206).

[4]Infections includes infection in the lungs, upper respiratory tract, dental and oral soft tissues and other organs under the INFECTIONS AND INFESTATIONS SOC. Infections generally are mild (Gr 1-2) but severe infections including sepsis, necrotizing fasciitis, and osteomyelitis have been reported.

[5]Guillain-Barre Syndrome has been reported in patients receiving MEDI4736 (durvalumab) in combination with tremelimumab (CP-675,206) but can potentially occur after durvalumab monotherapy.

[6]Rash includes the terms: rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, and eczema.

[7]In rare cases, severe dermatitis has been reported to manifest as Stevens-Johnson syndrome, toxic epidermal necrolysis, or rashes complicated by dermal ulceration or necrotic, bullous, or hemorrhagic manifectations.

Adverse events reported on MEDI4736 (durvalumab) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MEDI4736 (durvalumab) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Disseminated intravascular coagulation
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac disorders - Other (coronary artery disease); Pericardial effusion; Pericardial tamponade; Restrictive cardiomyopathy; Right ventricular dysfunction; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Hearing impaired
EYE DISORDERS - Eye disorders - Other (choroidal effusion with shut down of ciliary body)
GASTROINTESTINAL DISORDERS - Ascites; Constipation; Dental caries; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Mucositis oral; Proctitis; Small intestinal obstruction; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema trunk; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic hemorrhage
IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (drug-induced liver injury); Serum sickness
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Wound complication
INVESTIGATIONS - Blood bilirubin increased; CPK increased; Electrocardiogram T wave abnormal; GGT increased; Lipase increased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Serum amylase increased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hypoalbuminemia; Hypokalemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Rhabdomyolysis
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (brain metastasis swelling); Neoplasms

benign, malignant and unspecified (incl cysts and polyps) - Other (lung cyst); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor flare, tumor inflammation); Treatment related secondary malignancy; Tumor hemorrhage; Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Dizziness; Edema cerebral; Headache; Nervous system disorders - Other (axonal neuropathy); Nervous system disorders - Other (hemiparesis); Paresthesia; Seizure
PSYCHIATRIC DISORDERS - Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Hypoxia; Pleural effusion; Pneumothorax; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Dry skin
VASCULAR DISORDERS - Hypertension

Note: MEDI4736 (durvalumab) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.1.2 CAEPR for tremelimumab

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Tremelimumab (CP-675,206, NSC 744483)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1642 patients.* Below is the CAEPR for tremelimumab (CP-675,206).

> **NOTE**: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.1, March 25, 2019[1]

Adverse Events with Possible Relationship to Tremelimumab (CP-675,206) (CTCAE 5.0 Term) [n= 1642]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia[2]		***Anemia[2] (Gr 2)***
CARDIAC DISORDERS			
		Myocarditis[3]	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Endocrine disorders - Other (thyroiditis)[2]		
	Hyperthyroidism[2]		
	Hypophysitis[2]		
	Hypothyroidism[2]		
EYE DISORDERS			
	Uveitis		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis[2]		
Diarrhea			***Diarrhea (Gr 2)***
		Enterocolitis[2]	
		Gastrointestinal disorders - Other (intestinal perforation)[2]	
	Nausea		***Nausea (Gr 2)***
		Pancreatitis[2]	
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
	Fatigue		***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (autoimmune hepatitis)[2]	
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		***Alanine aminotransferase increased[2] (Gr 2)***
	Aspartate aminotransferase increased[2]		***Aspartate aminotransferase increased[2] (Gr 2)***
	Lipase increased[2]		***Lipase increased[2] (Gr 2)***
	Lymphocyte count decreased[2]		***Lymphocyte count decreased[2] (Gr 2)***
	Neutrophil count decreased[2]		***Neutrophil count decreased[2] (Gr 2)***
	Platelet count decreased[2]		***Platelet count decreased[2] (Gr 2)***
	Serum amylase increased[2]		***Serum amylase increased[2] (Gr 2)***
	White blood cell decreased[2]		***White blood cell decreased[2] (Gr 2)***

Adverse Events with Possible Relationship to Tremelimumab (CP-675,206) (CTCAE 5.0 Term) [n= 1642]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 2)***
	Hypokalemia		
		Metabolism and nutrition disorders - Other (diabetes mellitus)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthritis[2]		
		Musculoskeletal and connective tissue disorders - Other (Sjogren's syndrome)	
NERVOUS SYSTEM DISORDERS			
		Guillain-Barre syndrome[2]	
	Headache[2]		
		Myasthenia gravis[2,4]	
		Nervous system disorders - Other (encephalitis)[2]	
	Peripheral motor neuropathy[2]		
	Peripheral sensory neuropathy[2]		
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
		Nephrotic syndrome[2]	
	Renal and urinary disorders - Other (autoimmune nephritis)[2]		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
	Pneumonitis[2]		
	Respiratory, thoracic and mediastinal disorders - Other (interstitial lung disease)[2]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin[2]		***Dry skin[2] (Gr 2)***
Pruritus			***Pruritus (Gr 2)***
Rash maculo-papular[2]			***Rash maculo-papular[2] (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (cutaneous scleroderma-like syndrome)	
		Skin and subcutaneous tissue disorders - Other (Grover's disease)	
	Skin hypopigmentation		***Skin hypopigmentation (Gr 2)***
	Urticaria[2]		
VASCULAR DISORDERS			
		Vascular disorders - Other (giant cell temporal arteritis)[2]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Immune-related adverse events may occur in any organs including but not limited to the events listed in CAEPR table.

[3]Myocarditis has been reported with other anti-CTLA4 agents; however, it has not yet been observed in clinical trials of tremelimumab (CP-675,206).

[4]Myasthenia gravis was observed in trials of tremelimumab in combination with durvalumab.

Adverse events reported on tremelimumab (CP-675,206) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that tremelimumab (CP-675,206) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Eosinophilia
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest
EAR AND LABYRINTH DISORDERS - Tinnitus
ENDOCRINE DISORDERS - Endocrine disorders - Other (Graves' disease with ophthalmopathy)
GASTROINTESTINAL DISORDERS - Constipation; Dyspepsia; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Ileus; Mucositis oral; Rectal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Malaise; Pain; Sudden death NOS
INFECTIONS AND INFESTATIONS - Conjunctivitis; Infections and infestations - Other (oral herpes); Lung infection; Sepsis
INVESTIGATIONS - GGT increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Generalized muscle weakness; Myalgia
NERVOUS SYSTEM DISORDERS - Dizziness; Syncope
PSYCHIATRIC DISORDERS - Confusion; Depression; Insomnia
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Pleural effusion; Respiratory, thoracic and mediastinal disorders - Other (asthma)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Hyperhidrosis; Rash acneiform
VASCULAR DISORDERS - Flushing; Hypertension; Thromboembolic event; Vascular disorders - Other (hemorrhage); Vasculitis

Note: Tremelimumab (CP-675,206) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to

understanding of the Investigational Product and may require close monitoring . An AESI may be serious or non-serious.

AESIs for MEDI4736± tremelimumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. "These AESIs may require close monitoring in clinical studies with durvalumabmonotherapy and durvalumab combination therapy". An immune-mediated adverse event (imAE) is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.
If the Investigator has any questions in regards to an event being an imAE, the Investigator should promptly contact the Study Physician.
AESIs observed with MEDI4736± tremelimumab include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- hepatitis / transaminase increases
- Endocrinopathies (i.e. events of hypophysitis/ hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / Dermatitis
- Nephritis /Blood creatinine increases
- Pancreatitis / serum lipase and amylase increases
- Myocarditis
- Myositis / Polymyositis
- Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré and myasthenia gravis)Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, haematological and rheumatological events.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological aetiology are also considered AESIs.

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab and tremelimumab Investigator's Brochures. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (please see Appendix 1). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator..

7.3 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version

4.0 will be utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.4.4.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.4 Expedited Adverse Event Reporting

7.4.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.4.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

7.4.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires <u>both</u> routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions". Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **<u>MUST</u>** immediately report to the sponsor (NCI) **<u>ANY</u>** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **<u>ANY</u>** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

<u>ALL</u> <u>SERIOUS</u> adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

<u>Expedited AE reporting timelines are defined as:</u>

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational

agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:
- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.4.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism (Section 7.4):

- Any grade 1 or grade 2 laboratory abnormality that resolves within 7 days. Any grade 1 or grade 2 laboratory abnormality lasting for more than 7 days without resolution will require Expedited Adverse Event Reporting.
- Any grade 1 or grade 2 adverse event attributed as not related to study treatment.
- Any grade 1 or grade 2 adverse event attributed as possibly related or related to study treatment and is expected and resolves within 14 days. Any grade 1 or grade 2 adverse event attributed as possibly related or related to study treatment and is expected which does not resolve within 14 days will require Expedited Adverse Event Reporting.

7.5 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

Clinician graded CTCAE is the AE safety standard. Patients will respond to PRO-CTCAE items in a manner to complement CTCAE reporting, but no real-time review nor protocol directed action will be taken. The patient reported data will be entered directly from the patient's device into the RAVE database and may be available for the review with routine AEs.

7.6 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*,

treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.7 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in Section 7.1.

8.1 CTEP IND Agent(s)

8.1.1 MEDI4736 (NSC 778709)

Other Names: MEDI4736(durvalumab)

Classification: Anti-PD-L1 MAb

Molecular Weight: ~ 149 kDa

Mode of Action: MEDI4736 inhibits binding of programmed cell death ligand 1 (PD-L1) to PD-1 and CD80. In-vitro studies demonstrate that MEDI4736 relieves PD-L1-mediated suppression of human T-cell activation. MEDI4736 does not trigger antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity in cell-based functional assays.

Description: MEDI4736 is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody.

How Supplied: MEDI4736 is supplied by AstraZeneca/MedImmune, and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as single-use 500 mg/vial solution for infusion (50 mg/mL). MEDI4736 solution for infusion is formulated in 26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, pH 6.0.

Preparation: MEDI4736 solution for infusion must be diluted prior to administration. To prepare the infusion solution add the dose volume of MEDI4736 to an infusion bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP and mix by gentle inversion to ensure homogeneity of the dose in the bag. The final concentration must be between 1 mg/mL to 20 mg/mL. Saline bags must be latex-free and can be made of polypropylene, polyethylene, polyolefin copolymers, or polyvinyl chloride.

Storage: Store intact vials between 2-8°C (36-46°F). Do not shake.

If a storage temperature excursion is identified, promptly return MEDI4736 to between 2-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Stability testing of the intact vials is on-going**.**

Total in-use storage time from needle puncture of MEDI4736 vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2-8°C (36-46°F). Prior to the start of the infusion, ensure that the bag contents are at room temperature (approximately 25°C) to avoid an infusion reaction due to the administration of the solution at low temperatures. If there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

Route of Administration: IV infusion

Method of Administration: Infuse over approximately 60 minutes using an infusion set containing a low-protein binding 0.2 µm in-line filter. No incompatibilities between MEDI4736 and polyethylene, polypropylene, polyvinylchloride, or polyolefin copolymers have been observed. Flush the IV line with a volume of normal saline equal to the priming volume of the infusion set used at the completion of infusion. Do not co-administer other drugs through the same infusion line.

Patient Care Implications: Refer to the protocol for information on evaluation and management of potential immune-related adverse events.

Availability

MEDI4736is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

MEDI4736is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.2 Tremelimumab **(NSC 744483)**

Other Names: CP-675,206

Classification: Anti-CTLA-4 MAb

Molecular Weight: ~ 149 kDa

Mode of Action: Tremelimumab is specific for human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), a cell surface receptor that is expressed primarily on activated T cells. CTLA-4 delivers a negative regulatory signal to T cells upon binding of CD80 or CD86 ligands on antigen-presenting cells. Tremelimumab blocks the inhibitory signal resulting from CTLA-4 binding to CD80/86, leading to prolongation and enhancement of T-cell activation and expansion.

Description: Tremelimumab is a human immunoglobulin G2 kappa (IgG2κ) monoclonal antibody.

How Supplied: Tremelimumab is supplied by AstraZeneca, and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as single-use 400 mg/vial solution for infusion (20 mg/mL). Tremelimumab solution for infusion is formulated in 20 mM histidine/histidine-HCl, 222 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, and 0.27 mM disodium edetate dihydrate, pH 5.5.

Preparation: Tremelimumab solution for infusion must be diluted prior to administration. Allow the required number of vials to equilibrate to room temperature for 30 minutes. Do not shake the vials. To prepare the infusion solution add the dose volume of tremelimumab to an infusion bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP and mix by gentle inversion to ensure homogeneity of the dose in the bag. The final concentration must be between 0.10 mg/mL to 10 mg/mL. Polycarbonate syringes should not be used with tremelimumab. Saline bags must be latex-free and can be made of polyvinyl chloride (PVC) or polyolefins (eg, polyethylene), manufactured with bis (2-ethylhexyl) phthalate (DEHP) or DEHP free.

Storage: Store intact vials between 2-8°C (36-46°F). Do not freeze.

If a storage temperature excursion is identified, promptly return tremelimumab to between 2-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Stability testing of the intact vials is on-going**.** Total in-use storage time from needle puncture of tremelimumab vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2-8°C (36-46°F). If there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

Route of Administration: IV infusion

Method of Administration: Infuse over approximately 60 minutes using IV infusion lines made of PVC/DEHP or PVC/tri octyl trimellitate (TOTM) or polyethylene or polyurethane. All DEHP-containing or DEHP-free lines are acceptable. IV lines should contain a 0.22 or 0.2 μm in-line filter. The in-line filter can be made of polyethersulfone or polyvinylidine fluoride. IV lines containing cellulose-based filters should not be used with tremelimumab. Flush the IV line with a volume of normal saline equal to the priming volume of the infusion set used at the completion of infusion. Do not co-administer other drugs through the same infusion line.

Availability

Tremelimumab is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Tremelimumab is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.3 Agent Ordering and Agent Accountability

8.1.3.1 NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

8.1.3.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.1.4 Investigator Brochure Access for CTEP IND agents

The current version of the Investigator Brochure (IB) will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. Questions about IB access may be directed via email to IBcoordinator@mail.nih.gov or by phone (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET).

8.1.4.1 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Introduction

Correlative sciences will include mandatory pre treatment biopsies or archival tissue in all patients to use immunohistochemistry to analyze PD-L1 expression by immunohistochemistry as well as infiltration of CD3+, CD4+, CD8+ T-cells as a predictor of response to combined checkpoint blockade either alone or in combination with lower or higher dose radiation. The biopsies should be taken from the lesion that will be irradiated in the colorectal cohort (cohort 2), and this is also encouraged in the lung cancer cohort (cohort 1), although not mandatory. Although not mandatory in all patents, repeat biopsies should be obtained in cohort 1 patients that receive liver directed radiation therapy.

Additional biopsies following cycle 2 are required of the irradiated lesion in patients with colorectal cancer (cohort 2) to evaluate the effect of radiation on the tumor microenvironment. In both cohorts, additional biopsies taken outside of the radiation field before and after radiation treatment are encouraged when feasible to evaluate abscopal effects on the molecular and cellular level.

Exploratory studies will also be performed on biopsy tissue to examine the relationship between mutational burden and outcome and also correlate the transcriptome with protein expression and evaluate tumor cell composition with flow cytometry. Mutiplex immunofluorescence will be used to evaluate spatial relationships between immunologic factors in the tumor microenvironment. Peripheral blood will be obtained before treatment and after one cycle of study treatment for cytokine and PBMC analyses.

Assays will be conducted by the **Cancer Immune Monitoring and Analysis Centers (CIMAC), supplemented by assays performed at DFCI and UC Davis Medical Center.** The following is a summary of assays and scientific objectives that will be performed on the samples collected from this study as approved by the CIMAC leadership:

Priority	**Biomarker Name**	**Assay (CLIA: Y/N)**	**Use in protocol** (Integral, Integrated or exploratory?) **Purpose**	**Sample types and Time points of sample collection**		**Mandatory optional?**
1	PD-L1	IHC (CLIA: Y)	• Integrated • To identify biomarkers of response	Tumor FFPE	Baseline, On treatment	M
2	Tumor Immune phenotyping / spatial analysis	Multiplex IF (CLIA: N)	• Integrated (CD3, CD8) and Exploratory • Hypothesis generating	Tumor FFPE	Baseline, On treatment	Optional
3	Transcriptome analysis	RNAseq (CLIA: N)	• Exploratory • Hypothesis generating	Tumor Frozen	Baseline, On treatment	Optional
4	WES	NGS (CLIA: N)	• Exploratory • Hypothesis generating	Tumor, PBL	Baseline, On treatment	Optional
5	Circulating immune populations	CyTOF (CLIA: N)	• Exploratory • Hypothesis generating	PBL	Baseline, On treatment	Optional

Priority	**Biomarker Name**	**Assay (CLIA: Y/N)**	**Use in protocol** (Integral, Integrated or exploratory?) **Purpose**	**Sample types and Time points of sample collection**		**Mandatory optional?**
6	Circulating cytokines/	O-Link (CLIA: N)	• Exploratory • Hypothesis generating	Plasma	Baseline, On treatment	Optional

Additional exploratory mIF analyses will be performed at DFCI, and RNAseq / TCRseq of colorectal cohort patients is performed at UC Davis.

Prioritization

Given the range of correlative studies proposed for this protocol, there may not be enough tissue / blood to perform all the analyses proposed. Therefore, the studies will be prioritized as follows:

PBMCs

- Whole exome sequencing to determine mutational burden and neoantigen detection (normal blood control for tumor samples)
- CyTOF for quantification, immunophenotyping, and functional assessment of PBMCs
- Olink evaluation of plasma for systemic cytokine / chemokine signatures

TISSUE

- IHC to determine intratumoral and stromal PD-L1 (CD274)
- Multiplex IF to score the tumor microenvironment for integrated expression of immunologic biomarks
- Whole exome sequencing to determine mutational burden and neoantigen detection
- RNAseq to evaluate infiltrating immune cells population, immune gene signatures and neoantigen expression

Rationale

Because responses to immune checkpoint blockade vary across disease types and generally only occur in a minority of patients, identifying patients that derive long-term benefit would be of significant benefit. We plan to perform in depth immunological analysis of patient blood and tumor samples to identify predictive biomarkers. Additionally, a major goal of this study is to identify the impact of adding radiotherapy to immune checkpoint blockade; therefore, this sudy incorporates serial tissues samples pre- treatment, and during therapy when feasible. The design of this study allows us to compare immune mechanisms pre- to post-therapy. These studies will also help us evaluate the immunomodulatory effects of different doses of radiotherapy in combination with dual checkpoint blockade.

PD-L1 expression,– integrated biomarker

Tumor PD-L1 expression has been linked to response rates of PD-1 checkpoint blockade[80]. Response to dual blockade of the PD-1 and CTLA-4 checkpoint may be less dependent on PD-L1 expression[60]. Pre-clinical data suggests that radiotherapy may upregulate intratumoral PD-L1 expression[40] but little is known about the dose response of these effects. Additionally little is known about how the pattern of expression (i.e tumor cells vs. infiltrating immune cells) affects response. According to a recent publication[69] roughly 50% of NSCLCs express PD-L1 in tumor cells and 50% in tumor infiltrating immune cells. About 15% of CRCs express PD-L1 in tumor cells but about 50% in tumor infiltrating immune cells. Data presented at ASCO and SITC indicate that MEDI4736monotherapy response rates in NSCLC are 27% in PD-L1 positive tumors and 5% in PD-L1 negative tumors. In patients with dual checkpoint blockade (MEDI4736+ tremelimumab) the response rate was 35% in PD-L1 positive tumors and 22% in PD-L1 negative tumors. The purpose of these studies is to investigate if PD-L1 expression as a biomarker of response in patients treated with radiotherapy + dual checkpoint inhibition and to

evaluate the effects of radiotherapy + dual checkpoint inhibition on PD-L1 expression. We hypothesize that patients with detectable PD-L1 expression will be more likely to respond to therapy. We further hypothesize that PD-L1 expression will increase after radiotherapy and patients who upregulate PD-L1 after radiotherapy will be more likely to respond to therapy.

Spatial quantification of the tumor microenvironment
As described above, based on prior preliminary studies conducted in patients across several disease types, PD-L1 expression and greater numbers of infiltrating lymphocytes may predict response to PD-1 / PD-L1 inhibitors in certain settings [70, 84-86]. However, the biologic activity of PD-1 / PD-L1 inhibitors suggest that expression of PD-1 on tumor-infiltrating lymphocytes and PD-L2 on tumor-infiltrating lymphocytes and tumor immune cells could also be valuable predictive biomarkers. Additionally, spatial resolution may be of importance; co-localization of multiple protein biomarkers on the surface of tumor cells or tumor-infiltrating lymphocytes could add extra diagnostic and predictive value, especially when the amount of tissue available for analysis is limited.

While traditional immunohistochemistry generally only allows for the evaluation of one or two proteins at a time, multiplex immunofluorescence simultaneously evaluates expression and provides more quantifiable spatial resolution for multiple biomarkers. Our initial work has demonstrated the reproducibility and feasibility of this technique in identifying various populations of tumor infiltrating lymphocytes, as well as PD-L1 expressing tumor cells and PD-L1 and PD-1 expressing by infiltrating lymphocytes.

In recent studies across multiple patient cohorts of NSCLC patients roughly 25% of patients have low TILs (score 0-1), intermediate TILs (score 2), or high TILs (score 3) [81]. For analysis as a prognostic biomarker some studies have further grouped patients in to low (0-2) and high (3) TILs [82]. In colorectal cancer approximately 42% of patients have high TILs in the tumor stroma but 77% at the infiltrating margin [83]. TILs and a T-cell inflamed phenotype have also been linked with response to CTLA-4 checkpoint blockade in melanoma[73, 74]. Exclusion of T-cells in the tumor microenvironment has also been linked with lack of response to checkpoint inhibition[75] with down-regulation of CCL4 mediated dendritic cell recruitment as one potential mechanism[75]. RT has been demonstrated to induce TILs[45] and may potentially overcome this mechanism of resistance to checkpoint blockade. Our unpublished data suggests that RT can induce CCL4 expression and increase TILs. These studies will examine the density and subtype of TILS using markers such as CD3, CD4, and CD8. The purpose of these studies is to examine if high or low dose radiotherapy in combination with dual checkpoint blockade can increase the immunologic infiltrate and to examine T-cell exclusion as a mechanism of resistance to checkpoint blockade. We hypothesize that patients with baseline high TILs and patients with increased TILs after radiotherapy will be more likely to respond to therapy.

Mutational Burden
Mutational burden and antigenic load are thought to represent a surrogate for tumor antigenicity and have been linked with response to checkpoint blockade in NSCLC[76]. The purpose of

these studies is to examine mutational load as a biomarker of response to radiotherapy + dual checkpoint inhibition and to define potential tumor antigens.

RNA seq
The purpose of these studies will be to examine the intratumoral and peripheral gene signatures and correlate with treatment outcomes in a hypothesis generating manner. Genes examined will include cytokines, chemokines, markers of T-cell exhaustion, and canonical pathways of immune activation or suppression including indolamine 2,3 dioxygenase. RNAseq will be used to identify infiltrating immune cell populations using deconvolution techniques and also confirm expression of predicted neoantigens.

CyTOF
The purpose of these studies will be a detailed examination of immune cell subsets and functionality in the periphery and in the tumor and to correlate these readouts with treatment response in a hypothesis generating manner.

Olink
The purpose of these studies will be to examine systemic cytokine and chemokine signatures pre-therapy and during therapy and to correlate these readouts with treatment response in a hypothesis generating manner.

Methods:

Sample allocation
IHC and multiplex immunofluorescence will be performed by the DFCI CIMAC Tissue Biomarker Lab led by Dr. Scott Rodig. Tumor core biopsies will be fixed in 10% neutral buffered formalin and paraffin embedded according to standard protocols. If sufficient tissue is available an aliquot will be placed in RNAlater and flash frozen for batched RNA extraction and analysis (TCRseq and RNAseq). Optional: If sufficient tissue is available for biopsies a sample will be placed in RPMI media and brought to the laboratory of cancer immunology for immediate processing into a single cell suspension and stained for flow cytometry. Blood samples will be separated into PBMCs and plasma. Plasma will be snap frozen and stored at -80 for batched analysis of systemic cytokine/chemokines. An aliquot of PBMCs will be cryopreserved in cryostor10 solution for batched DNA extraction and flow cytometry.

PD-L1 expression, integrated biomarker
Biopsies will be obtained as described above. Formalin fixed-paraffin embedded (FFPE) tumor slides will be prepared and H&E stained. PD-L1 staining will be performed on tumor and stromal cells. Depending on tissue availability, additional immunologic subsets may also be delineated with IHC to complement the findings in regards to PD-L1 expression and TILs using some or all of the following antibodies: PD-1, PD-L2, CD68, Ki67, CD25, FoxP3, Indoleamine 2,3 deoxygenase-1 (IDO1), CD11c, CD83, CD86, CD56, CD14, CD16, TIM-3, Lag-3, and Tie2.

We have recently developed immunohistochemical staining on paraffin embedded tissues for immunologic markers such as PD-L1, PD-L2, and PD-1 through the DFCI CIMAC pathology lab (Scott Rodig, M.D., Ph.D. Core Director). PD-L1 IHC has recently been established in a

CLIA approved laboratory. We have published the methods, protocols, and data establishing the sensitivity and specificity of immunohistochemical staining (IHC) assays using the monoclonal antibodies recognizing PD-L1 (CD274, B7-H1) and other antibodies mentioned above including the standard CD3, CD4, and CD8 lymphocyte markers in several recent manuscripts[78, 79, 87-89].

Following chromogenic IHC for PD-L1 we will score the percentage of cells staining positively for PD-L1. In addition, an intensity score, reflecting the average positive staining intensity on a 0-3 scale will be determined and used to calculate a modified H-score (range 0-300).

Publications to date have determined various cut-points as the optimal for predicting clinical response to immune checkpoint therapy (1%, 5%; 50%). We examine these cut-points in an initial examination of our data. The percentage of positive staining cells and the modified H-score will also be analyzed as continuous variables for optimized thresholds as exploratory endpoints.

Spatial quantification of the tumor microenvironment
In addition to PD-L1 and tumor infiltrating lymphocytes, other immune markers such as PD-L2 and CD68 may also indicate tumor mediate immune regulation and could also predict response to immune therapy either alone or in conjunction with other markers. Additionally, while traditional immunohistochemistry generally only allows for the evaluation of one or two proteins at a time, multiplex immunofluorescence (IF) simultaneously evaluates expression and provides more quantifiable spatial resolution for multiple biomarkers. Our initial work has demonstrated the reproducibility of this technique in identifying various populations of tumor infiltrating lymphocytes, as well as PD-L1 expressing tumor cells and PD-L1 and PD-1 expressing infiltrating lymphocytes; therefore we propose to use multiplex IF to explore associations between response and expression of PD-1/PD-L1 in the tumor versus tumor/stroma interface, as well as co-localized PD-L1 / PD-1 expression.

Mutational Burden
WES will be performed by DFCI CIMAC Translational Immunogenomics Lab led by Dr. Catherine Wu according to CIMAC approved protocols.

RNA seq
RNA extraction and integrity will be performed by DFCI CIMAC Translational Immunogenomics Lab led by Dr. Catherine Wu and by UC Davis under the direction of Dr. Arta Monjazeb.

CyTOF.
The DFCI CIMAC Immune Assessment Lab led by Mariano Severgnini and Emily Thrash offers CyTOF; a single-cell proteomic technology that allows for the analysis of 40+ cellular parameters using antibodies tagged with heavy metal isotopes to elucidate complex phenotypic and functional characteristics of heterogeneous immune populations. The CIMACs will

offer CyTOF analysis for PBMC samples using a standardized panel of over 30 markers, delineating immune populations as well as their activation status and checkpoint marker expression. Current panel design is under validation across CIMAC centers and includes 14 immunological core markers (https://cimac-network.org/cytof/). The 10021 panel is likely to evaluate the differential effects of treatment arms on the frequency of CD8, CD4 T cells, regulatory T cells, B cells, NK cells, and myeloid cell subsets including dendritic cells, basophils, and neutrophils, in addition to changes in functional markers (memory, activation, chemokine receptors related to Th1/Th2/Th17, costimulatory markers such as ICOS and coinhibitory markers such as LAG3, TIM3) across time points. The samples will be run on a CyTOF2 mass cytometer (Fluidigm) and analyzed at DFCI scientists using tools such as Cytobank and Astrolabe.

Olink
The Mt Sinai CIMAC led by Sacha Gnjatic will perform Olink. The Proseek Olink Proteomics platform operating on a Fluidigm Biomark HD microfluidic PCR system is a quantitative and reproducible assay to measure levels of molecules related to cytokines, chemokines and growth factors, and in addition this platform also allows detection of circulating immune co-stimulatory and inhibitory molecules, and other relevant immune-oncology markers, in a 92-plex format. The assay can be applied to peripheral serum or plasma, as well as tissue culture supernatants, and requires only 1 microliter of sample. Mount Sinai-CIMAC is the first center in the US that has been trained and certified to perform these assays in house. The Proximity Extension Assay (PEA) technology that underlies these assays relies on dual antibody recognition and incorporates several innovative QC steps (including three different external controls and two internal controls) to evaluate each step of the assay protocol, resulting in an extremely robust assay.

9.1 Integrated Correlative Studies

9.1.1 *PD-L1 expression,*

PD-L1 expression has demonstrated variable utility as a predictive marker in the setting of immune checkpoint blockade and may be impacted by local radiotherapy. We hypothesize that there will be a correlation between PD-L1 expression levels and response as well as a potential increase in the setting of localized radiotherapy. Similarly, we predict that increased T-cell infiltration into the tumor microenvironment will predict for response to therapy.

9.1.1.1 Collection and Handling of Specimen(s)

Immunohistochemical staining of PD-L1, CD3, CD4 and CD8 will be used as integrated markers in the clinical trial, which could be used in future trials to identify a group of patients who would have a good response to the treatment as a stratification variable. Tumor specimens will be collected at baseline in patients enrolled on both cohorts. Pre-treatment archived specimens will

be retrieved if no fresher tissue can be obtained prior to treatment initiation on day 1. Post-treatment tissues will be collected and fixed by 10% neutral buffered formalin overnight, dehydrated and paraffin embedded. Four-micrometer-thick sections will be cut. The paraffin blocks and unstained slides will be stored at room temperature. All IF staining will be performed in the Center for Immuno-Oncology Pathology Core at Dana-Farber/Harvard Cancer Center Specialized Histopathology Core, which will be a central research laboratory for this multiple-center clinical trial. Unstained slides from other centers will be shipped to Dr Evisa Gjini, Thorn building 603B, Brigham and Women Hospital, 75 Francis Street, Boston, MA, 02215.

9.1.1.2 Site(s) Performing Correlative Study

Laboratory information
The IHC staining will be conducted in the DFCI CIMAC Tissue Biomarker Lab, a research laboratory with GLP standard by Dr. Scott Rodig, who is a hematopathologist at the Brigham and Women's hospital with prior expertise evaluating PD1, PDL1 and other immunologic markers in paraffin embedded tumor samples [92].

9.2 Exploratory/Ancillary Correlative Studies

9.2.1 *Monitoring Peripheral Blood for Changes in Immune Function*

Correlative sciences will be expanded from our previously determined biology of patients treated with both radiation and immune checkpoint blockade. Subpopulations of PBMCs will be isolated, including but not limited to dendritic cells, T cells, B cells, and CD4+Ki67+, CD8+Ki67+, CD4+ICOS+, CD8+ICOS+. populations. Phenotype changes in these cell populations by CyTOF will be determined as a function of treatment. These include regulatory and effector immune panels, naïve and memory CD4, CD8 and NK lymphocyte populations. Given its importance in immune regulation and association, we will evaluate Tie-2 expressing monocytes (TEM).

9.2.1.1 Collection and handling of Specimen(s)

Serial blood/plasma samples will be collected at baseline and then prior to cycle 2. A panel of cytokines and chemokines will be tested in plasma using Olink. Absolute lymphocyte count (ALC) will be monitored.
Peripheral blood mononuclear cells (PBMCs) will be collected from whole blood to assess immune cell populations. PBMCs will be cryoforzen and plasma will be snap frozen for batched analysis. CyTOF will be performed in order to identify different T cell populations, their activation status, and the production of different cytokines as well as other immune cell populations

9.2.1.2 Site(s) Performing Correlative Study

Laboratory information
CyTOF will be performed by the DFCI CIMAC Immune Assessment Lab led by Dr. Stephen Hodi, Mariano Severgnini and Emily Thrash. Olink will be performed at the Mt. Sinai CIMAC led by Dr. Sacha Gnjatic.

9.2.2 *Spatial quantification of the tumor microenvironment*

We hypothesize that co localization of multiple immune markers including PD-L1, PD-L2, PD-1, CD3, and CD8 will be associated with favorable response. We also predict that in the colorectal cohort, these factors will be influenced by either low or high-dose radiation.

9.2.2.1 Site(s) Performing Correlative Study

Laboratory information
The IF staining will be conducted in the DFCI CIMAC Tissue Biomarker Lab, a research laboratory with GLP standard under the direction of Dr. Scott Rodig a hematopathologist at the Brigham and Women's hospital with prior expertise evaluating PD1, PDL1 and other immunologic markers in paraffin embedded tumor samples [92].

9.2.3 *Sequencing of DNA and RNA*

Previous studies have suggested that mutational burden may predict for response among patients treated with PD-1 or CTLA-4 inhibitors. Tissue collected from mandatory biopsies in conjunction with sequencing performed on peripheral blood will determine mutational burden to correlate with response and also RNA expression to better correlate the tumor microenvironment and associate with IHC and IF protein expression data.

9.2.3.1 Collection and handling of Specimen(s)

Tumor specimens will be collected at baseline in patients enrolled on both cohorts. Pre treatment archived specimens will be retrieved if no fresher tissue can be obtained prior to treatment initiation on day 1. Post treatment tissues will be collected and fixed by 10% neutral buffered formalin overnight, dehydrated and paraffin embedded. Four-micrometer-thick sections will be cut. The paraffin blocks and unstained slides will be stored at room temperature.

9.2.3.2 Site(s) Performing Correlative Study

Laboratory information
The sequencing will be conducted in the DFCI CIMAC Translational Immunogenomics Lab and UC Davis Comprehensive Cancer Center under the direction of Dr. Arta Monjazeb, a research

laboratory under the direction of Dr. Catherine Wu and Dr. Monjazeb have extensive prior experience evaluating sequencing and RNA expression data.

9.3. Electronic Collection of PRO-CTCAE data

Site users of ePRO and the Patient Cloud require the same access as those using Rave. Access to the trial in the Patient Cloud is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS).

Site users are referred to the Medidata Learning Tool for reference information on Patient Cloud ePRO for CRAs.

Patient will view the survey questions on his/her device. The patient will have a window of 48 hours to complete the survey. Once the patient hits the submit button, the questions will no longer be on his/her device and will be directly sent to the RAVE database and available to the site CRAs for compliance monitoring.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 4 weeks prior to start of protocol therapy. Scans and x-rays must be done ≤5 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. Note that all study visits in the calendar are specified by week, but should be performed on the same day of the week when feasible and every effort should be made to schedule them +/-2 days.

Cohort 1 – Non small cell lung cancer

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13-52	Off Treatment[c]
MEDI4736(durvalumab)		A				A				A				A[e]	
Tremelimumab		B				B				B				B[e]	
Radiation therapy			C				C				C			C[e]	
Informed consent	X														
Demographics	X														
AE/SAE Assessments[m]		X				X				X				X[e]	X
Medical history	X	X				X				X				X[e]	
Concurrent meds[d]	X													X	X
Physical exam	X	X				X				X				X[e]	X
Vital signs[p]	X	X				X				X				X[e]	X
Performance status	X	X				X				X				X[e]	X
CBC w/diff, plts	X	X[k]				X				X				X[e]	X
Serum chemistry[a]	X	X[k]				X				X				X[e]	X
EKG[j]	X														
Hepatitis B and C and HIV[n]	X														
Urinalysis	X[i]														
Tumor measurements	X		Tumor measurements should be performed during week 7 or 8 and then repeated every *12* weeks +/- 5 days. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												
Radiologic evaluation[l]	X		Radiologic measurements should be performed during week 7 or 8 and then every *12* weeks +/- 5 days while on treatment .												X[o]
B-HCG	X[b]	X				X				X				X[e]	X[e]
Head MRI [dh]	X													X[d]	
Research blood samples	X					X									
Biopsy of site(s) of disease	X[f]							X[g]							
PRO-CTCAE[q]	X		X		X		X		X				X	X	X

A: *MEDI4736(durvalumab): Administered intravenously at a dose of 1500mg every 4 weeks for a maximum of 13 doses.*
B: *Tremelimumab: Administered intravenously at a dose of 75mg every 4 weeks for a maximum of 4 doses.*
C: *Radiation therapy: Administered only on week 2 for Arm A(high dose radiation) and every 4 weeeks for a maximum of 4 times in Arm B (low dose radiation)*
a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. Also amylase, creatinine clearance, gamma glutamyltransferase, lipase, and magnesium, CPK, TSH. Free T3 or free T4 also measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system. .
b: Serum pregnancy test (women of childbearing potential). Women of child-bearing potential must have a negative serum **beta**-HCG pregnancy test during screening and a negative urine **beta**-HCG pregnancy test within 24 hours of starting treatment.
c: Every 12 weeks during weeks 12-52 and then 30,60, 90 days after discontinuation
d: Every 12 weeks
e: Every 4 weeks
f: Archival tissue may be used in place of biopsy in this cohort.
g: To be performed week 7 or 8. Optional in patients with irradiated lesions outside the liver. For patients who receive radiation to the liver, this second biopsy is required unless unsafe to perform.
h: Head CT may be substituted for MRI if patient cannot tolerate MRI. Subsequent MRI's to be performed only if previously treated brain metastases or when clinically indicated.
i: At baseline (screening) and then as clinically indicated.
j: Abnormal findings should be repeated and require appropriate clinical evaluation. Normal EKGs do not require repeating.
k: If screening laboratory assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1
l: CT Chest, Abdomen, and Pelvis (CAP)
m: During scheduled history and physical exams and during monitoring of AE's, attention should be paid to the side effects resulting from radiation and any potential enhancement of these due to the administration of immunotherapy.
n: Negative serologies over the preceding year may replace screening study
o: when off treatment for reasons other than progression after week 7-8, until week 52.
p: Vital signs timepoints for infusions are pre-dose, every 30 minutes; post-dose 30 and 60 minutes (+/- 10 minutes)
q: PRO-CTCAE items to be completed at baseline, every 2 weeks for 8 weeks and then every 4 weeks for a total of 8 cycles. All patients on any arm of study will answer the same list of PRO-CTCAE questions.

The following visits and assessments are required after discontinuing study treatment:

Days following discontinuation:

30, 60 and 90 days (+/-5 days): physical exam, vital signs, body weight, CBC with diff, serum chemistries[a], pregnancy test for WOCB (urine or serum) AE/SAE assessments, concurrent medications, and performance status

Cohort 2 – Colorectal cancer

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13-52	Off Treatment[c]
MEDI4736(durvalumab)		A				A				A				A	
Tremelimumab		B				B				B				B	
Radiation therapy			C				C				C			C	
Informed consent	X														
Demographics	X														
AE/SAE Assessments[l]	X	X				X				X				X[e]	X
Medical history	X	X				X				X				X[e]	
Concurrent meds[d]	X													X	
Physical exam	X	X				X				X				X[e]	X
Vital signs[p]	X	X				X				X				X[e]	X

Performance status	X	X				X				X				X[e]	X
CBC w/diff, plts	X	X[h]				X				X				X[e]	X
Serum chemistry[a]	X	X[h]				X				X				X[e]	X
EKG[f]	X														
Hepatitis B and C and HIV[m]	X														
Urinalysis	X[f]														
Tumor measurements	X		Tumor measurements should be performed during week 7-8 and then repeated every *12* weeks +/- 5 days. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												
Radiologic evaluation[k]	X		Radiologic measurements should be performed during week 7 or 8 and then every *12* weeks +/- 5 days while on treatment.												X[o]
B-HCG	X[b]	X				X				X				X[e]	X[e]
Research blood samples	X					X									
Biopsy of site(s) of disease	X[i]							X[j]							
PRO-CTCAE[q]	X		X		X		X		X				X	X	X

A: *MEDI4736(durvalumab): Administered intravenously at a dose of 1500mg every 4 weeks for a maximum of 13 doses.*
B: *Tremelimumab: Administered intravenously at a dose of 75mg every 4 weeks for a maximum of 4 doses.*
C: *Radiation therapy: Administered only on week 2 for Arm A (high dose radiation) and every 4 weeeks for a maximum of 4 times in ARM B (low dose radiation)*
a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. Also Also amylase, creatinine clearance, gamma glutamyltransferase, lipase, and magnesium,CPK, TSH. Free T3 or free T4 also measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system..
b: Serum pregnancy test (women of childbearing potential). Women of child-bearing potential must have a negative serum **beta**-HCG pregnancy test during screening and a negative urine**beta**-HCG pregnancy test within 24 hours of starting treatment.
c: Every 12 weeks during weeks 12-52 and then 30,60, 90 days after discontinuation
d: Every 12 weeks
e: Every 4 weeks
f: At baseline (screening) and then as clinically indicated.
g: Abnormal findings should be repeated and require appropriate clinical evaluation.Normal EKGs do not require repeating.
h: If screening laboratory assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1.
i: Archival tissue may be used in place of biopsy in this cohort.
j. To be performed week 7 or 8. Optional in patients with irradiated lesions outside the liver. For patients who receive radiation to the liver, this second biopsy is required unless unsafe to perform.
k: CT Chest, Abdomen, and Pelvis (CAP)
l:: During scheduled history and physical exams and during monitoring of AE's, attention should be paid to the side effects resulting from radition and any potential enhancement of these due to the administration of immunotherapy.
m: Negative serologies over the preceding year may replace screening study
o: when off treatment for reasons other than progression after week 7-8, until week 52.
p: Vital signs timepoints for infusions are pre-dose, every 30 minutes; post-dose 30 and 60 minutes (+/- 10 minutes)
q: PRO-CTCAE items to be completed at baseline, every 2 weeks for 8 weeks and then every 4 weeks for a total of 8 cycles. All patients on any arm of study will answer the same list of PRO-CTCAE questions.

The following visits and assessments are required after discontinuing study treatment:

Days following discontinuation:

30, 60 and 90 days (+/-5 days): physical exam, vital signs, body weight, CBC with diff, serum chemistries[a], pregnancy test for WOCB (urine or serum) AE/SAE assessments, concurrent medications, and performance status.

Table Urinalysis

Urinalysis should be done at baseline (screening) and then as clinically indicated

Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

Note: Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 12 weeks after an initial scan at 7-8 weeks to guide further therapy. In addition to a baseline scan, confirmatory scans should also be obtained 6-8 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with MEDI4736and tremelimumab.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: In this protocol radiation is being tested for its ability to potentiate systemic immune therapy. Therefore, none of the irradiated lesions will be considered measurable for the determination of systemic response. However, local response within in the irradiated field will be assessed as below.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a

lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. Note: When evaluable, response of irradiated lesions will be tracked, but these lesions will not count as target lesions when determining systemic response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the

beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

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

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

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used

as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

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

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or

scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the 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 (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Confirmation is required for this trial.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated

Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

11.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

11.1.7 Response Review

N/A

11.2 Antitumor Effect – Hematologic Tumors

N/A

11.3 Other Response Parameters

11.3.1 Definition of Tumor Response Using Immune-Related Response Criteria (irRC)

irRC will be used as a secondary endpoint in comparison to the primary endpoint of response as per RECIST v1.1

The sum of the longest diameter of lesions (SPD) at tumor assessment using the immune-related response criteria (irRC) for progressive disease incorporate the contribution of new measurable lesions. Each net Percentage Change in Tumor Burden per assessment using irRC criteria accounts for the size and growth kinetics of both old and new lesions as they appear.

11.3.2 Impact of New Lesions on irRC

New lesions in and of themselves do not qualify as progressive disease. However, their contribution to total tumor burden is included in the SPD which in turn feeds into the irRC criteria for tumor response. Therefore, new non-measurable lesions will not discontinue any subject from the study.

11.3.3 Definition of Target Lesions Response Using irRC

- **irComplete Response (irCR):** Complete disappearance of all target lesions. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.
- **irPartial Response (irPR):** Decrease, relative to baseline, or 50% or greater in the sum of the products of the two largest perpendicular diameters of all target and all new measurable target lesions (i.e., Percentage Change in Tumor Burden). Note: the appearance of new measurable lesions is factored into the overall tumor burden, but does not automatically qualify as progressive disease until the SBD increases by $\geq$25% when compared to SPD at nadir.
- **irStable Disease (irSD):** Does not meet criteria for irRC or irPR, in the absence of progressive disease.
- **irProgressive Disease (irPD):** At least 25% increase Percentage Change in Tumor Burden (i.e. taking SPD of all target lesions and any new lesions) when compared to SPD at nadir.

11.3.4 Definition of Non-Target Lesions Response Using irRC

- **irComplete Response (irCR):** Complete disappearance of all non-target lesions. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.
- **irPartial Response (irPR) or irStable Disease (irSD):** Non-target lesion(s) are not considered in the definition of PR; these terms do not apply.
- **irProgressive Disease (irPD):** Increases in number or size of non-target lesion(s) does not constitute progressive disease unless/until the Percentage Change in Tumor Burden increases by 25% (i.e. the SPD at nadir of the target lesions increases by the required amount).

11.3.5 Definition of Overall Response Using irRC

Overall response using irRC will be based on these criteria:

- **Immune-Related Complete Response (irCR):** Complete disappearance of all tumor lesions (target an non-target) together with no new measurable/unmeasurable lesions for at least 4 weeks from the date of documentation of complete response.
- **Immune-Related Partial Response (irPR):** The sum of the products of the two largest perpendicular diameters of all target lesions is measured and captured as the SPD baseline. At each subsequent tumor assessment, the SPD of the two largest perpendicular diameters of all target lesions and of new measurable lesions are added together to provide the Immune Response Sum of Product Diameters (irSPD). A decrease, relative to baseline, of the irSPD compared to the previously SPD baseline of 50% or greater is considered an irPR.
- **Immune-Related Stable Disease (irSD):** irSD is defined as the failure to meet criteria for immune complete response or immune partial response, in the absence of progressive disease

• **Immune-Related Progressive Disease (irPD):** It is recommended in difficult cases to confirm PD by serial imaging. Any of the following will constitute PD:
▪ At least 25% increase in the SPD of all target lesions over baseline SPD calculated for the target lesions.
▪ At least 25% increase in the SPD of all target lesions and new measurable lesions (irSPD) over the baseline SPD calculated for the target lesions.

Criteria for determining overall response by irRC are summarized as follows:

Immune-Related Response Criteria Definitions

Target Lesion Definition	Non-Target Lesion Definition	New Measurable Lesions	New Unmeasurable Lesions	Percent change in tumor burden (including measurable new lesions when present)	Overall irRC Response
Complete Response	Complete Response	No	No	–100%	irCR
Partial Response	Any	Any	Any	≥ –50%	irPR
				<–50% to <+25%	irSD
				>+25%	irPD
Stable Disease	Any	Any	Any	<–50% to <+25%	irSD
				>+25%	irPD
Progressive Disease	Any	Any	Any	≥+25%	irPD

11.3.6 Immune-Related Best Overall Response Using irRC (irBOR)

irBOR is the best confirmed overall response over the study as a whole, recorded between the date of first dose until the last tumor assessment before subsequent therapy (except for local palliative radiotherapy for painful bone lesions) for the individual subject in the study. For the assessment of irBOR, all available assessments per subject are considered.

irCR or irPR determinations included in the irBOR assessment must be confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 4 weeks after the criteria for response are first met.

11.3.7 Local response is defined as irRC applied to the irradiated lesions. This is not applicable in the case of an irradiated bone lesion.

11.3.8 Abscopal response rate
Abscopal response is defined as described previously [51] to be a decrease in the longest diameter of at least 30% in any measurable (>1cm) non-irradiated lesion from baseline. A

complete abscopal response is defined as the complete disappearance of a measurable non-irradiated lesion and a partial abscopal response was defined as at least a 30% decrease in the longest diameter. Progressive disease in this context is defined as at least a 20% increase in the longest diameter of the best measurable non-irradiated lesion, whereas stable disease was defined as insufficient shrinkage or growth to qualify for a partial abscopal response or complete abscopal response or progressive disease.

11.3.9 irRECIST
irRECIST utilizes the principles of iRC described above except uses unidirectional measurements as opposed to bidirectional measurements. This exploratory endpoint will also explore % change in the tumor burden as compared to baseline scan.

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

The Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second stage of a Phase 2 trial will require sign-off by the Protocol Principal Investigator and the Protocol Statistician.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

12.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Read-Only, CRA, Lab Admin, SLA or Site Investigator) on either the

LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the recommended phase 2 dose (RP2D), and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

12.2.3 Data Submission for PRO-CTCAE assessments

Electronic collection of PRO-CTCAE through the ePRO is source documentation. The surveys are not stored on the devices. Rather, each survey is available for a window of 48 hours. Once the patient submits the survey, the responses go directly into the RAVE database and no longer are stored on the device. The site CRAs can access the RAVE workbench and see if the patient has completed all the questions and the date of completion.

There are no other records to audit or review.

12.3 CTEP Multicenter Guidelines

12.4 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and

disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

13.1.1 Primary Endpoint: The primary endpoint of this study is overall response rate as determined by RECIST 1.1.

13.1.2 Secondary Endpoints: Secondary endpoints include progression-free and overall survival, overall response according to irRC, and assessments of safety.

Clinical laboratory tests, vital signs and weight measurements, physical exams, performance status evaluations, imaging scans and any other medically indicated assessments, including subject interviews, will be performed to detect new abnormalities and deteriorations of any pre-existing conditions.

13.2 Endpoint Definitions

13.2.1 Primary Endpoint

At each restaging, patients will be classified as achieving one of the following according to RECIST criteria: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or unevaluable for response, which includes early death from malignancy, toxicity, or other causes in addition to missing or unknown response. Best overall response will be calculated as the best response recorded from the date of randomization for each patient, taking as reference for progressive disease the smallest measurements recorded since the start of treatment. Objective response rate (ORR) is defined as the proportion of patients within a treatment arm who have a best response of either CR or PR. The denominator used to calculate ORR within a treatment will be the number of patients randomized to the respective treatment arm. All randomized patients will be used in randomized comparisons across arms. For single arm evaluation of response, all patients who started treatment will be considered evaluable.

13.2.2 Secondary Endpoints

Progression-free survival (PFS): Time from date of randomization until objective disease progression (per RECIST) or death, whichever occurs first. For patients without progression, follow-up will be censored at the date of last adequate restaging, unless death occurs within 12 weeks following the date last known progression-free, in which case the death will be counted as a PFS event.

Overall survival (OS): Time from randomization to death from any cause. For patients lost to follow-up or who have no documentation of death at the time of final analysis, follow-up will be censored at the date of last assessment of vital status.

Objective Response per Immune-Related Response Criteria (irORR): The proportion of patients within a treatment arm who have a best response of irCR or irPR according to Immune-Related Response Criteria. The denominator used to calculate irORR within each treatment will be the

number of patients randomized to the respective treatment arm.

13.3 Randomization

13.3.1 NSCLC
Patients enrolled in the NSCLC cohort will be randomly assigned in equal proportions to therapy with MEDI4736(durvalumab)/tremelimumab alone, MEDI4736(durvalumab)/tremelimumab with low-dose RT, or MEDI4736(durvalumab)/tremelimumab with high-dose RT. Forty patients will be assigned to each of the three therapies (120 in total).

13.3.2 Colorectal Cancer
Patients enrolled in the colorectal cancer cohort will be randomly assigned in equal proportions to either MEDI4736(durvalumab)/tremelimumab with low-dose RT or MEDI4736(durvalumab)-tremelimumab with high-dose RT. A total of 60 patients will be enrolled.

For each disease cohort, the randomization will follow a permuted block scheme with random block sizes of 3 or 6 for cohort 1 and 2 or 4 for cohort 2. The randomization schemes will be developed by the trial statistician and coordinated via CTEP.

13.4 Sample Size/Accrual

13.4.1 Sample Size

NSCLC: Best overall response rate is the endpoint on which the sample size for cohort 1 is based. We estimate an overall response rate of approximately 5% for the combination of MEDI4736and tremelimumab alone based on a comparison of preliminary response rates from patients treated with dual checkpoint blockade of PD-1 and CTLA-4 (Hellman et al. ASCO 2016) as compared with PD-1 inhibitor monotherapy [6]. Two, pair-wise comparisons of therapy with high- or low-dose radiation against the control of MEDI4736(durvalumab)/tremelimumab alone will be conducted. Since a positive outcome for each comparison in this trial is the superiority of MEDI4736(durvalumab)/tremelimumab with high- or low-dose RT compared with MEDI4736(durvalumab)/tremelimumab alone, we propose one-sided chi-squared tests for the null hypothesis of equality of the response rates with a 10% type-I error for each comparison. To assess for early evidence of futility or superiority of MEDI4736(durvalumab)/tremelimumab plus RT, each pairwise comparison will be based on a group sequential design with O'Brien-Fleming stopping boundaries for superiority and Gamma family boundaries (gamma=1) for futility.

When the total sample size in each comparison is 80 patients (40 per arm), a chi-squared test will have 81% power to detect a difference between a 5% response rate and 22% response rate. Interim and final analyses will be conducted after 40 and 80 patients have objective response classifications (corresponding to 50% and 100% of the total information). The critical values of the test statistic for superiority of MEDI4736(durvalumab)/tremelimumab with RT in each comparison for the interim and final analyses would be 2.054 and 1.317, corresponding to nominal significance levels of 0.02 and 0.094, respectively. If the p-value at the interim analysis is greater than 0.463 (i.e., the test statistic is less than 0.0922), there will be insufficient evidence to reject the null hypothesis and the trial for that comparison (and enrollment to the respective RT arm)

will stop early for futility. Under this design, the probability of stopping for futility at the interim analysis is 0.56 if the null hypothesis is true. Sample size and power calculations were conducted using EaST 5.4.Note that enrollment to the MEDI4736(durvalumab)/tremelimumab-alone arm will continue as long as enrollment continues in at least one RT arm.

Colorectal Cancer: Best overall response rate is the endpoint on which the sample size is based for cohort 2. There is a low historical response rate in microsatellite stable colorectal cancer [14]; therefore, we will employ two, parallel, Simon optimal two-stage designs to identify therapy combinations worthy of further study in this patient population. A promising response rate in this population would be 20%. Sixty patients will be randomly assigned to high-dose or low-dose radiotherapy plus MEDI4736(durvalumab)/tremelimumab (30 per therapy). The high-dose and low-dose designs will be conducted separately. Ten patients will be enrolled in the first stage for each therapy. If there is at least one response among the first ten patients, then an additional 20 patients will be enrolled to that treatment arm for a total of 30 patients in each comparison. If four or more patients in a comparison have response then that treatment combination would be considered promising. Each design has a type-I error of 5% (target alpha=0.10) and 80% power to detect a difference between a null rate of 5% and a promising response rate of 20%. If the null hypothesis is true, the probability is 0.60 that accrual in that treatment arm will stop at the end of the first stage. If the cohort combining LDFRT is stopped early for futility, we will review the data and possibly amend the protocol at that time.

13.5 Accrual

The projected accrual to this trial is approximately 6 non-small cell lung cancer patients and 3 colorectal cancer patients per month. We estimate that 24 months will be required to complete study accrual.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	5	5	0	0	**10**
Asian	5	5	0	0	**10**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	15	15	5	5	**40**

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
White	40	40	10	10	**100**
More Than One Race	5	5	5	5	**20**
Total	**70**	**70**	**20**	**20**	**180**

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13.6 Interim Safety Analysis

NSCLC: For an early and detailed safety assessment, complete review of the adverse event data for the first 10 patients assigned to MEDI4736(durvalumab)/tremelimumab/high-dose RT and for the first 10 patients assigned to treatment with MEDI4736(durvalumab)/tremelimumab/low-dose RT will occur after completion of one cycle (4 weeks) of therapy. If three of more patients within a therapy arm experience one or more dose-limiting toxicities, the addition of RT will be considered too toxic and enrollment to that arm will stop.

Colorectal Cancer: Concurrent with the end of the first stage of each Simon design, a complete safety review of adverse event data will be conducted for each treatment after completion of two cycles of therapy. If three of more patients within a therapy experience one or more severe or pre-specified dose-limiting toxicities, enrollment to that arm will stop.

The table below summarizes the probability of observing three or more severe or unexpected toxicities in the first 10 patients of a cohort for various underlying true probabilities. If the true incidence of severe or unexpected toxicities is 25% or higher, then the probability is at least 0.47 that three or more patients will be observed with these toxicities at the time of the early safety monitoring.

Operating Characteristics of Early Safety Monitoring

True Incidence of Unexpected or Severe Toxicity	Probability of Observing Three or More Patients with Toxicity among First 10
10%	0.07
15%	0.18
20%	0.33
25%	0.47
30%	0.62

13.7 Analysis of Primary Endpoints

NSCLC: The proportion of patients with response (CR or PR according to RECIST) will be compared for each pair-wise comparison of RT-containing therapy and control using chi-squared tests. The difference between the proportions responding will be presented with a 90% confidence interval.

Colorectal Cancer: Response rates within each two-stage design will be calculated and presented with one-sided 90% confidence intervals estimated using the method of Atkinson and Brown, which allows for the two-stage design.

13.8 Analysis of Secondary Endpoints

13.8.1 Safety

Assessments of safety and tolerability will be performed on an ongoing basis. At the conclusion of the study, safety data will be summarized for each treatment arm within each cohort. The proportions of subjects with grade-3 or higher adverse events will be presented with exact binomial confidence intervals. Although it is unexpected after a successful early safety assessment, if at any time after the early safety review 33% or more of patients in a cohort are observed with severe toxicities, the regimen in that cohort will pause and a comprehensive safety analysis will be conducted.

13.8.2 Overall Survival and Progression-Free Survival

The distributions of progression-free and overall survival will be summarized using the method of Kaplan-Meier. Median times for each therapy arm will be accompanied by 90% confidence intervals based on log(-log(endpoint)) methodology. For cohort 1, the pairwise comparisons between the MEDI4736(durvalumab)/tremelimumab alone and MEDI4736(durvalumab)/tremelimumab with RT arms will be conducted using log-rank tests.

13.8.3 Response per irRC

The proportions of patients with response according to irRC will be presented with 90% exact binomial confidence intervals. For cohort sizes of 30 (cohort 2) and 40 patients (cohort 1), the confidence intervals will be no wider than 0.32 and 0.28, respectively. For cohort 1, the pairwise comparisons of irORR between RT and the control arm will be conducted using chi-squared tests.

13.8.4 Local Control Rate and Abscopal Response Rates

The proportions of patients with local control within the irradiated field will be reported within each RT treatment arm and presented with 90% exact binomial confidence intervals. Similar presentations will be used for abscopal response rates. For cohort sizes of 30 (cohort 2) and 40 patients (cohort 1), the confidence intervals will be no wider than 0.32 and 0.28, respectively.

13.8.5 Prognostic Effect of PD-L1 Expression

The prognostic effect of PD-L1 expression within the tumor microenvironment will be investigated for each treatment arm. Each patient will be retrospectively classified according to pre-treatment PD-L1 expression (positive or negative). Clinical response (CR or PR vs. SD/PD/Unevaluable) will be compared according to PD-L1 expression using Fisher's exact tests.

13.8.6 Prognostic Effect of T-cell infiltration

The prognostic effect of infiltrating CD8+ T-cells within the tumor microenvironment will be investigated for each treatment arm. Each patient will be retrospectively classified according to pre-treatment infiltration (positive or negative). Clinical response (CR or PR vs. SD/PD/Unevaluable) will be compared according to infiltration using Fisher's exact tests.

Paired biopsies are mandated in the colorectal arm and also in lung cancer patients that receive liver directed radiation unless there are concerns regarding safety. To give a sense of power for studies to be done on paired tissue, differences will be taken for all measures and the hypotheses is that biomarkers if PD-L1 expression and T-cell infiltration will increase (measured as a continuous quantitative variable) post therapy. Thus, assuming that within each cohort we will obtain post treatment biopsies of at least 25 patients, using a two-sided 0.05 level paired t-test there is at least 80% power to detect a 0.59 SD change in mean of a quantitative correlative parameter using a two-sided test with 5% type I error. Quantitative measure will be transformed to attain normality or appropriate non-parametric tests will be conducted. Power for these tests will be further improved if a greater percentage of paired biopsies are obtained. We will obtaining biopsy samples from participating sites as the trial proceeds and will continuously monitor the percentage of patients for whom a post treatment biopsy is not obtained so we can try to address any issues or questions regarding this. Our plan is to pursue paired tissue analyses separately within each cohort, but since a goal of the study is to more generally evaluate the impact radiation on PD-L1 expression and tumor infiltrating lymphocytes, if needed we can consider analyses that combine data from the 2 cohorts of patients if numbers are not sufficient in the individual cohorts.

13.8.7 Exploratory Analysis of PRO-CTCAE

The PRO-CTCAE data will be evaluated for data quality, to characterize baseline symptom status of patients on study and the change over time, to explore the development of symptomatic AEs and the change over time, and to explore the patient scores with other relevant clinical information including, but not limited to clinician graded AEs. Feasibility of the electronic collection as well compliance of patients with the reporting will be captured.

13.9 Reporting and Exclusions

13.9.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with MEDI4736and tremelimumab with or without RT.

13.9.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3)

stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

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PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

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APPENDIX A PERFORMANCE STATUS CRITERIA

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

Appendix B Drug Information and Contact Sheet

Version 3 (January

Important – what you should do

If you notice any side effects while taking durvalumab, with or without tremelimumab, tell your study doctor or nurse immediately

- The sooner you report any side effects, the faster they can be treated before they get worse
- It is very important that you do not ignore your side effects or try to treat them on your own
- If you go to the hospital in an emergency, or see a doctor who is not your usual study doctor, take this information sheet with you, so they can better help you

Please tell all healthcare professionals (doctors, nurses, pharmacists) you see that you are being treated with durvalumab with/without tremelimumab, even if you are seeing them for a different reason

Ask them to contact your doctor using the contact details on the back of this leaflet

People to contact

Remember! If you experience any side effects while taking durvalumab with/without tremelimumab you should contact your study doctor or nurse immediately. If not treated, these side effects could become serious

Study doctor name:

Contact no:

Study nurse name:

Contact no:

Important information for healthcare providers

Please notify the study investigator immediately, using the details above, if a participant presents with any of the events described on this sheet

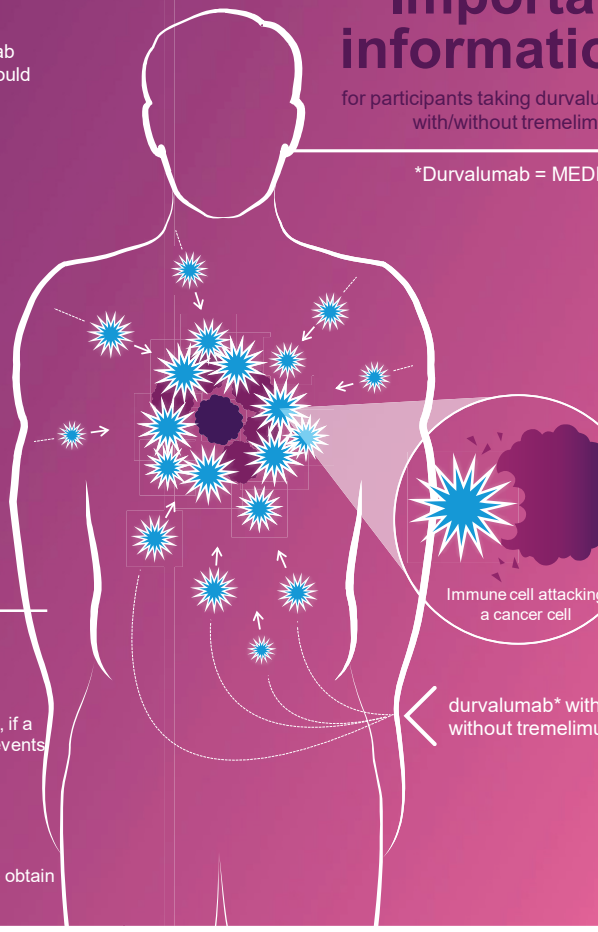
Prompt, appropriate treatment is imperative

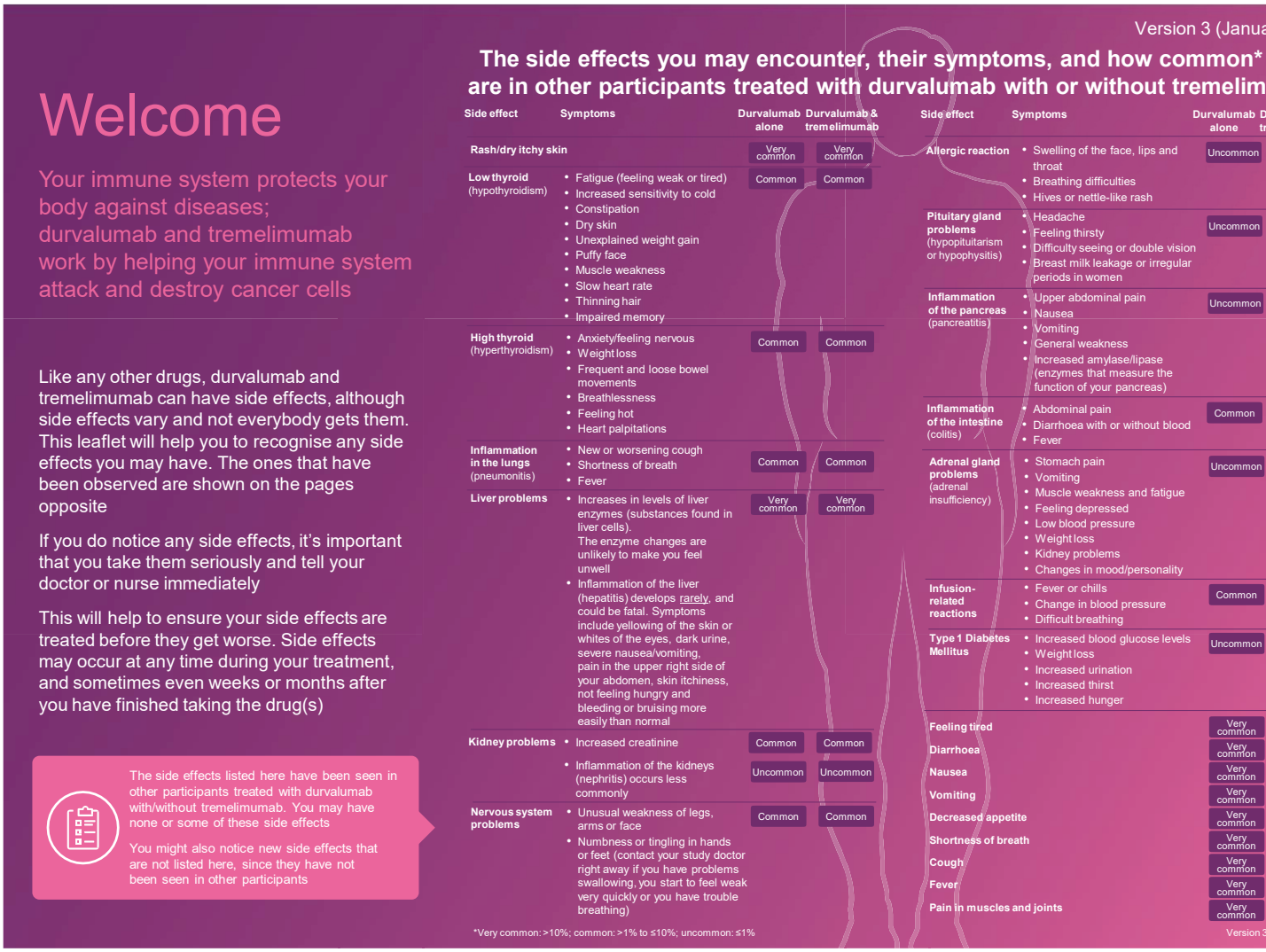
Corticosteroids play a pivotal role in controlling these side effects. Please obtain guidance from the study investigator

Importa
informatic

for participants taking durvalu
with/without tremelim

*Durvalumab = MED





APPENDIX C Guidance Document for Research Blood Samples

I. Research blood Sample Requirements:

- ❖ 4 -5 lavender top (EDTA), 6 ml vacutainer tubes, should be collected at each time point, following the protocol, referring to section, 10. Study Calendar.
- ❖ It is important that each tube be filled to at least 5ml, to ensure sufficient sample volume.
- ❖ Vacutainer tubes should be immediately inverted 5 times

Sites may either process PBMCs on site, following standard protocols and ship frozen pellets and plasma separately (**preferred method**) or immediately express ship unprocessed vacutainer tubes using an overnight courier, ex. Fed Ex. **The integrity of the blood samples requires they be processed within 24 hours of collection.**

II. Research Sample Shipping Directions:

1. Complete the ***Blood Sample Shipping Record*** (Template on next page) and include a copy of it with the sample shipment. Please enter the specific information in the highlighted areas.
2. Email the completed ***Blood Sample Shipping Record*** to Mariano_Severgnini@DFCI.HARVARD.EDU, providing notification of the shipment and include in the body of the email the shipping/tracking information (ex., FedEx tracking #xxxx).
3. Do not draw or ship samples the day before a weekend or

Unprocessed EDTA tubes: must be shipped on the day of collection
Samples are to be shipped overnight, Monday-Thursday ONLY, at ambient temperature, by overnight carrier, such as FedEx or UPS**.**

Processed samples: it is suggested to batch ship these samples at a time agreed upon by the collection site and DFCI.

PBMCs-Ship overnight, Monday-Thursday ONLY, using cryotanks containing liquid nitrogen or a styrofoam box containing dry ice, using appropriate labels, following all safety/shipping regulations. Shipments must be made by an overnight carrier, such as FedEx or UPS. Cryotanks have temperature monitors connected to an alarm system at Cryoport headquarters. Shipping temperature should be around -150C. Please contact cryoport via email at cs@cryoport.com or at (949)470-2300 for further information re: the cryotanks or temperature recorders.
Plasma-Ship overnight, Monday-Thursday ONLY, using a styrofoam box containing dry ice, using appropriate labels, following all safety/shipping regulations. Shipments must be made by an overnight carrier, such as FedEx or UPS.

Ship Samples to the address on the top left corner of the Blood Sample Shipping Record

Blood Sample Shipping record

Ship To:	Mariano Severgnini Immune Assessment Core Laboratory, (CIO) Dana-Farber Cancer Institute 450 Brookline Ave, JF406 Boston, MA 02215	**From:**	[Insert name, nam site, site # and ad here]
Phone:	(617) 632-2421 or (617) 632-2422	**Phone:**	[Insert phone #]
Email:	Mariano_Severgnini@DFCI.HARVARD.EDU	**Email:**	[Insert email]

Subject ID	[Unique Patient Identifier#]
List of Samples	[example- unprocessed EDTA tubes/frozen PBMCs/frozen plasma # vials, sampl date, Cycle time point]
	[example- unprocessed EDTA tubes/frozen PBMCs/frozen plasma # vials, sampl date, Cycle time point]

Subject ID	[Unique Patient Identifier#]
List of Samples	[example- unprocessed EDTA tubes/frozen PBMCs # vials, sample date, Cycle time point]
	[example- unprocessed EDTA tubes/frozen PBMCs/frozen plasma # vials, sampl date, Cycle time point]

Subject ID	[Unique Patient Identifier#]
List of Samples	[example- unprocessed EDTA tubes/frozen PBMCs/frozen plasma # vials, sampl date, Cycle time point]
	[example- unprocessed EDTA tubes/frozen PBMCs/frozen plasma # vials, sampl date, Cycle time point]

Please include a copy of this completed document with the shipment and email the recipient above to provide notification

Comments:

Guidance Document for Research Tissue Samples

I. Research Tissue Sample Requirements:

- Archival, pre-, and on-treatment tissue -Formalin-fixed paraffin embedded block(s) and or unstained/unbaked slides (15-20), stored at room temperature.
  - In general, samples should be placed in fixative at a 10:1 ratio and fixed for at least 24-48 hours but thicker tissue samples may require longer fixation.
- Optional: If sufficient excess tissue is available at biopsy (generally if more than one biopsy has been performed) then at least 10mg and preferably 20 - 50mg of tumor tissue can be placed in RNAlater (1mL), then snap frozen in liquid nitrogen and stored at -70 to -80°C. These samples can batched and then shipped overnight on dry ice.
- All specimens shall be collected following the protocol, referring to section, 10. Study Calendar.

For labelling the blocks please refer to the following guidance;

The block label should be unique and should indicate a) the subject ID and b) time of the biopsy.

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examples:

Pre-treatment biopsies should be labeled as: **XXXXX-XXX PRE**,
Week 7 biopsies should be labeled as: **XXXXX-XXX W7**
On-treatment biopsies should be labeled as: **XXXXX-XXX ONTX**
Post-treatment biopsies should be labeled as: **XXXXX-XXX POST**
where XXXXX-XXX is the unique subject id (EXAMPLE: WI020-027)

II. Research Sample Shipping Directions:

1. Complete the ***Tissues Sample Shipping Record*** (Template on next page) and include a copy of it with the sample shipment. Please enter the specific information in the highlighted areas. Please also include a copy of the Pathology report (de-identified, noting subject # on the report) that correlates to the tissue specimens.

1. Email the completed ***Tissue Sample Shipping Record*** to, Evisa_Gjini@DFCI.HARVARD.EDU.
In the email please include the shipping/tracking information (ex., FedEx tracking #xxxx).

2. Please ship all tissue and or slides following your site specific shipping policies to ensure safe handling, travel and arrival.

Ship Samples to the address on the top left corner of the Tissue Sample Shipping Record

Tissue Sample Shipping Record

Ship To:	Dr. Evisa Gjini Brigham & Women's Hospital 20 Shattuck Street Thorn building 603B Boston, MA 02215	**From:**	[Insert name, name of site, site # and address here]
Phone:	(617) 732-8289	**Phone:**	[Insert phone #]

Email:	Evisa_Gjini@DFCI.HARVARD.EDU	**Email:**	[Insert email]

Subject ID	[Unique Patient Identifier#]
List of Sample(s)	[example- Accession #xxxxx and sample type -1 tissue block]
	[example- Accession #xxxxx and sample type -20 slides]
Timepoint of Sample(s)	[example – pretreatment, on treatment, on progression, archival prior t previous PD-1 therapy (NSCLC cohort only)]
Location from which tissue was obtained (if known).	[Please be as specific as possible: example – irradiated liver lesion, unirradiated liver lesion, irradiated lung lesion, etc.]

Subject ID	[Unique Patient Identifier#]
List of Sample(s)	[example- Accession #xxxxx and sample type -1 tissue block]
	[example- Accession #xxxxx and sample type -20 slides]
Timepoint of Sample(s)	[example – pretreatment, on treatment, on progression, archival prior t previous PD-1 therapy (NSCLC cohort only)]
Location from which tissue was obtained (if known).	[Please be as specific as possible: example – irradiated liver lesion, unirradiated liver lesion, irradiated lung lesion, etc.]

Please include a copy of this completed document, the related path report (if applicable) with the shipment and email the recipient above to provide notification

Comments:

APPENDIX D: RECIST GUIDELINE (version 1.1)

https://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf#search=%22Recist 1.1%22

APPENDIX E: PRO-CTCAE Items for Collection

PRO-CTCAE is intended to enhance the quality of adverse event data reporting in clinical trials, provide data that complements and extends the information provided by clinician reporting using CTCAE, represent the patient perspective of the experience of symptomatic adverse events, and improve detection of potentially serious adverse events.

The selection of PRO-CTCAE should be complementary to the clinician identified AEs for ongoing monitoring.

Please refer to the PRO-CTCAE Terms of Use for more information.

A Phase 2 Study of MEDI4736(durvalumab) and Tremelimumab Alone or in Combination with High or Low-Dose Radiation in Metastatic Colorectal and NSCLC				
NSCLC Cohort: To assess safety and tolerability of combined checkpoint blockade with MEDI4736(durvalumab) and tremelimumab alone or with high or low-dose radiation in NSCLC				
Colorectal Cohort: To assess safety and tolerability of combined checkpoint blockade with MEDI4736 and tremelimumab with high or low-dose radiation				
For Protocol 10021: System Organ Class	**MEDI4736 (Durvalumab) Adverse event term - CAEPR**	**Tremelimumab Adverse event term - CAEPR**	**Possible Related PRO-CTCAE Items**	**Attributes**
Gastrointestinal Disorders	Diarrhea	Diarrhea	**Diarrhea**	Frequency
	Nausea	Nausea	**Nausea**	Frequency & Severity
	Vomiting	Vomiting	**Vomiting**	Frequency & Severity
		Abdominal pain	**Abdominal pain**	Frequency, Severity, & Interference
General Disorders	Fatigue	Fatigue	**Fatigue**	Severity & Interference
	Pain	Pain	**General Pain**	Frequency, Severity, & Interference
Metabolism and Nutrition Disorders	Anorexia	Anorexia	**Decreased appetite**	Severity & Interference
Nervous System		Headache	**Headache**	Frequency,

Disorders				Severity, & Interference
		Pneumonitis	**Shortness of breath**	Severity & Interference
Respiratory, Thoracic Disorders		Pneumonitis	**Cough**	Severity & Interference
	Pruritus	Pruritus	**Itching**	Severity
Skin and Subcutaneous Tissue Disorders	Rash maculo-papular	Rash maculo-papular	**Rash**	Presence/absence
		Dry Skin	**Skin dryness**	Severity

References

- PRO-CTCAE Website: https://healthcaredelivery.cancer.gov/pro-ctcae/
- PRO-CTCAE Items Library
- PRO-CTCAE NCI Scientific Leadership Team
- PRO-CTCAE Development Team
- Publications

1. APPENDIX F MEDIDATA PATIENT CLOUD REGISTRATION

a. Introduction

Electronic collection of patient-reported outcomes (ePRO) through Medidata Patient Cloud ePRO is preferred but not mandatory. Traditional paper submission is the other option. Patients who will be submitting PRO data via Patient Cloud ePRO must be registered to Patient Cloud ePRO by an authorized site user after the patient has been registered to the study. Patients may use their own device or one provisioned by the site.
Sites can use a site-specific tablet for multiple study participants. If a site-specific tablet is used, CRAs need to setup the tablet for multiple users. Multi-user mode lets multiple study participants log in to Patient Cloud ePRO with their passwords or their PIN codes on the same device.

b. CRA Site Users

Site users of Patient Cloud ePRO require the same access as Rave. Access to the trial in the Patient Cloud ePRO is granted through the iMedidata. Site users will receive an invitation to Patient Cloud ePRO and the site user must accept the invitation to begin patient registration. Users who have not previously activated their iMedidata/Rave account at the time of initial approval of site registration will also receive a separate invitation from

iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Please note, site users will not be able to access the study in the Patient Cloud ePRO until all required Rave and study specific trainings are completed. Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

c. CRA Instructions for Setting the Patient Cloud ePRO App to Multi-User Mode

Sites conducting studies entirely on-premise, where participants travel to the sites to fill out questionnaires, can use multi-user mode. Multi-user mode lets multiple study participants log in to Patient Cloud with their passwords or their PIN codes on the same device. . If patients will be using devices supplied by the institution, site staff will need to help the patient to access the device if the device is locked.

The study provider will download the Patient Cloud ePRO app to the device and set the Patient Cloud ePRO App to multi-user mode if applicable.

To switch from personal mode (default setting) to multi-user mode:

1. Tap **About** at the bottom of the log in screen.
2. Scroll to the bottom and tap **Advanced User**.
3. Tap **Mode**, then select **Multi-User**.
4. Tap **Yes** to confirm.
5. Tap the back arrows to return to the log in screen.

Note: If enabling multi-user mode on a device, it is highly recommended that completion reminders are turned off on that device.

For a video demonstration, see Show Me How to Switch to Multi-User Mode.

d. Patient Users

To use the Patient Cloud ePRO, patients will need to use their own device (IOS, Android phone or tablet). Short term data will only appear on the patient's device until responses are completed and submitted. The patient data will import directly into the database once the patient selects the "Submit" button and will no longer be visible on the patient's device.

Sites can provide a site-specific tablet for multiple study participant use on site. If a site-specific tablet is used, study staff need to setup the tablet for multiple users. Multi-user mode lets multiple study participants log into Patient Cloud ePRO with their passwords or their PIN codes on the same device. **Refer to Appendix E on Setting the Patient Cloud ePRO App to Multi-User Mode.**

e. Patient Instructions for Accessing the Patient Cloud Using Your Personal Device

Downloading the Patient Cloud ePRO App

If you are using your personal device, and you do not have the Patient Cloud ePRO app, use the following instructions. When downloading the app, you must use the Apple ID or Google account associated with the device. If the Patient Cloud ePRO app is already on the device, or if you are using a provider's device, you can skip this section.
You will need an email address that you agree to use for this purpose. The e-mail address is needed to identify you on the Patient Cloud Application and for you to receive notifications to let you know when forms are due. Your e-mail address will only be used for this survey study, and will not be used for mail or marketing purposes.
If you decide to use the electronic method to complete the questionnaires, and do not have an e-mail address, you may sign up for one at no charge at many different websites. A few sites that are commonly used and will allow you to create an email address very easily are Yahoo, Gmail, and Outlook.
For iOS:

1. An Apple ID is required for downloading the Patient Cloud ePRO app.
2. Tap the *App Store* icon.
3. Search for *Medidata Patient Cloud* and follow the installation instructions.

Note: Patient Cloud ePRO is listed as an iPhone App in the App store. When using an iPad, please view the search results under iPhone apps.

For Android:

1. A Google account is required for downloading the Patient Cloud ePRO app
2. Tap the *Play Store* icon.
3. Search for *Medidata Patient Cloud* and follow the installation instructions.

Registering

You must register in order to complete and submit your study forms. When you register, you will create a username, which is your email address, and a password that allows you to log in to the Patient Cloud ePRO app.

Note**:** You must have an activation code to begin this process. If you do not have an activation code, please contact your provider.

There are two possible ways to register. Your provider may have sent you a link to a web address where you may register from any web browser, including the one on your device. The other way to register is on the Patient Cloud ePRO app.

1. If registering from the Patient Cloud app, tap Register on the bottom of the log in page. If registering on the web, open the URL shield.imedidata.com on a web browser.

2. Enter your activation code and tap Activate.
3. On the next page, read the instructions and tap Next.
4. Read the privacy notice and tap I agree. Then tap OK to confirm.
5. Enter and confirm your email address. Tap Next.
6. Enter and confirm your password. Tap Next.
7. Choose a security question by scrolling through the dropdown menu to display the question of your choice.
8. Enter your security question response.
9. Tap Create my account to complete your registration.

If you registered on the Patient Cloud ePRO app, it automatically logs you out. If you registered on the web, you are presented with the option to download the Patient Cloud ePRO app. You can then proceed to log in with the credentials you created.

Logging in to the App

1. Enter your Email and Password that you created during the registration process. (If you previously set a PIN code, just enter your four-digit PIN.)
2. Tap Log in.

Note: If you do not remember your password, tap **Forgot Password**, and follow the instructions provided.

Setting a PIN Code

The first time you log in to the Patient Cloud ePRO app, you are given the option to create a PIN code. A PIN code allows you to bypass the step of entering your email and password every time you need to log in to the Patient Cloud ePRO app. Instead, you can enter a four-digit PIN.

1. If you wish to set a PIN code the first time you log in, tap Yes when prompted.
2. Note: You can also set your PIN at a later time by tapping the options menu on the top left of most pages and selecting Set PIN.
3. Enter a four-digit PIN.
4. Re-enter the four-digit PIN to confirm.

If you forget your PIN code, tap **Forgot PIN** and you can access the app using your email and password. You may reset your PIN by tapping the options menu on the top left of most pages and selecting Set PIN.

Resetting Your Password

You can reset your password by using the options menu at the top left of most pages.

1. Tap the options menu icon.
2. Tap Reset Password.

3. Follow the instructions to reset your password.

Completing and Submitting Forms

Once logged in, forms related to your study display on the Tasks page. If you are enrolled in multiple studies, select the appropriate study first, and then select a form. New forms can appear on the Tasks page at any time, depending on how the study is designed.

There are two types of forms displayed on the Task List page:

- *Scheduled Forms* (with a  icon): These forms have a "Due Date" indicator in them so you are aware of the last day by which you will need to complete the form. If the form is due in less than one day, you will see the due time in hours.
- *Anytime Forms* (with a  icon): These forms have "Last Completed Time" indicator on them which tells the most recent date or time when you completed the form. If you start a form, but do not complete it, you will see an 'Incomplete" status beneath the form name, along with a half-moon icon.

1. Select the appropriate form.
2. Follow the on-screen instructions until you reach the end of the form where you are given the opportunity to review and change your responses prior to submitting.
3. Review your responses by scrolling down the list.
4. If you need to change an answer, tap the question to go back and change the answer.
5. When you are ready to submit, tap Submit Your Data.

Note: Once a form is submitted, you will be unable to edit any of your responses. In some cases, you may be asked to acknowledge your submission by entering your password.

f. Patient Compliance

The patient data imports directly from a device into the Rave database. There are no documents to audit. The patient-submitted electronic responses are the source documentation.

g. Security

All data is encrypted on the device (256 bit encryption and Hyper Text Transfer Protocol Secure [https]) and the app requires each user to have a unique username and password for access. If the user is idle for too long (5 minutes inactivity time), the app will time out and the user will need to log in again.
The data will only reside on the device for a short period of time. Once the user clicks "Submit," the data is securely transferred over HTTPS between the device and internal

relay to the Rave database. Except for the patient's email address, no identifying information is stored in iMedidata. The email address is stored for what purpose? The patient's email links the device (used) and (ePRO) account to where the data is stored. The patient's email is not visible to anyone in the system.
The Patient information (email/password) does not reside in Medidata Rave EDC and the patient accounts are hidden in iMedidata from sites and LPOs.
The Patient Cloud ePRO application is 21 CFR Part 11 compliant and acts as a gateway between the device and Medidata Clinical Cloud (MCC).
Messages and information communicated to and from the Patient Cloud ePRO are encrypted and therefore this information cannot be read if intercepted while in transit.

h. Site checklist for activities prior to consenting a patient

- ☐ Site staff must have already completed required eLearning for the Patient Cloud ePRO application. See last bullet with hyperlink to training video library.Contact the LPO to request appropriate Rave access to register patients in Patient Cloud ePRO
- ☐ Accept study invitation at iMedidata.com
    - Note: you must be rostered in RSS and have received an invitation to Patient Cloud ePRO
- ☐ Verify the IOS or Android operating system is using the most current version
- ☐ Verify Patient Cloud ePRO app is using the most current version
- ☐ If using institutional shared devices, first patient only: Verify Patient Cloud ePRO app is in Multi-User mode
- ☐ Refer to Review Quick Reference Guides for videos and other procedural information