Phase II Study to Assess the Efficacy of Durvalumab (MEDI4736) and Tremelimumab Plus Radiotherapy or Ablation in Patients with Metastatic Colorectal Cancer

PROTOCOL FACE PAGE FOR MSK THE RAPEUTIC/D !AGNOSTIC PROTOCOL

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List of Abbreviations

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

Abbreviation or Specialized Term	Definition
GI	gastrointestinal
HCl	hydrochloride
HCV	hepatitis C .,;rus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency \irus
ICF	infonned consent fonn
ICH	International Conference on Hannonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN	interferon
IgG1K	immunoglobulin G1 kappa
IHC	immunohistochemistry
IL	interleukin
IM	immunogenicity
IRB	Institutional Review Board
irAE	immune-related adverse event
irRC	immune-related response criteria
IV	intravenous(ly)
IVRS	interactive voice response system
IWRS	interactive web response system
MAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Acti'<ities
MDSC	Myeloid derived suppressor cell
miRNA	micro ribonucleic acid
MMR	mismatch repair
mRNA	messenger ribonucleic acid
MRI	magnetic resonance imaging
MRSD	maximum recommended starting dose
MTD	maximum tolerated dose
NCI	National Cancer Institute
NOAEL	no-observed adverse-effect-level
NSCLC	non-small cell lung cancer
OBD	optimal biological dose
ORR	objective response rate

Abbreviation or Specialized Term	Definition
OS	overall sur\ival
PBMC	peripheral blood mononuclear cell
PD	progressiw disease
PD-1	programmed death 1
PD-L1	programmed death ligand 1
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
Q2W	every 2 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	Radiofrequency ablation
RT	Radiation therapy
SAE	serious adverse event
SD	stable disease
SID	subject identification
SMC	Safety Monitoring Committee
SPD	sum of products of diameters
SRT	Safety Re\iew Team
SUSAR	suspected unexpected serious adverse reaction
TIL	tumor infiltrating lymphocyte
TNF-0	tumor necrosis factor alpha
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US FDA	United States Food and Drug Administration
USA	United States of America
WFI	water for injection
WHO	Wod Health Organization
w/v	weight/\Clume

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1.1 PROTOCOL SUMMARY AND/OR SCHEMA

Names of Investiaational druas: Durvalumab and Tremelimumab
Title of Study: Phase II Study to Assess the Efficacy of Durvalumab and Tremelimumab plus Radiotherapy or Ablation in Patients with Metastatic Colorectal Cancer
Study Centers: MSKCC
Study Period: 24 months I Phase of Development: II
Objectives: The primary objective is Overall Response Rate in disease that is not ablated or radiated (Complete Response and Partial Response). The secondary objectives are: 1. Safety and tolerability of durvalumab and tremelimumab plus radiotherapy (RT) or ablation 2. Oi.erall Sun.ival of durvalumab and tremelimumab plus RT or ablation 3. Progression free survival rate at 1 year 4. Progression free survival rate at 2 years The exploratory objectives are to evaluate biomarkers that may correlate with activity of durvalumab and tremelimumab plus RT or durvalumab and tremelimumab plus ablation in colorectal cancer (CRC), or orosoectii.elv identifv CRC oatients likelv to resoond to treatment.
Study Design: This will be a Simon two-stage design, phase II study. It will be conducted to determine the efficacy and safety of (1) durvalumab and tremelimumab plus RT in subjects with metastatic CRC who are undergoing RT as standard therapy; and, (2) durvalumab and tremelimumab plus ablation in subjects with metastatic CRC who are undergoing ablation as standard therapy. Eligible patients will hai.e metastatic colorectal cancer and received at least two prior standard therapies for metastatic disease for which they are considered appropriate. Patients will be stratified according to eligibility for RT (cohort 1) or ablation (cohort 2). Patients in cohort 1 will have at least one metastatic lesion for which palliatiw RT is considered appropriate standard therapy, and at least one other measurable index lesion that will not undergo RT. Patients in cohort 2 will have at least one metastatic lesion for which palliatii.e ablation is considered appropriate standard therapy, and at least one other measurable index lesion that will not undergo ablation. All subjects will undergo ablation or begin RT within 7 days after dose #1 of durvalumab and tremelimumab. Subjects will receii.e durvalumab and tremelimumab every four weeks (Q4W), for 4 months, and then continue durvalumab alone every four weeks (Q4W) until confirmed progression of disease, initiation of alternative cancer therapy, unacceptable toxicity, or other reasons to discontinue treatment occur. Patients who had a prior response, continued on durvalumab monotherapy and did not discontinue tremelimumab due to toxicity may resume combination therapy with tremelimumab plus durvalumab for 4 doses upon disease progression, followed by durvalumab monotherapy. Repeat palliative RT in cohort 1, or ablation in cohort 2, will be permitted in select cases. Repeat palliatii.e RT or ablation may include measurable index lesion(s) that is(are) being followed for response measurements if at least one index lesions remains to be followed. Patients will be evaluated by physical exam and routine blood tests ei.ery 2 weeks during the first 4 months then every 4 weeks during the study period. CT or MRI will be performed during screening, and then at 8 week intervals. Tumor measurements and determination of tumor responses will be performed according to RECIST 1.1. Subjects may continue to receive durvalumab and tremelimumab beyond radiographic progression in the absence of clinical deterioration. All subjects will be followed up to 2 years for survival or until the study closes. The primary endpoint of this trial is the response rate in CRC treated with RT plus durvalumab and tremelimumab (cohort 1) or ablation plus durvalumab and tremelimumab (cohort 2). A two-stage Simon's optimal design will be employed to test the null hypothesis that the true response rate is S5% versus the altematii.e hypothesis that the true response rate is at least 25% with type I and II error rates of 10% each. Each cohort will be evaluated separately for this purpose. In the first stage, we will accrue 9 patients in each cohort. If 0 objectii.e tumor responses (PR or CR) are observed among the 9 subjects treated in a cohort, then subject enrollment will be terminated in that cohort. If at least 1 response is observed among the 9 subjects treated in either cohort, then the study will be expanded to enroll a total of 24 treated subjects in that cohort. If one cohort is filled and at least 1 response is observed, it may be expanded under the investigator's discretion, regardless of the other cohort's accrual status. In the likelihood that we observe at least one resoonse in each of the 9

subjects treated in stage 1 of the two cohorts, iiwill be at the discretion of the investigators which cohort to expand based on phannacodynamic data (such as circulating CEA, changes in composition/activation status of lymphocyte subsets present in peripheral blood mononuclear cell preparations or tumor immunohislochemistry analysis, and/or circulating cytokines/ chemokines). At the end of the study, if 2 or less objective tumor responses are observed in a cohort, then the study will be considered not worthy of further imestigation in that particular cohort. If at the end of the study 3 tumor responses per RECIST 1.1 are observed in a cohort, then further investigation of durvalumab and tremelimumab plus RT and/or durvalumab and tremelimumab plus ablation will be considered worthwhile. The study will complete when all subjects have either progressed or discontinued from the study for other reasons. This study requires accrual of a minimum of 1S subjects and up to a maximum of 33 subjects. The accrual time is estimated to be 2 years. Baseline and on treatment tumor biopsies for research purposes will be mandatory in the first 9 patients in each cohort. On treatment biopsies will be perfonned 1 week after the completion of radiation or ablation (of the radiated/ ablated lesion) and then 4 weeks after dose #1 of durvalumab andremelimumab (of a non-radiated/ ablated lesion). Tumor immunohistochemistry may be perfonned for PD-L 1 expression and quantification of tumor infiltrating lymphocyte (TIL) subtypes, including CDS+ T-cells, CD4+ T-cells, Regulatory T-cells (Treg), and Myeloid Derived Suppressor Cells (MDSCs). Peripheral blood samples will be obtained in all patients al baseline then weeks 2, 4 and S. Plasma may be analyzed for change in antibody responses to a broad panel of antigens (seromics). Flow cytometry may be perfonned for peripheral blood immune cell phenotype and their activation status, including CDS+ T-cells, CD4+ T-<:ells, Tregs, and MDSCs. The amount of PDL-1 expression, changes in immune cell repertoire and activation status within the tumor and peripheral blood as well as immune responses against specific tumor antigens will be correlated with clinical outcome in an exploratory manner in order to identify predictiw makers for response, and to further our understanding of durvalumab and tremelimumab plus RT, and durvalumab and tremelimumab plus ablation in CRC.

Diagnosis and Main Criteria for Inclusion in the Study:

Inclusion Criteria

1. Willing and able to provide written infonned consent.
2. Hislologically- or cylologically- confinned CRC.
3. Metastatic CRC.
4. Subjects have received at least two standard chemotherapy regimens for which they would be considered eligible (al least one containing a 5-ft uoropyrimidine), or systemic chemotherapy is not indicated in the setting of low volume metastatic disease.
5. Al least one tumor for which palliative RT is considered appropriate standard therapy (cohort 1); or, at least one tumor for which pallialiw ablation is considered appropriate standard therapy (cohort 2).
6. Al least one index lesion that will not undergo RT or ablation, and is measurable based on RECIST 1.1.
7. 1S years of age on day of signing infonned consent.
S. Consent for tumor biopsies (stage 1only) and blood draws (all patients) for research purposes.
9. Consent for use of available archived tissue and tumor obtained during a standard procedure, for research purposes.
10. Perfonnance status of ECOG 0 or 1.
11. Female subjects must either be of non-reproductiw potential (i.e., post-menopausal by history: 60 years old and no menses for ;,:1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative serum pregnancyest upon study entry.
12. Adequate organ function, defined as:
    - Absolute Neutrophil Count 1,500/mm^3.
    - Platelet count 100,000/mm^3.
    - Serum crealinine s 1.5 x ULN or CrCl O mUmin.
    - AST and ALT s 2.5 x ULN or s 5 x ULN for subjects with liwr metastases.
    - Bilirubin s 1.5 x ULN or Direct bilirubin s ULN.
    - Hemoglobin S.O g/dl

Exclusion Criteria

1. Currently participating in/ has participated in a study of an invesligalional agent or using an inwstigational device within 4 weeks.
2. Chemotheranv, monoclonal antibodv, taroeted small molecule theranv, within 4 weeks orior to

dose #1 or who has not recovered (i.e., s Grade 1 or at baseline) from adverse events due to a previously administered agent (excluding alopecia or toxicity not anticipated to interfere with planned treatment on study). 3. Known or suspected MSI-H CRC. 4. Any prior Grade ;,3 immune-related adverse event (irAE) while receiving any previous, immunotherapy agent, or any unresolved irAE >Grade 1, except endocrinopathies and asymptomatic amylase/lipase. 5. If subject receiwd major surgery, they must haw recovered adequately from the toxicity and/or complications from the intervention per clinical discretion of the investigator prior to starting therapy. 6. Concurrent active malignancy that requires systemic treatment. 7. Untreated CNS metastases and/or carcinomatous meningitis. 8. Actiw autoimmune disease requiring systemic immune suppressive treatment within the past 2 years. 9. Actiw, non-infectious pneumonitis. 10. Actiw or prior documented inflammatory bowel disease 11. Prior allogeneic organ transplant. 12. Actiw infection requiring systemic therapy. 13. Psychiatric/ substance abuse disorders that would interfere with cooperation with the requirements of the trial. 14. Known Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies). 15. Known actiw and untreated Hepatitis B or C. 16. Liw vaccine within 30 days prior to the first dose of trial treatment. 17. Current or prior use of immunosuppressiw medication within 14 days before the first dose of durvalumab or tremelimumab with the exceptions of premedication and intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10mg/day of prednisone, or an equivalent corticosteroid. The use of topical steroids is permitted. 18. Hypersensiti-.ity to durvalumab or tremelimumab, or any excipients on the formulation. 19. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results. 20. Female patients who are pregnant or breastfeeding or male or female patients of reproductiw potential who are not willing to employ effective birth control from screening to 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period 21. QT interval corrected for heart rate (QTc) ;, 470ms calculated from 1 electrocardiogram (ECG) using Fridericia's Correction 22. History of primary immunodeficiency 23. Known history of pre-.ious clinical diagnosis of tuberculosis 24. Subjects with uncontrolled seizures
Number of Subjects: 18 to 33, including patients in cohort 1 (n-9) and cohort 2 (n-9), if response is observed, the cohort with the hiaher resnnnse rate mav enroll uo to 24

2.1 OBJECTIVES AND SCIENTIFIC AIMS

- The primary objective is Overall Response Rate in disease that is not ablated or radiated of durvalumab and tremelimumab plus RT or durvalumab and tremelimumab plus ablation in subjects with metastatic CRC, according to RECIST v1.1. A response in a non-ablated or non-radiated lesion is an abscopal effect.
- The secondary objectives are to determine:
  - Safety and tolerability of durvalumab and tremelimumab plus RT or ablation
  - Overall Survival of durvalumab and tremelimumab plus **RT** or ablation
  - Progression free survival rate at 1 year
  - Progression free survival rate at 2 years

- The exploratory objectives are to evaluate biomarkers that may correlate with actMty of durvalumab and tremelimumab plus RT or ablation in CRC, or prospectively identify CRC patients likely to respond to treatment.

3.1 BACKGROUND AND RATIONALE

3.2 Immune responses against cancer

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 i'nmune 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. Programmed cell death ligand 1 (PO-L1) is one such protein, and is upregulated in a broad range of cancers with a high frequency, with up to BB% expression in some tumor types. In a number of these cancers, including lung (MI et al, 2011), renal (Thompson et al, 2005; Thompson et al, 2006; Krambeck et al, 2007), pancreatic (Nomi et al, 2007; Loos et al, 200B; Wang et al, 2010), ovarian cancer (Hamanishi et al, 2007), and hematologic malignancies (Andorsky et al, 2011; Brusa et al, 2013) tumor cell expression of PO-L1 is associated with reduced survival and an unfavorable prognosis.

Programmed cell death ligand 1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PO-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, PO-L1 on antigen-presenting cells binds to P0-1 or COBO on activated T cells and delivers an inhibitory signal to the T cell (Keir et al, 200B; Park et al, 2010). This results in reduced T-cell activation and fewer activated T cells in circulation. In the tumor microenvironment, PO-L1 expressed on tumor cells binds to P0-1 and COBO 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 (Zou and Chen, 200B).

Immune responses directed against tumors are one of the body's natural defenses against the growth and proliferation of cancer cells. T cells play a critical role in antitumor immunity and their infiltration and activity have been linked to improved prognosis in a number of cancers (Pages et al, 2010; Nakano et al, 2001; Suzuki et al, 2011; Burt et al, 2011). Immune evasion, primarily through suppression of T-cell activity, is now recognized as one of the hallmarks of cancer. Such evasion can occur via a range of mechanisms including production of suppressive cytokines such as IL-10, secretion of chemokines and growth factors that recruit and sustain suppressive regulatory T cells (Tregs) and inflammatory macrophages, and expression of inhibitory surface molecules such as B7-H1. Tumor types characterized as being responsive to immunotherapy-based approaches include melanoma (Weber et al, 2012), renal cell carcinoma (RCC; McOennott, 2009), bladder cancer (Krescmik and Griffith, 2009), and malignant mesothelioma (Bograd et al, 2011). Inhibition of CTL.A4 signaling is a validated approach to cancer therapy, as shown by the approval in 2011 of ipilimumab for the treatment of metastatic melanoma based on statistically significant and clinically meaningful improvement in OS (Hodi et al, 201O; Robert et al, 2011).

In general, tumor response rates to anti-CTLA-4 therapy are low (~10%). However, in patients who respond, the responses are generally durable, lasting several months even in patients with aggressive tumors such as refractory metastatic melanoma. Because these agents work through activation of the immune system and not by directly targeting the tumor, responses can occur late and some patients may have perceived progression of their disease in advance of developing disease stabilization or a tumor response. In some cases, early growth of pre-existing lesions or the appearance of new lesions may have been due to immune-cell infiltration into the tumor and not due to proliferation and extension of neoplastic cells, per se (Wolchok et al, 2009). Overall, although the impact on conventionally-defined PFS can be small, durable response or stable disease seen in a proportion of patients can lead to significant prolongation of OS. The melanoma data with ipilimumab clearly demonstrate that a small proportion of patients with an objective response had significant prolongation of OS, supporting the development of this class of agents in other tumors. Although Phase 2 and Phase 3 studies of tremelimumab in metastatic melanoma did not meet the primary endpoints of response rate and OS, respectively, the data suggest activity of tremelimumab in melanoma {Kirkwood et al, 2010; Ribas et al, 2013). In a large Phase 3 randomized study comparing tremelimumab with dacarbazine {DTIC}/temozolomide in patients with advanced melanoma, the reported median OS in the final analysis was 12.58 months for tremelimumab versus 10.71 months for DTIC/temozolomide {HR = 1.1416, p = 0.1272; Ribas et al, 2013).

3.2 Durvalumab

The non-clinical and clinical experience is fully described in the current version of the durvalumab Investigator's Brochure {IB Version 9.0).

Durvalumab is a human monoclonal antibody {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.} As durvalumab is an engineered mAb, it does not induce antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity. The proposed mechanism of action for durvalumab is interference of the interaction of PD-L1.

PD-L1 is expressed in a broad range of cancers with a high frequency, up to 88% in some types of cancers. In a number of these cancers, including lung, the expression of PD-L1 is associated with reduced survival and an unfavorable prognosis. In lung cancer, only 12% of patients with tumors expressing PD-L1 survived for more than 3 years, compared with 20% of patients with tumors lacking PD-L1 (Mu et al 2011.). Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance anti-tumor immune responses in patients with cancer. Results of several non-clinical studies using mouse tumor models support this hypothesis, where antibodies directed against PD-L1 or its receptor PD-1 showed anti-tumor activity {Hirano et al 2005, Iwai et al 2002, Okudaira et al 2009, Zhang et al 2008.).

Durvalumab has been given to humans as part of ongoing studies as a single drug or in combination with other drugs. As of the DCO dates {15Apr2015 to 12Jul2015, durvalumab IB Version 9.0), a total of 1,883 subjects have been enrolled and treated in 30 ongoing durvalumab clinical studies,

including 20 sponsored and 10 collaborative studies. Of the 1,883 subjects, 1,279 received durvalumab monotherapy, 440 received durvalumab in combination with tremelimumab or other anticancer agents, 14 received other agents (1 gefitinib, 13 MEDI6383), and 150 have been treated with blinded investigational product. No studies have been completed or terminated prematurely due to toxicity.

As of 09Feb2015, PK data were available for 378 subjects in the dose-escalation and dose-expansion phases of Study CD-ON-durvalumab-1108 following treatment with durvalumab 0.1 to 10 mg/kg every 2 weeks (Q2W) or 15 mg/kg every 3 weeks (Q3W). The maximum observed concentration (Cmax) increased in an approximately dose-proportional manner over the dose range of 0.1 to 15 mg/kg. The area under the concentration-time curve from 0 to 14 days (AUCo.1•) increased in a greater than dose-proportional manner over the dose range of 0.1 to 3 mg/kg and increased dose-proportionally at <!: 3 mg/kg. These results suggest durvalumab exhibits nonlinear PK likely due to saturable target-mediated CL at doses < 3 mg/kg and approaches linearity at doses <!: 3 mg/kg. Near complete target saturation (soluble programmed cell death ligand 1 [sPD-L1] and membrane bound} is expected with durvalumab <!: 3 mg/kg Q2W. Exposures after multiple doses showed accumulation consistent with PK parameters estimated from the first dose. In addition, PK simulations indicate that following durvalumab 10 mg/kg Q2W dosing, > 90% of subjec1s are expected to maintain PK exposure <!: 40 µg/mL throughout the dosing interval.

As of 09Feb2015, a total of 388 subjects provided samples for ADA analysis. Only 8 of 388 subjects (1 subject each in 0.1, 1, 3, and 15 mg/kg cohorts, and 4 subjec1s in 10 mg/kg cohort) were ADA positive with an impact on PK/pharmacodynamics in 1 subject in the 3 mg/kg cohort.

3.3 Tremelimumab

The non-clinical and clinical experience is fully described in the current version of the tremelimumab Investigator's Brochure (IB Version 6.0).

Tremelimumab is an IgG 2 kappa isotype mAb directed against the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) also known as CD152 (cluster of differentiation 152). This is an immunomodulatory therapy (IMT) that is being developed by AstraZeneca for use in the treatment of cancer.

Binding of CTLA-4 to its target ligands (B7-1 and B7-2) provides a negative regulatory signal, which limits T-cell activation. Anti-CTLA-4 inhibitors antagonize the binding of CTLA-4 to B7 ligands and enhance human T-cell activation as demonstrated by increased cytokine (interleukin [IL]-2 and interferon [IFN] gamma) production in vitro in whole blood or peripheral blood mononuclear cell (PBMC) cultures (Tarhini and Kirkwood 2008.). In addition, blockade of CTLA-4 binding to B7 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and anti-tumor activity in animal models, including killing of established murine solid tumors and induction of protective anti-tumor immunity. (Refer to the tremelimumab IB, Edition 5.0, for more information.) Therefore, it is expected that treatment with an anti-CTLA-4 antibody, such as tremelimumab, will lead to increased activation of the human immune system, increasing anti-tumor activity in patients with solid tumors.

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. As of the data cut-off date of 12 November 2014

(for all studies except D4190C00006, which has a cut-off date of 4 December 2014), 973 patients have received tremelimumab monotherapy (not including 497 patients who have been treated in the blinded Phase 2b study, D4880C00003) and 208 patients have received tremelimumab in combination with other agents. Details on the safety profile of tremelimumab monotherapy are summarized in Section 0. Refer to the current tremelimumab IB for a complete summary of non-clinical and clinical information; see Section 6.6 for guidance on management of tremelimumab-related toxicities.

Tremelimumab exhibited a biphasic PK profile with a long terminal phase half-life of 22 days. Overall, a low incidence of *ADAs* (<6%) was observed for treatment with tremelimumab.

3.4 Durvalumab in combination with tremelimumab

The rationale for combining durvalumab and tremelimumab is that the mechanisms of CTLA-4 and PD-1 are non-redundant, suggesting that targeting both pathways may have additive or synergistic activity (Pardall 2012.). In fact, combining immunotherapy agents has been shown to result in improved response rates (RRs) relative to monotherapy. For example, the concurrent administration of nivolumab and ipilimumab to patients with advanced melanoma induced higher objective response rates (ORRs) than those obtained with single-agent therapy. ImportanUy, responses appeared to be deep and durable (Walchak et al 2013.).

Similar results have been observed in an ongoing study of durvalumab + tremelimumab in NSCLC (Antonia et al 2014.). Study D4190C00006 is a Phase Ib dose-escalation study to establish safety, PK/PDx, and preliminary anti-tumor activity of durvalumab + tremelimumab combination therapy in patients with advanced NSCLC. The dosing schedule utilized is durvalumab every 2 weeks (q2w) or every 4 weeks (q4w) up to Week 50 and 48 (12 months), combined with tremelimumab q4w up to Week 24 for 7 doses then every 12 weeks for 2 additional doses for up to 12 months. The study is ongoing and continues to accrue.

Study D4190C00006: As of 20Feb2015, durvalumab PK (n = 55) and tremelimumab PK (n = 26) data were available from 10 cohorts (1a, 2a, 3a, 3b, 4, 4a, 5, 5a, 8, and 9) following durvalumab every 4 weeks (Q4W) or QM dosing in combination with tremelimumab Q4W regimens. An approximately dose-proportional increase in PK exposure (Cmax and area under the concentration-time curve from 0 to 28 days [AUCo.2aD of both durvalumab and tremelimumab was observed over the dose range of 3 to 15 mg/kg durvalumab Q4W and 1 to 10 mg/kg tremelimumab Q4W. Exposures following multiple doses demonstrated accumulation consistent with PK parameters estimated from the first dose. It is to be noted that steady state PK parameters are based on limited numbers of subjec1s. The observed PK exposures of durvalumab and tremelimumab following combination were consistent with respective monotherapy data, indicating no PK interaction between these 2 agents.

As of 20Feb2015, ADA data were available from 60 subjects for durvalumab and 53 subjects for tremelimumab in Study D4190C00006. Four of 60 subjects were ADA positive for anti-durvalumab antibodies post treatment. One of 53 subjec1s was ADA positive for anti-tremelimumab antibodies post treatment. There was no clear relationship between ADA and the dose of either durvalumab or tremelimumab, and no obvious association between ADA and safety or efficacy.

Durvalumab has also been combined with other anticancer agents, including gefitinib, dabrafenib, and trametinib. To date, no PK interaction has been observed between durvalumab and these agents.

3.5 Safety

3.5.1 Durvalumab safety

Potential risks, based on the mechanism of action of durvalumab and related molecules, include immune-mediated reactions, such as enterocolitis, dermatitis, hepatitis/hepatotoxicity, endocrinopathy, pneumonitis, and neuropathy or neurologic events. Additional important potential risks include infusion-related reactions, hypersensitivity, anaphylaxis or serious allergic reactions, serious infections, and immune complex disease.

Study CD-ON-durvalumab-1108: The safety profile of durvalumab monotherapy in the 694 subjects with advanced solid tumors treated at 10 mg/kg Q2W in Study CD-ON-durvalumab-1108 has been broadly consistent with that of the overall 1,279 subjects who have received durvalumab monotherapy (not including subjects treated with blinded investigational product) across the clinical development program. 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. As of 07May2015, among the 694 subjects treated with durvalumab 10 mg/kg *Q2N* in Study CD-ON-durvalumab-1108, a total of 378 subjects (54.5%) experienced a treatment-related AE, with the most frequent (occurring in :!! 5% of subjects) being fatigue (17.7%), nausea (8.6%), diarrhea (7.3%), decreased appetite (6.8%), pruritus (6.3%), rash (6.1%), and vomiting (5.0%). A majority of the treatment-related AEs were Grade 1 or Grade 2 in severity with :!! Grade 3 events occurring in 65 subjects (9.4%). Treatment-related :!! Grade 3 events reported in 3 or more subjects (:!! 0.4%) were fatigue (12 subjects, 1.7%); increased aspartate aminotransferase (AST; 7 subjec1s, 1.0%); increased gamma-glutamyltransferase (GGT; 6 subjects, 0.9%); increased alanine aminotransferase (ALT; 5 subjects, 0.7%); and colitis, vomiting, decreased appetite, and hyponatremia (3 subjects, 0.4% each). Six subjects had treatment-related Grade 4 AEs (upper gastrointestinal hemorrhage, increased AST, dyspnea, neutropenia, colitis, diarrhea, and pneumonitis) and 1 subject had a treatment-related Grade 5 event (pneumonia). Treatment-related serious adverse events (SAEs) that occurred in :!! 2 subjects were colitis and pneumonitis (3 subjects each). A majority of the treatment-related SAEs were Grade 3 in severity and resolved with or without sequelae. AEs that resulted in permanent discontinuation of durvalumab were considered as treatment related in 18 subjects (2.6%), with colitis being the most frequent treatment-related AE resulting in discontinuation (3 subjects). A majority of the treatment-related AEs resulting in discontinuation of durvalumab were :!! Grade 3 in severity and resolved with or without sequelae.

Study D4191C00003/ATLANTIC: The safety profile of durvalumab monotherapy in Study CD-ON-durvalumab-1108 is generally consistent with that of Study D4191C00003/ATLANTIC in subjects with locally advanced or metastatic non-small-cell lung cancer (NSCLC) treated with durvalumab 10 mg/kg *Q2N*. As of 05May2015, 264 of 303 subjects (87.1%) reported any AE in Study

D4191C00003/ATLANTIC. Overall, events reported in :?: 10% of subjec1s were dyspnea (18.8%), fatigue (17.8%), decreased appetite (17.5%), cough (14.2%), pyrexia (12.2%), asthenia (11.9%), and nausea (11.2%). Nearly two-thirds of the subjects experienced AEs that were Grade 1 or 2 in severity and manageable by general treatment guidelines as described in the current durvalumab study protocols. Grade 3 or higher AEs were reported in 107 of 303 subjects (35.3%). A total of 128 subjects (42.2%) reported AEs that were considered by the investigator as related to investigational product. Treatment-related AEs (all grades) reported in :?: 2% of subjects were decreased appetite (6.6%); fatigue (5.9%); asthenia (5.0%); nausea (4.6%); pruritus (4.3%); diarrhea, hyperthyroidism, hypothyroidism, and pyrexia (3.3% each); rash (2.6%); weight decreased (2.3%); and vomiting (2.0%). Treatment-related Grade 3 AEs reported in :?: 2 subjects were pneumonitis (3 subjects) and increased GGT (2 subjects). There was no treatment-related Grade 4 or 5 AEs. Ninety-four of 303 subjects (31.0%) reported any SAE. SAEs that occurred in :?: 1.0% of subjects were dyspnea (6.6%); pleural effusion, general physical health deterioration (2.3% each); pneumonia (2.0%); hemoptysis, pulmonary embolism (1.3% each); and pneumonitis, respiratory failure, disease progression (1.0% each). Nine subjects had an SAE considered by the investigator as related to durvalumab. Each treatment-related SAE occurred in 1 subject each with the exception of pneumonitis, which occurred in 3 subjects. Fifteen of 303 subjects (5.0%) have died due to an AE (pneumonia [3 subjects]; general physical health deterioration, disease progression, hemoptysis, dyspnea [2 subjects each]; pulmonary sepsis, respiratory distress, cardiopulmonary arrest [verbatim term (Vf)], hepatic failure, and sepsis [1 subject each]). None of these events was considered related to durvalumab. Twenty-three of 303 subjects (7.6%) permanently discontinued durvalumab treatment due to AEs. Events that led to discontinuation of durvalumab in :?: 2 subjects were dyspnea, general physical health deterioration, and pneumonia. Treatment-related AEs that led to discontinuation were increased ALT and increased hepatic enzyme, which occurred in 1 subject each.

3.5.2 Tremelirnumab safety

Potential risks, based on the mechanism of action of tremelimumab and related molecules (ipilimumab) include potentially immune-mediated gastrointestinal (GI) events including enterocolitis, intestinal perforation, abdominal pain, dehydration, nausea and vomiting, and decreased appetite (anorexia); dermatitis including urticaria, skin exfoliation, and dry skin; endocrinopathies including hypophysitis, adrenal insufficiency, and hyperthyroidism and hypothyroidism; hepatitis including autoimmune hepatitis and increased serum ALT and AST; pancreatitis including autoimmune pancreatitis and lipase and amylase elevation; respiratory tract events including pneumonitis and interstitial lung disease (ILD); nervous system events including encephalitis, peripheral motor and sensory neuropathies, and Guillain-Barre syndrome; cytopenias including thrombocytopenia, anemia, and neutropenia; infusion-related reactions; anaphylaxis; and serious allergic reactions. The profile of AEs and the spectrum of event severity have remained stable across the tremelimumab clinical program and are consistent with the pharmacology of the target. To date, no tumor type or stage appears to be associated with unique AEs (except for vitiligo that appears to be confined to patients with melanoma). Overall, 944 of the 973 patients (97.0%) treated with tremelimumab monotherapy as of the data cutoff date of 12 November 2014 (for all studies except D4190C00006 that has a cutoff date of 04 December 2014 and not including 497 patients who have

been treated in the ongoing blinded Phase IIb Study D4880C00003) experienced at least 1 *PE.* The events resulted in discontinuation of tremelimumab in 10.0% of patients, were serious in 36.5%, were Grade <!:3 in severity in 49.8%, were fatal in 67.7%, and were considered to be treatment related in 79.1% of patients. The frequency of any /!Es and Grade <!:3 /!Es was generally similar across the tremelimumab dose groups. However, a higher percentage of patients in the 10 mg/kg every 28 days and 15 mg/kg every 90 days groups compared with the All Doses <10 mg/kg group experienced treatment-related /!Es, *SPEs,* /!Es resulting in discontinuation of investigational product (IP}, and deaths.

3.5.3 Durvalumab + tremelimumab *safety*

No safety studies in animals have been performed combining tremelimumab with durvalumab. */!143* both CTLA-4 and PD-L1 have mechanisms of actions that enhance activation of immune cells, their potential to induce cytokine release was tested in a whole-blood assay system. Durvalumab and tremelimumab, either alone or in combination, did not induce cytokine release in blood from any donor.

Study D4190C00006: The safety profile of durvalumab and tremelimumab combination therapy in the 102 subjects with advanced NSCLC in Study D4190C00006 is generally consistent with that observed across 177 subjec1s treated with durvalumab and tremelimumab combination therapy (not including subjects treated with blinded investigational product). */!143* of 15Apr2015, 95 of 102 subjects (93.1%) reported at least 1 *PE.* All subjects in the tremelimumab 3 and 10 mg/kg dose cohorts experienced /!Es; subjects in the durvalumab 20 mg/kg and tremelimumab 1 mg/kg Q4W cohort experienced the lowest *PE* rate (77.8%). Treatment-related /!Es were reported in 74 of 102 subjects (72.6%), with events occurring in > 10% of subjec1s being diarrhea (27.5%), fatigue (22.5%), increased amylase and pruritus (14.7% each}, rash (12.7%), colitis (11.8%), and increased lipase (10.8%). Treatment-related <!: Grade 3 /!Es reported in <!: 5% of subjects were colitis (8.8%), diarrhea (7.8%), and increased lipase (5.9%). Five subjects reported treatment-related Grade 4 events (sepsis, increased ALT, and increased AST in 1 subject; increased amylase in 2 subjec1s; myasthenia gravis in 1 subject; and pericardia! effusion in 1 subject) and 2 subjects had treatment-related Grade 5 events (polymyositis and an uncoded event of neuromuscular disorder [VT]); the Grade 4 event of myasthenia gravis and Grade 5 polymyositis occurred in 1 subject. There were 2 subjects (both in the MEDI4736 20 mg/kg + tremelimumab 3 mg/kg Q4W cohort) with dose-limiting toxicities (DLTs): 1 subject with Grade 3 increased AST, and 1 subject with Grade 3 increased amylase and Grade 4 increased lipase. Fifty-six subjects (54.9%) reported SPE.s, with events occurring in > 5% of subjects being colitis (9.8%) and diarrhea (7.8%). Thirty-six subjects (35.3%) experienced treatment-related S/!Es. Twenty-seven subjec1s (26.5%) permanently discontinued treatment due to /!Es. Treatment-related /!Es resulting in discontinuation in <!: 2 subjects were colitis (7 subjects), pneumonitis (5 subjects), diarrhea (3 subjects), and increased AST (2 subjec1s). Additional safety results from this study are presented in Section 1.3.1 and the durvalumab IB.

In the literature (Walchak et al 2013.), using the combination of the same class of drugs (e.g., anti-PD-1 and anti-CTLM antibodies), specifcally nivolumab + ipilimumab in a study involving patients with malignant melanoma, the safety profile of this combination had shown occurrences of /!Es assessed by the Investigator as treatment-related in 93% of treated patients, with the most frequent events being rash (55% of patients), pruritus (47% of patients), fatigue (38% of patients), and diarrhea (34% of patients). Grade 3 or 4 /!Es, regardless of causality, were noted in 72% of

patients, with Grade 3 or 4 events assessed by the Investigator as treatment-related in 53%. The most frequent of these Grade 3 or 4 events assessed by the Investigator as treatment-related include increased lipase (in 13% of patients), AST (in 13%), and ALT levels (in 11%). Frequent Grade 3 or 4 selected *PE.s* assessed by the Investigator as treatment-related in the combination therapy included hepatic events (in 15% of patients), GI events (in 9%), and renal events (in 6%). Isolated cases of pneumonitis and uveitis were also observed.

3.6 Colorectal cancer

Worldwide, CRC is the third most common form of cancer in men, with 663,000 cases (10% of the total) and second most common in women, with 571,000 cases (9.4% of the total) per year. Each year there are about 608,000 deaths from colon cancer which is approximately 8% of all cancer deaths making colorectal cancer the fourth most common cause of cancer death (Ferlay, Shin et al. 2010). In 2012 in the U.S. an estimated 103,170 new cases were diagnosed with 51,690 deaths . Treatment of CRC depends largely on the stage of the disease, which is most commonly rated according to tumor, nodes, and metastasis (TNM) criteria. The initial treatment is surgery. However, post-surgery metastatic disease occurs in 40%-60% of patients and the prognosis for patients who develop advanced metastatic disease is poor. Over the past decade, progress has been made in the role of systemic therapy for the palliation of advanced colorectal cancer. With the introduction of oxaliplatin, irinotecan, anti-VEGF therapies, and anti-EGFR therapies, the median life expectancy of patients has been increased to about 29 months (Meyerhardt and Mayer 2005). Despite these therapeutic advances, patients with unresectable, metastatic and/or recurrent CRC, remain incurable. There is a substantial unmet medical need for more effective and less toxic therapies, especially for those patients with advanced disease that have not responded or have become resistant to the existing standard treatments. The development of novel approaches to treatment is greatly needed in order to improve outcomes in such patients.

3.6.1 Immune Augmentation in Colorectal Cancer

Immune augmentation, including checkpoint-directed therapies, has been studied in patients with CRC, and isolated tumor responses have been observed. Our group performed a study of CTLA-4 blockade with tremelimumab (15 mg/kg every 90 days) in 47 patients with previously treated CRC. Grade 3/4 treatment-related adverse events (PE.s) included diarrhea (n = 5; 11%), ulcerative colitis (n = 1; 2%), fatigue (n = 1; 2%), autoimmune thrombocytopenia (n = 1; 2%), and hypokalemia (n = 1; 2%). Of 45 response-evaluable patients, 44 did not reach second dose (43 progressive disease; one discontinuation). Twenty-one patients (45%) lived 180 days after enrollment. One patient (2%; 90% CI, < 1% to 10%) had a stable pelvic mass and substantial regression in an adrenal mass (partial response) (Chung, Gore et al. 2010). Another study was a dose escalation study of PDL-1 blockade with MPDL3280A (0.01-20 mg/kg every three weeks) in 20 patients with solid tumors and lymphoma. Tumor regression was observed in 1 of 4 patients with CRC (partial response). In a first-in-human single-dose, dose-escalation (0.3 to 10 mg/ kg) study of PD-1 blockade with nivolumab in solid tumors, 14 patients with CRC were enrolled. In the phase I multi-dose, dose escalation (1 to 10 mg/kg every 2 weeks) study, 19 patients with CRC were enrolled. Treatment was reasonably well

tolerated in both studies. Durable tumor regression (complete response) beyond 3 years was observed in one patient (Brahmer, Drake et al. 2010, Topalian, Hodi et al. 2012, Lipson, Sharfman et al. 2013).

3.6.1.1 PD/L-1 and CTLA-4 Combination Therapy in Colorectal Cancer

Combination immune augmentation, including anti-PD/L-1 plus anti-CTLA-4, is being studied in patients with CRC. One isolated response has been observed, similar to resul1s of PD/L-1 blockade or CTLA-4 blockade alone. Checkmate-142 (NCT02060188) is an ongoing study of nivolumab plus ipilimumab in CRC. One response was observed out of 20 patients. 10 MSS colorectal patients were treated with nivolumab 1 mg/kg +ipilimumab 3 mg/kg, and 10 MSS colorectal patients were treated with nivolumab 3 mg/kg + ipilimumab 1 mg/kg. Toxicities were consistent with other studies of this combination therapy (Overman, Kopetz et al. 2016). NCT01975831 (IRB#13-198) is an ongoing study of durvalumab plus tremelimumab in multiple tumor types, including CRC (n=15). This study is ongoing and results have not yet been reported.

3.6.2 Rationale for immune therapy plus radiotherapy or ablation in colorectal cancer

RT and ablation, such as cryoablation or radiofrequency ablation, are both standard therapies in patients with metastatic colorectal cancer. Ablation results in tumor destruction by direct heat or cold, and RT results in tumor destruction by ionizing radiation. Either ablation or RT alone is not expected to result in objective systemic benefit alone. However, each modality has been associated with induction of systemic inmunity that can be augmented by co-stimulatory blockade with PD-1 leading to potential for tumor shrinkage.

The phenomenon of tumor destruction by RT or ablation leading to shrinking of tumors away from the site of initial treatment has been termed the *abscopal effect.* Albeit rare, when the abscopal effect occurs, the clinical implications can be profound.

The rationale of the abscopal effect is that *in situ* tumor destruction releases a large amount of tumor antigens. Antigen-presenti ng cells, such as dendritic cells, then take up these antigens in the periphery and migrate to lymph nodes where they activate CD4+ and CDS+ T-lymphocytes that recognize these tumor-antigens. Immune augmentation via immune co-stimulatory molecules then permits the ensuing immune response to strengthen and destroy cancer.

The combination of tumor cryoablation and immunomodulation has been shown in animal models, by our colleagues, to generate such a systemic anti-tumor response (Waitz, Fasso et al. 2012). Specifically, local tumor destruction with cryoablation can lead to exposure of DCs with sufficient quantities of tumor antigens to ultimately lead to DC maturation and activation. Recently, our collaborators (Dr. James Allison's group at MSKCC) showed that combination therapy with cryoablation and CTLA4 blockade successfully mediated rejection of metastatic prostate cancer lesions and prevented the growth of secondary tumors in preclinical murine models (Waitz, Fasso et al. 2012). Levy et al. from MSKCC showed in a BALB/c mouse model of metastatic colon cancer that cryoablation of a solitary tumor mass plus cyclophosphamide, to selectively depletes regulatory T cells (Tregs), leads to regression of established tumors and protection against tumor rechallenge (Levy, Sidana et al. 2009). Den Brok et al. have also demonstrated this effect *in vAlo* using the well-defined murine B16-0VA melanoma cell line using RFA They demonstrated that RFA alone results

in a weak but detectable immune response against OVA, as well as other 816 antigens. Whereas, the combination of co-stimulatory blockade by anti-CTLA-4 together with RFA approximately doubled the number of mice alive at 70 days post-tumor rechallenge compared with mice that received control antibody plus ablation alone (den Brok, Sutmuller et al. 2004).

A similar effect has been shown with RT and blockade of PD-1/PDL-1 interaction. Deng et al. showed that anti-PDL-1 enhanced the effect of RT in a fl..1C38 colorectal tumor model, with substantial delay in tumor growth 34 days after treatment with combination therapy. Tumors measured 27.85 (± 27.85) mm after canbination therapy, compared to 278.6 (± 94.20) mm and 457.6 (± 44.24) mm after RT alone, or anti-PDL-1 alone, respectively.A similar benefit was shown in the TUBO breast cancer cell line, with reduced TUBO tumor growth after mice were re-challenged in the opposite flank, implying systemic immunity. This immunological effect was associated with activation of COB+ T-cells and reduced tumor-infiltrating myeloid-derived suppressor cells (MDSC) (Deng, Liang et al. 2014).

More recently, Dr. Postow from our group reported this abscopal effect in a patient who developed a systemic response to localized RT after having had disease progression while receiving CTLA-4 blockade (ipilimumab). Specifically, a right hilar lymph-node and spleen metastases, which were not the target of RT, showed regression only after the patient received palliative RT after several months of CTLA-4 blockade. A delayed response to the ipilimumab was considered unlikely (Postow, Callahan et al. 2012).

The preclinical models and the clinical observation provide compelling rationale to further study tumor ablation and RT in combination with immune augmentation by co-stimulatory blockade.

CRC is an appropriate target for such a study because this disease is (1) frequently associated with Tumor Infiltrating Lymphocytes (TIls), is (2) routinely treated with combination therapies including RT or ablation, and (3) there is substantial unmet need for novel therapies beyond the currently available systemic therapies.

A study of RT or ablation, plus single agent pembrolizumab (PD-1 blockade) alone is ongoing at MSKCC in metastatic CRC (IRB #15-069/ NCT02437071). Initial results have been presented at ASCO and showed that PD-1 blockade has a manageable safety profile when administered in combination with either RT or ablation in patients with mCRC. Grade 1-2 drug-related AEs occurred in 95% and 75% of patients who received RT or ablation, respectively. There were no grade 3 drug-related AEs, or drug-related AEs that led to pembrolizumab discontinuation. Responses were not observed in patients who received microwave ablation or cryoablation plus pembrolizumab (no patients underwent RFA). Pembrolizumab plus RT showed modest clinical activity in pMMR CRC, with one partial response and two mixed responses (Segal et al. ASCO 2016 #3539).

The current study is investigating whether the CTLA4 plus PDL-1 blockade will have additive or synergistic activity in combination with tumor ablation or radiation therapy.

3.7 **Rationale for dose and schedule**

The durvalumab + tremelimumab doses and regimen selected for this study are based on the goal of selecting an optimal combination dose of durvalumab and tremelimumab that would yield sustained target suppression (sPD-L1), demonstrate promising efficacy, and have an acceptable safety profile.

In order to reduce the dosing frequency of durvalumab to align with the q4w dosing of tremelimumab, while ensuring an acceptable PK/PDx, safety, and efficacy profile, cohorts were narrowed to 20 mg/kg durvalumab q4w. PK simulations from the durvalumab monotherapy data indicated that a similar area under the plasma drug concentration-time curve at steady state (AUC••; 4 weeks) was expected following both 10 mg/kg q2w and 20 mg/kg q4w durvalumab. The observed durvalumab PK data from the D4190C00006 study were well in line with the predicted monotherapy PK data developed preclinically. This demonstrates similar exposure of durvalumab 20 mg/kg q4w and 10 mg/kg q2w, with no alterations in PK when durvalumab and tremelimumab (doses ranging from 1 to 3 mg/kg) are dosed together. While the median Cmax at steady state (Cmax,ss) is expected to be higher with 20 mg/kg q4w (approximately 1.5 fold) and median trough concentration at steady state (Cirough,ss) is expected to be higher with 10 mg/kg q2w (approximately 1.25 fold), this is not expected to impact the overall safety and efficacy profile, based on existing preclinical and clinical data.

I'vbnotonic increases in PDx activity were observed with increasing doses of tremelimumab relative to the activity observed in patients treated with durvalumab monotherapy. There was evidence of augmented PDx activity relative to durvalumab monotherapy with combination doses containing 1 mg/kg tremelimumab, inclusive of both the 15 and 20 mg/kg durvalumab plus 1 mg/kg tremelimumab combinations.

Patients treated with doses of tremelimumab above 1 mg/kg had a higher rate of adverse events (AEs), including discontinuations due to AEs, serious AEs (SAEs), and severe AEs. Between the 10 mg/kg durvalumab + 1 mg/kg tremelimumab and 10 mg/kg durvalumab + 3 mg/kg tremeli'numab cohorts treated at the q2w schedule, the number of patients reporting any AE, Grade 3 AEs, SAEs, and treatment-related AEs was higher in the 10 mg/kg durvalumab + 3 mg/kg tremelimumab cohort than the 10 mg/kg durvalumab + 1 mg/kg tremelimumab cohort. A similar pattern was noted in the q4w regimens, suggesting that, as the dose of tremelimumab increased above 1 mg/kg, a higher rate of treatment-related events may be anticipated. Further, the SAEs frequently attributed to immunotherapy, pneumonitis and colitis, were more commonly seen in cohorts using either 3 or 10 mg/kg of tremelimumab compared to the 1-mg/kg dose cohorts. Together, these data suggest that a combination using a tremelimumab dose of 1 mg/kg appeared to minimize the rate of toxicity when combined with durvalumab. As a result, all combination doses utilizing either the 3 or 10 mg/kg doses of tremelimumab were eliminated in the final dose selection.

In contrast, cohorts assessing higher doses of durvalumab with a constant dose of tremeli'numab did not show an increase in the rate of AEs. The data suggested that increasing doses of durvalumab may not impact the safety of the combination as much as the tremelimumab dose. Further, safety data between the 10-mg/kg and 20-mg/kg cohorts were similar, with no change in safety events with increasing dose of durvalumab.

In Study D4190C00006, of all treatment cohorts, the cohort of 11 patients treated in the 20 mg/kg durvalumab + 1 mg/kg tremelimumab group had the fewest AEs, Grade <!:3 AEs, SAEs, and treatment discontinuations due to AEs, but still showed strong evidence of clinical actMty. This cohort had a lower number of treatment-related Grade <!:3 AEs or treatment-related SAEs. No dose-limiting toxicities were reported.

Preliminary clinical activity of the durvalumab and tremelimumab combination did not appear to change with increasing doses of tremelimumab. The 15- and 20-mg/kg durvalumab q4w cohorts demonstrated objective responses at all doses of tremelimumab, and increasing doses of tremelimumab did not provide deeper or more rapid responses.

Efficacy data suggested that the 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose cohort may demonstrate equivalent clinical activity to other dose combinations. A total of 5 of 11 patients in the 20 mg/kg durvalumab + 1 mg/kg tremelimumab cohort were evaluable for efficacy with at least 8 weeks of follow-up. Of these, there were 2 patients (40%) with partial response (PR), 1 patient (20%) with stable disease (SD), and 1 patient (20%) with progressive disease (PD). (The fifth patient had only a single scan, which was conducted outside the window for these evaluations.)

Additionally, of all cohorts, the 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose cohort had the fewest AEs, Grade <!:3 AEs, SAEs, and treatment discontinuations due to AEs, but still showed some evidence of clinical actMty. All together, the data suggested that a 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose combination should be selected for further development.

3.7.1 Rationale for 4 cycles of combination therapy followed by durvalumab monotherapy

Long-term follow up on melanoma patients treated with ipilimumab, an anti-CTL.A4 targeting antibody (dosed every 3 weeks [q3w] for 4 doses and then discontinued), shows that patients responding to ipilimumab derive long-term benefit, with a 3-year OS rate of approximately 22%. Furthermore, the survival curve in this population reached a plateau at 3 years and was maintained through 10 years of follow up (Schadendorf et al 2013.).

Similar data have been presented for other anti-PD-1/PD-L 1 targeting antibodies:

Nivolumab (anti-PD-1) was dosed q2w for up to 96 weeks in a large Phase I dose-escalation and expansion study, and showed responses were maintained for a median of 22.94 months for melanoma (doses 0.1 mg/kg to 10 mg/kg), 17 months for NSCLC (doses 1, 3, and 10 mg/kg), and 12.9 months for renal cell carcinoma patients (doses 1 and 10 mg/kg) at the time of data analysis (Hodi et al 2014, Brahmer et al 2014, Drake et al 2013.). Furthermore, responses were maintained beyond treatment discontinuation in the majority of patients who stopped nivolumab treatment (either due to protocol specified end of treatment, complete response [CR], or toxicity) for up to 56 weeks at the time of data analysis (Topalian et al 2014.).

lltPDL3280a (anti-PD-L 1) and the combination of nivolumab with ipilimumab, in which patients were dosed for a finite time period and responses maintained beyond treatment discontinuation have been reported (Herbst et al 2013, Wolchok et al 2013.).

Similar long term results may be expected with use of other immune-mediated cancer therapeutics including anti-CTLA-4 antibodies such as tremelimumab, anti PD-L1antibodies such as durvalumab, or the combination of the two.

3.7.2 Fixed dosing for durvalumab and tremelimumab

A population PK model was developed for durvalumab using monotherapy data from a Phase 1 study *(study 1108; N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors).* Population PK analysis indicated only minor impact of body weight (WT) on PK of durvalumab (coefficient of s 0.5). The impact of body WT-based (10 mg/kg Q2W) and f1JCed dosing (750 mg Q'Z!N) of durvalumab was evaluated by comparing predicted steady state PK concentrations ($5^{1}{}_{h,}$ median and $95^{1}{}_{h}$ percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 1O mg/kg (based on median body WT of -75 kg). A total of 1000 patients were simulated using body WT distribution of 40-120 kg. Simulation results demonstrate that body WT-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= *0.01 to 15 mg/kg Q4W or Q90D; metastatic melanoma)* [Wang et al. 2014]. Population PK model indicated minor impact of body WT on PK of tremelimumab (coefficient of s 0.5). The WT-based (1 mg/kg Q4W) and f1JCed dosing (75 mg/kg Q4W; based on median body WT of -75 kg) regimens were compared using predicted PK concentrations ($5^{1}{}_{h,}$ median and $95^{1}{}_{h}$ percentiles) using population PK model in a simulated population of 1000 patients with body weight distribution of 40 to 120 kg. Similar to durvalumab, simulations indicated that both body WT-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-subject variability with f1JCed dosing regimen.

Similar findings have been reported by others [Ng et al 2006, Wang et al. 2009, Zhang et al, 2012,Narwal et al 2013]. Wang and colleagues investigated 12 monoclonal antibodies and found that f1JCed and body size-based dosing perform similarly, with f1JCed dosing being better for 7 of 12 antibodies . 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 pharmacokinetic/pharmacodynamics parameters [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 pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 750 mg Q2W IIIEDI4736 (equivalent to 10 mg/kg Q2W), 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) and 75 mg Q4W tremelimumab (equivalent to 1 mg/kg Q4W) is included in the current study.

Fixed dosing of durvalumab and tremelimumab is recanmended only for subjects with > 30kg body weight due to endotoxin exposure. Patients with a body weight less than or equal to 30 kg should be dosed using a weight-based dosing schedule.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This will be a Simon two-stage design, phase II study. It will be conducted to determine the efficacy and safety of (1) durvalumab and tremelimumab plus RT in subjects with metastatic CRC who are undergoing RT as standard therapy; and, (2) durvalumab and tremelimumab plus ablation in subjects with metastatic CRC who are undergoing ablation as standard therapy.

4.3 Intervention

Patients will be stratified according to eligibility for RT (cohort 1) or ablation (cohort 2). Patients in **cohort 1** will have at least one metastatic lesion for which palliative RT is considered appropriate standard therapy, and at least one other measurable index lesion that will not undergo RT. Patients in **cohort** 2 will have at least one metastatic lesion for which palliative ablation is considered appropriate standard therapy, and at least one other measurable index lesion that will not undergo ablation. Subjects in cohort 2 may undergo tumor ablation of one or more lesions at the discretion of the interventional radiologist. All subjects will undergo ablation or begin RT within 7 days after starting durvalumab and tremelimumab.

Subjects will receive durvalumab and tremelimumab every four weeks (Q4W), for 4 months, and then continue durvalumab every four weeks (Q4W) until confirmed progression of disease, initiation of alternative cancer therapy, unacceptable toxicity, or other reasons to discontinue treatment occur. Patients who had a prior response, continued on durvalumab monotherapy and did not discontinue tremelimumab due to toxicity may, after discussion with the Principal Investigator, continue treatment beyond disease progression with either durvalumab monotherapy or resume combination therapy with tremelimumab plus durvalumab for 4 doses upon disease progression, followed by durvalumab monotherapy.

Repeat palliative RT in cohort 1, or ablation in cohort 2, will be permitted in select cases. Repeat palliative RT or ablation may include measurable index lesion(s) that is (are) being followed for response measuremen1s if at least one index lesions remains to be followed. Patients will be evaluated by physical exam and routine blood tests every two weeks during the first 4 months of the study period, then every 4 weeks. CT or MRI will be performed during screening, and then at 8 week intervals. Tumor measurements and determination of tumor responses will be performed according to RECIST 1.1.

Subjects with evidence of disease progression during the durvalumab + tremelimumab combination portion of the treatment regimen may continue to receive durvalumab and tremelimumab beyond radiographic disease progression in the absence of clinical deterioration, and after discussion with the Principal Investigator.

All subjects will be followed for 2 years for survival or until the study closes. Exploratory research studies to evaluate the effect of this therapy will be performed in patients using research blood draws (all patients), and tumor biopsy at baseline, one week after completing radiation/ablation and four weeks after starting immunotherapy for research purposes (stage 1 only).

4.4 Estimated Duration of Subject Participation

Subjects will continue treatment every four weeks until confirmed progression of disease, initiation of alternative cancer therapy, unacceptable toxicity, or other reasons to discontinue treatment occur. All subjects will be followed for survival for 2 years unless the Principal Investigator or MedImmune/ Astra Zeneca decides to end the study.

5.1 THERAPEUTIC/DIAGNOSTIC AGENTS

5.2 Ablation

The ablation will be performed percutaneously under image guidance as standard therapy at the discretion of the interventional radiologist in accordance with institutional standard practice.

Ablation will be performed within 7 days after the first of durvalumab and tremelimumab. Up to 3 lesions measuring up to 3 cm may be ablated, as long as at least one measurable lesion remains to measure the abscopal effect.

5.3 Radiotherapy

Radiotherapy (RT} will be performed using external beam ionizing radiation as standard therapy in accordance with institutional standard practice.

RT will be initiated within 7 days after the first of durvalumab and tremelimumab. Up to 3 lesions may be radiated, as long as at least one measurable lesion remains to measure the abscopal effect.

Target volumes for RT will be defined in accordance with International Commission on Radiation Units and I'v'easurements (ICRU} Report #50: Prescribing, Recording and Reporting Photon Beam Therapy, and ICRU Report #71: Prescribing, Recording and Reporting Electron Beam Therapy.

The target lesion for RT will be defined as the gross tumor volume (GTV}. The clinical target volume (CTV} will be the same as the GTV. The planning target volume (PTV} will be a minimum volumetric expansion of the GTV by 2 mm (5 mm recommended}, but ultimately will be left to the discretion of the attending radiation oncologist.

CT simulation will be performed for planning purposes. Details of the CT simulation (40 CT, gating, use of contrast, immobilization} will be left to discretion of the attending radiation oncologist.

RT will be planned in 3-D and may be delivered using conventional, IMRT or rapid arc methodology. 6-18 MV photons and/or electron beam RT will be used as determined by the specific clinical situation. 95% of the PTV should receive the prescription radiation dose, as determined appropriate by the radiation oncologist. Normal tissue constraints will not be exceeded during the planning process.

When photon therapy is used, portal imaging, cone beam CT, or 20 kV on board imaging for QC will occur for each treatment. When electron therapy is used, light field verification of the target will occur at the start of treatment.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

1. Be willing and able to provide written informed consent for the trial.
2. Histologically- or cytologically- confirmed CRC.
3. Metastatic CRC.
4. Subjects have received at least two standard chemotherapy regimens for which they would be considered eligible (at least one containing a 5-fluoropyrimidine), or systemic chemotherapy is not indicated in the setting of low volume metastatic disease.
5. *M.* least one tumor for which palliative RT is considered appropriate standard therapy (cohort 1); or, at least one tumor for which palliative ablation is considered appropriate standard therapy (cohort 2).
6. *Pl.* least one index lesion that will not undergo RT or ablation, and which is measurable based on RECIST 1.1.
7. Be 18 years of age on day of signing informed consent.
8. Consent for tumor biopsies (for patients enrolled in stage 1 only) and blood draws for research purposes (for all patients).
9. Consent for use of available archived tissue and tumor obtained during a standard procedure, for research purposes.
10. Have a performance status of 0 or 1 on the ECOG Performance Scale.
11. Female subjects must either be of non-reproductive potential (i.e., post-menopausal by history: 60 years old and no menses for ::::1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative serum pregnancy test within 2 weeks prior to starting treatment.
12. Demonstrate adequate organ function as defined in Table 6.1, all screening labs should be performed within 4 weeks prior to treatment initiation.

Table 6.1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Hemoglobin	<!: 8.0 g/dL
Absolute neutrophil count (ANC)	<?:1,500 hncL
Plalele1s	<?:100,000 / mcL
Renal	
Serum creatinine OR Measured or calculated" creatinine	S1.5 X upper limit of nonnal (ULN) OR Serum creatinine CL>40 mL.tnin bythe Cockcroft-Gault

clearance (GFR can also be used in place of creatinine or CrCI)	formula (Cockcroft and Gault 1976) or by24-hwr urine collection for determination of creatinine clearance.
Hepatic	
Serum total bilirubin	S 1.5 XULN QB
	Direct bilirubin s ULN for subjecls with total bilirubin lewis > 1.5 ULN
AST (SGOT) and ALT (SGPT)	S 2.5 XULN OR :S 5 XULN for subjecls with liwr metastases
-vreatinine clearance should be calrulated per institutional standard.	

6.3 Subject Exclusion Criteria

1. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.

2. Chemotherapy, monoclonal antibody, targeted small molecule therapy, within 4 weeks prior to dose #1 or who has not recovered (i.e., :S Grade 1 or at baseline) from adverse events due to a previously administered agent (excluding alopecia or toxicity not anticipated to interfere with planned treatment on study}.

3. Known or suspected MSI-H CRC.

4. Ally prior Grade 3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1, including anti-PD-1, anti-PD-L1, anti-CD137, anti-CTLA-4 antibody or any other antibody or drug specifically targeting T-cell co-sti'nulation or checkpoint pathways, except for endocrinopathies and asymptomatic amylase/lipase,

5. If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention per clinical discretion of the investigator prior to starting therapy.

6. Concurrent active malignancy that requires systemic treatment.

7. Known CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable without evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. The use of topical steroids is permitted.

8. Active autoimmune disease requiring systemic immune suppressive treatment within the past 2 years. NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.

9. Has active, non-infectious pneumonitis.

10. Active or prior documented inflammatory bowel disease.

11. History of allogeneic organ transplant.

12. Has an active infection requiring systemic therapy.

13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

14. Has a known history of Human Immunodeficiency Virus (HIV) {HIV 1/2 antibodies).

15. Has known active and untreated Hepatitis B (e.g., HBsAg reactive) or active Hepatitis C (e.g., HCV RNA [qualitative] is detected).

16. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

17. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab with the exceptions of premedication and intranasal, topical and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10mg/day of prednisone, or an equivalent corticosteroid.

18. Hypersensitivity to durvalumab or tremelimumab, or any excipients on the formulation.

19. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.

20. 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 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period

21. QT interval corrected for heart rate (QTc) <: 470ms calculated from 1 electrocardiogram (ECG) using Fridericia's Correction

22. History of primary immunodeficiency

23. Known history of previous clinical diagnosis of tuberculosis

24. Subjects with uncontrolled seizures

7.1 RECRUITMENT PLAN

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

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

The investigators take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. There will be no limitation to access with regard to race or gender. Patients will be required to read, agree to, and sign an IRS-approved informed consent form prior to

registration on this trial. The registration procedure will be conducted as described in section 15.0. Patients will not receive payment for their participation on this study.

8.0 PRETREATMENT EVALUATION

To be completed within 4 weeks prior to starting durvalumab and tremelimumab:

- CT scan with contrast (chest, abdomen and pelvis). If patient is unable to receive CT contrast, or the abdominal/pelvic target lesion is indeterminate on CT scan then MRI with contrast (abdomen and pelvis) plus CT chest without contrast may be perfromed. Non-contrast CT CAf' may be used if the target lesion(s) do not require contrast for accurate measurements.
- 12-lead Electrocardiogram (EKG).
- Signed informed consent for study participation.
- History and physical examination, including height, weight, vital signs (temperature, pulse rate, respiration rate, blood pressure), and performance status (ECOG).
- Serum pregnancy test for all women of childbearing potential (within two weeks prior to day #1 of treatment).
- CBC with differential and platelet count, serum chemistries (Na, Cl, BUN, Creatinine, K, C02, and glucose), LFTs (AST, ALT, alkaline phosphatase, total bilirubin), calcium, albumin, total protein,TSH (Free T3, Free T4 if TSH abnormal), GGT, PT/PTT, amylase/lipase and CEA
- Urinalysis
- Serology for HepBsAg, HepBcAb and hepatitis C antibody (negative test acceptable prior to screening period)
- Blood test for research purposes.
- Perform baseline tumor biopsy for research purposes (for patients enrolled in stage 1 only).

9.0 TREATMENT/INTERVENTION PLAN

9.1 Investigational Products

The Investigational Products Supply section of AstraZeneca/MedImmune will supply durvalumab and tremelimumab to the investigator as a solution for infusion after dilution.

9.1.1 Formulation/packaging/storage

Durvalumab:

Durvalumab will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/ml durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose

dihydrate, and 0.02% {weight/volume) polysorbate SO; it has a pH of 6.0. The nominal fill volume is 10 ml. Investigational product vials are stored at 2°C to S°C {36°F to 46°F) and must not be frozen. Durvalumab must be used within the individually assigned expiry date on the label.

Tremelimumab

Tremelimumab will be supplied by AstraZeneca as a 400-mg vial solution for infusion after dilution. The solution contains 20 mg/ml of tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.02% {w/v) polysorbate SO, and 0.27 mMdisodium edetate dihydrate {EDTA); it has a pH of 5.5. The nominal fill volume is 20 ml. Investigational product vials are stored at 2°C to S°C {36°F to 46°F) and must not be frozen. Tremelimumab must be used within the individually assigned expiry date on the label.

9.1.2 Dose and treatment regimens

9.1.2.1 Durvalumab + tremelimumab combination therapy

Patients will receive 1500 mg durvalumab via IV infusion q4w for up to 4 doses/cycles and 75 mg tremelimumab via IV infusion q4w for up to 4 doses/cycles, and then continue 1500 mg durvalumab q4w starting on Week 16. Tremelimumab will be administered first. Durvalumab infusion will start approximately 1 hour after the end of tremelimumab infusion. The duration will be approximately 1 hour for each infusion. A 1-hour observation period is required after the first infusion of durvalumab and tremelimumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion).

9.1.2.2 Duration of treatment and criteria for retreatment

Retreatment with durvalumab + tremelimumab is allowed {once only) for patients meeting the retreatment criteria below. The same trea1ment guidelines followed during the initial treatment period will be followed during the retreatment period, including the same dose and frequency of treatments and the same schedule of assessments.

Patients receiving durvalumab monotherapy may undergo retreatment with the combination of durvalumab + tremelimumab, described below:

1. Patients who complete the 4 dosing C}Cles of the combination of durvalumab and tremelimumab portion of the regimen {with clinical benefit per Investigator judgment), but subsequently have evidence of PD during the durvalumab monotherapy portion of the combination regimen, with or without confirmation according to RECIST 1.1, may restart treatment with the combination.

Before restarting their assigned treatment, the Investigator should ensure that the patient:

1. Does not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient

2. Still fulfills the eligibility criteria for this study, including re-consenting to restart durvalumab and tremelimumab

3. Has had a baseline tumor assessment within 28 days before restarting their assigned treatment; all further scans should occur with the same frequency as during the initial months of treatment until study treatment is stopped

During the retreatment period, patients receiving durvalumab + tremelimumab may resume durvalumab dosing at 1500 mg q4w with 75 mg of tremelimumab q4w for 4 doses each. Patients will then continue with durvalumab monotherapy at 1500 mg q4w, beginning at Week 16, 4 weeks after the last dose of combination therapy.

Treatment through progression is at the Investigator's discretion, and the Investigator should ensure that patients do not have any significant, unacceptable, or irreversible toxicities that indicate that continuing treatment will not further benefit the patient. A patient with a confirmed progression receiving durvalumab + tremelimumab cannot continue therapy or obtain retreatment if dosing is ongoing in the combination portion of therapy {q4w dosing) and progression occurs in a target lesion that has previously shown a confirmed response.

Patients who the Investigator determines may not continue treatment will enter follow-up.

9.1.2.3 Study drug preparation of durvalumab and tremelimumab

Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W durvalumab {equivalent to 20 mg/kg Q4W) and 75 mg Q4W tremelimumab (equivalent to 1 mg/kg Q4W) is included in the current study.

Preparation of durvalumab doses for administration with an IV bag

The dose of durvalumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration.

No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed. Dose of 1500mg durvalumab for patients >30 kg will be administered using an IV bag containing 0.9% (w/v) saline or dextrose, with a final durvalumab concentration ranging from 1 to 20 mg/ml, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Remove 30.1 ml of IV solution from the IV bag prior to addition of durvalumab. Next, 30.0 ml of durvalumab (i.e., 1500 mg of durvalumab} is added to the IV bag such that final concentration is within 1 to 20 mg/ml (IV bag volumes 100 to 1000 ml). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Patient weight at baseline should be used for dosing calculations unless there is a <!:10% change in weight. Dosing day weight can be used for dosing calculations instead of baseline weight per institutional standard.

For patients <30kg, Calculate the dose volume of durvalumab and tremelimumab and number of vials needed for the subject to achieve the accurate dose.

Durvalumab will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral or central vein. Following preparation of durvalumab, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2, or 0.22-µm in-line filter. Less than 55 minutes is considered a deviation.

The IV line will be flushed with a volume of IV solution (0.9% [w/v] saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. The table below summarizes tine allowances and temperatures.

Durvalumab hold and infusion times

Maximum time from needle puncture to start of administration	4 hours at room temperature, 24 hours at 2°C to 8
Maximum time for IV bag infusion, including interruptions	8 hours at room temperature

In the event that either preparation time or infusion time exceeds the time limits ouUined in the table, a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

Preparation of tremelimumab doses for administration with an IV bag

The dose of tremelimumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the tremelimumab vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

It is recommended that the prepared final IV bag be stored in the dark at 2"C-8°C (36°F-46°F) until needed. If storage time exceeds these limits, a new dose must be prepared from new vials. The

refrigerated infusion solutions in the prepared final IV bag should be equilibrated at room temperature for about 2 hours prior to administration. Tremelimumab does not contain preservatives and any unused portion must be discarded.

No incompatibilities between tremelimumab and polyvinylchloride or polyoletin IV bags have been observed. Doses of 75 mg tremelimumab for patients >30 kg will be administered using an IV bag containing 0.9% (w/v) saline or dextrose, with a final tremelimumab concentration ranging from 0.1 mg/ml to 10 mg/ml, and delivered through an IV administration set with a 0.2 µm or 0.22 µm in-line tilter. Remove 3.8 mlof IV solution from the IV bag prior to addition of tremelimumab. Next, 3.8 ml of tremelimumab (i.e., 75 mg of tremelimumab) is added to the IV bag such that final concentration is within 0.1 mg/ml to 10 mg/ml (IV bag volumes 50 to 500 ml). Mx the bag by gently inverting to ensure homogeneity of the dose in the bag.

Patient weight at baseline should be used for dosing calculations unless there is a <:10% change in weight. Dosing day weight can be used for dosing calculations instead of baseline weight per institutional standard.

For patients <30 kg, Calculate the dose volume for tremelimumab and number of vials needed for subject to achieve the accurate dose.

Tremelimumab will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral or central vein. Following preparation of tremelimumab, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2, or 0.22-µm in-line filter. Less than 55 minutes is considered a deviation.

The IV line will be flushed with a volume of 0.9% (w/v) saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. The table below summarizes ti'ne allowances and temperatures.

Tremelimumab hold and infusion times

Maximum time from needle puncture to start of administration	4 hours at room temperature, 24 hours at 2°C to 8°c
Maximum time for IV bag infusion, including interruptions	8 hours at room temperature

In the event that either preparation time or infusion time exceeds the time limits outlined in the table, a new dose must be prepared from new vials. Tremelimumab does not contain preservatives, and any unused portion must be discarded.

9.1.2.4 Monitoring of dose administration

Patients will be monitored during and after the infusion with assessment of vital signs at the times specified in the Study Protocol.

In the event of a sGrade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a SGrade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is <!:Grade 3 or higher in severity, study drug will be discontinued.

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

9.1.2.5 Accountability and dispensation

Disposition of unused investigational study drug

The site will account for all investigational study drug dispensed and also for appropriate destruction. Certificates of delivery and destruction must be signed.

9.2 Concomitant Medications

9.2.1 Permitted Concomitant Medication

Investigators may prescribe concomitant medications or treatments (e.g., acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as "excluded" as listed in Section 9.2.2.

9.2.2 Excluded Concomitant Medications

The following medications are considered exclusionary during the study.

1. Any investigational anticancer therapy, other than the protocol specified therapies

2. Any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment, other than any stated comparator or combination regimens. Concurrent use of hormones for noncancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable. Local surgery for treatment of isolated lesions for palliative intent is acceptable.

3. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and

TNF-a blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of topical steroids, inhaled and intranasal corticosteroids are permitted.

4. Live attenuated vaccines within 30 days of durvalumab and tremelimumab dosing (i.e., 30 days prior to the first dose, during treatment with durvalumab and tremelimumab for 30 days post discontinuation of durvalumab and tremelimumab.) Inactivated vaccines, such as the injectable influenza vaccine, are permitted.

9.3 Dose Modification and Toxicity Management

Durvalumab and tremelimumab

For adverse events (AEs) that are considered at least partly due to administration of durvalumab the following dose adjustment guidance may be applied:

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity where required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of durvalumab or tremelimumab along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted for durvalumab and tremelimumab (see Appendix A).
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

In addition, there are certain circumstances in which durvalumab or tremelimumab should be permanently discontinued.

Following the first dose of durvalumab or tremelimumab, subsequent administration of durvalumab or tremelimumab can be modified based on toxicities observed (see Appendix A). Dose reductions are not permitted.

Based on the mechanism of action of durvalumab or tremelimumab leading to T-cell activation and proliferation, there is the possibility of observing immune related Adverse Events (irAEs) during the conduct of this study. Potential irAEs include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or PD) signs or S}fllptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.

Dose modification recommendations and toxicity management guidelines for immune-mediated reactions, for infusion-related reactions, and for non-immune-mediated reactions are detailed in Appendix A

In addition, management guidelines for adverse events of special interest (AESIs) are detailed below. All toxicities will be graded according to NCI CTCAE v4.03

9.4 Diet/Activity/Other Considerations

9.4.1 Diet

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

9.4.2 Contraception

Females of childbearing potential who are sexually active with a non-sterilized male partner must use 2 methods of effective contraception (Table 1) 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, whichever is the longer time period; cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

> Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectany) or post-menopausal (defined 12 months with no menses without an alternative medical cause).

Non-sterilized males who are sexually active with a female partner of childbearing potential must use 2 acceptable methods of effective contraception (see Table 1) 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, whichever is the longer time period.

Table 1 Highly Effective• Methods of Contraception

Barrier/Intrauterine Methods	Hormonal Methods
▪ Copper T intrauterine device • Levonorgesterel -releasing intrauterine system (e.g., Mrena®)b	• Etonogestrel implants: e.g. Implanon or Norplan • Intravaginaldevice: e.g.ethinylestradioland etonogestrel • Medroxyprogesterone injection:e.g.Depa-Provera • Normal and low dose combined oral contraceptive pill • Norelgestromin/ethinylestradiol transdermal system • Cerazette (desogestrel)
" lighly effecwe (i.e.failure rate*ct* <1% PEI' yea-) b Thisis alsocor&idered a horrTDnal rrethod	

9.4.3. Blood donation

Subjects should not donate blood while participating in this study,or for at least 90 days following the last infusion of durvalumab or tremelimumab.

9.5 Clinical Criteria for Early Trial Termination

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

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

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

9.7 RESEARCH BLOOD AND BIOPSY SPECIMENS

9.7.1 Research blood

For all patients, blood specimens will be obtained for research purposes during screening or on day 1,then at weeks 2, 4 and 8 (± 3 days). An additional blood draw beyond week 8 is permitted based upon interesting clinic/immunological findings.

Specimens should be collected prior to drug administration. Four (4) tubes of blood are to be collected in BD Vacutainer® CPT™ Cell Preparation Tubes with Sodium Heparin. Each tube should contain approximately 10 cc of blood. Peripheral blood mononuclear cells and plasma will then be isolated per institutional practice in the Immune I'v'onitoring Facility (IMF).

9.7.2 Research biopsy

For patients enrolled in stage 1, a pre-treatment tumor biopsy will be obtained during screening. On-treatment biopsies will be performed 1week after completing radiation or ablation (from the radiated/ ablated lesion), and then 4 weeks after dose #1 of durvalumab plus tremelimumab (from a non-radiated/ ablated lesion)

Patients will be permitted to continue enrollment and treatment on protocol in the event that insufficient material was obtained from the biopsy. The on treatment biopsy will not be required if this is no longer considered appropriate at the time of the planned procedure, for example, if the tumor is no longer accessible or the procedure is deemed to be unsafe. Tumor lesion planned for on-treatment biopsy may be an index lesion if ;:: 2 cm in at least one diameter.

If clinically practical, subjects will undergo up to 5 core biopsies. Three core biopsies will be placed in formalin and processed for FFPE, 2 core biopsies will be immediately frozen in liquid nitrogen and then stored at -80°C (appendix C). All tissue obtained during biopsy procedures will be sent to the IMF facility for analysis under this study as indicated below. If the patient undergoes a routine procedure, tissue may be obtained for future correlative analyses.

9.7.3 Correlative studies

Pharmacodynamic changes may be evaluated for associations with clinical activity, and safety (adverse event) data. Tissue may be used for correlative studies such as IHC, tumor mutation analysis, proteomic analysis, and immunodiversity. PDL-1 immunohistochemistry will be done by a

MedImmune/ Ira Zeneca designated laboratory or at MSKCC using the Ventana SP263 assay in accordance with the package insert on Ventana Benchmark platform. Archived samples submitted for PD-L1 testing should be s 3 months old.

9.7.3.1 Whole Blood

Flow cytometry will be performed at baseline and during treatment to assess baseline and changes in composition/activation status of lymphocyte subsets present in peripheral blood mononuclear cell preparations (PBMCs). Lymphocyte subsets to be assayed may include, but are not limited to CDS+ and CD4+ T-cell subsets (activated; effector/memory; regulatory) and populations of those cells as defined by the expression of activation, exhaustion, or signaling markers such as ICOS, HLA-DR, PD-1, CTLA-4, and/or intracellular IFNy. NK cell populations may be monitored in a similar fashion with a focus on characterizing subsets defined by the expression of activation markers (e.g. NKG2D; IL-21R) and/or by markers that are associated with the potential of NK cells to lyse target cells (e.g., CD107a, granzyme, perforin). Additional flow cytometry-based assays will focus on defining and monitoring the abundance of myeloid-derived suppressor cells (I'vDSCs), a cell type which appears to negatively impact anti-tumor actMty and which has been shown to promote immune escape by limiting activated CDS T-cell infiltration into the tumor microenvironment (Lesokhin, Hohl et al. 2012). Immune cells may be evaluated using HLA-A2-restricted tetramer assays to detect and quantify the presence of T cells directed against specific antigens which are anticipated to be presented to the immune system due to study treatment. Detecting on-treatment increases in these T cell populations may be considered evidence of adaptive immune responses in CRC.

9.7.3.2 Plasma

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

9.7.3.3 Tissue Biopsies and/or archived tissue

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

cancer-interacting lymphocytes derived from biopsied material. DNA will be extracted from tumor samples and normal blood lymphocytes and undergo sequence analysis, such as whole exome sequencing in order to (1) search for tumor mutations that may correlate with immune response; and (2) to search for tumor specific mutations that are absent from germ line DNA and be potential novel immune targets, neo-epitopes. Other biomarkers may be evaluated as determined by additional data. Remaining specimens may be stored for future studies related to CRC immunity.

100 EVALUATION DURING TREATMENTnNTERVENTION

Study Calendar

Period	Screening	Treabnent						Endof study vlslt[17]
Cycle[1]	<4 weeke[2]	1		2-4		5+		
						odd	even	
Day		1	1:9 (:t7 dawl	1	1:9 (:t7 dawl	1	1	
Informed consent	X							
Medical history	X							
EKG	X							
CT/MRI[3]	X			X		X		X
Height[4]	X							
Physical examination	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X
Vital signs/ Performance status[4]	X	X	X	X	X	X	X	X
Report medicatiais	X	X	X	X	X	X	X	X
PulseoJCimetry		X	X	X	X	X	X	X
Report side effects			X	X	X	X	X	X
CBCs,[6]	X	X	X	X	X	X	X	X
Comps,[7]	X	X	X	X	X	X	X	X
Thyroid function (TSH, fT3,fT4)s,[8]	X			X		X		
GGr8	X							
Amytase[9]	X							
Lipase[9]	X							
CEA[10]	X	X		X		X		X
PT/PTT	X							
Hepatitis Band C	X							
Pregnancy test if female (Serum)[12]	X							
Urinalysis	X							
Researdl blood tests s.[13]	X		X	X		X		
Obtainarchived tissue "'	X							
Researdl b.Jmor biopsy[15]	X	X						
RT (Cohort 1) •D		X						

JIblation (Cohort 2) ••		X				
Durvalumab		X		X		X
Tremelimumab		X		X		

1. Each cy::le is approJCimately 4 weeks ilduration. Cle X *Day* 15 loisiis *may* occur within ±7 days of scheduled date.
2. Procedures must be perfonned within 4 weeks prior to dose 1 of durvalumab and tremelimumab on Day 1.
3. CT or MRI will be perfonned prior to starting RT or ablation and during screening, then at 8 week (±1 wk) intervals and at final loisit if more than 8 weeks from prior imaging. If patient is unable to receive CT contrast or the abdominal/ pelloic target lesion is indetenninate on CT then MRI with contrast (abdomen and pell.is) plus CT without contrast (chest) may be perfonned. Imaging may be dela)9d up to 2 weeks if patient is receiloing additional RT or ablation.
4. Vital signs to indude heart rate, respiratory rate, temperature and blood pressure
5. Blood to be collected up to 72 hours prior to sdleduled dosing.
6. Hematology to include standard complete blood cell (CBC) panel.
7. Comprehensive metabolic panel included sodium, potassium, chloride, bicarbonate, BUN, creatinine, gluoose, total protein, albumil, bilirubin, alkaline phosphatase, AST, ALT, calcium.
8. Free T3, free T4, and TSH
9. Tesis done at baseline then as clinically indicate
10. CEA to be obtained during screening, day 1 and then within two weeks (or on day) of subsequent imaging.
11. Serology for HepBsAg, HepBcJIb and hepatitis C antibody (unless preloiouslylesled negatiw).
12. Serum pregnancy lest is required within 2 weeks prior to day #1 treatment
13. Blood draws for research purposes perfonned during screening or day 1,then weeks 2, 4 and 8 for all patienis.
14. ApproJCimately 20 x5 µm slides (unstained) will be requested on all patients for research purposes.
15. Research tumor biopsywill be perfonned at baseline, then 1week (±3 days) after completing radiation or ablation (from the radiated/ablated lesion) and 4 weeks (±1 week) after dose #1 of durvalumab plus tremelimumab (from a non-radiated/ablated lesion).
16. RT begins or ablation is perfonned during cy::le 1,within 7 days after starting durvalumab and tremelimumab.
17. EOS loisit occurs 4 weeks (±1 wk) after discontinuing the study. CT scan or MRI to be done only if last imaging was conducted greater than eight weeks prior to the date of the Final Visit.

10.1 Assessments

Physical examination

Physical examinations will be performed according to institutional practice and according to the assessment schedule in the calendar.

Electrocardiograms

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

At. Screening, a single ECG will be obtained on which QTcF must be <470 ms.

In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding.

Situations in which ECG results should be reported as AEs are described in Section 10.0.

Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules.

On infusion days, patients receiving durvalumab + tremelimumab treatment will be monitored during and after infusion of IP as presented in the bulleted list below.

Supine BP will be measured using a semi-automatic BP recording device with an appropriate cuff size, after the patient has rested for at least 5 minutes. BP and pulse will be collected from patients receiving durvalumab + tremelimumab treatment before, during, and after each infusion at the following times (based on a 60-minute infusion):

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [i.e., the beginning of the infusion]).
- Approximately 30 minutes during the infusion **(halfway** through infusion).
- M the end of the infusion (approximately 60 minutes ±5 minutes).
- A 1-hour observation period is required after the first infusion of durvalumab and tremelimumab.
- If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion).

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. The date and time of collection and measurement will be recorded on the appropriate eCRF. Additional monitoring with assessment of vital signs is at the discretion of the Investigator per standard clinical practice or as clinically indicated.

11.0 TOXICITIES/SIDE EFFECTS

11.1 SAFETY MONITORING

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

11.1.1 Adverse Events and Serious Adverse Events

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

Definition of Adverse Event and Non-Serious Adverse Event

The following definition of AE will be used for the study: "Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to medicinal (investigational) product."

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

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

Reporting and Treating Non-Serious Events

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

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

All AE.s, including clinically significant laboratory and assessment abnormalities will be recorded according to "Common Terminology Criteria for Adverse Events" V4.03 (CTCAE) and must be recorded in the CRDB. Events occurring prior to initiation of first dose should be recorded on the Medical History page of the CRDB. Any *AE* occurring at initiation of first dose of study drugs should be recorded on the Adverse Event page of the CRDB. AE.s should be recorded in the CRDB using the medical terminology found in the source documentation. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology. It is the investigator's responsibility to provide his/her assessment of the relationship of the event to the study drug and the severity of the event using the following scales:

- Relationship

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

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

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

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

- Severity

The severity of all adverse events should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) V4.03. For those adverse events not listed in the CTCAE, the following grading system should be employed:

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

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

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

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

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

Definition of Serious Adverse Event

The following definition of SAE applies for the study: "A serious AE means any AE occurring at any dose that results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious AE when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. A life-threatening AE is any AE that places the subject or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred (e.g., it does not include a reaction that, had it occurred in a more severe form, might have caused death)." Reporting and Treating Serious Adverse Events as per section 17.2.

Recording Adverse events

Adverse events will be recorded using a recognized medi::al term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to AstraZeneca/Med Immune Patient Safety.

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Changes in NCI CTCAE grade and the maximum CTC grade attained
- Whether the AE is serious or not
- Investigator causality rating against durvalumab or tremelimumab (yes or no)
- Action taken with regard to durvalumab + tremelimumab/comparator/combinati on agent

- OutcCJTle

In addition, the following variables will be collected for SAEs as applicable:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to ...
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Description of AE
- Causality assessment in relation to Study procedure(s)

Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

Ally overdose of a study subject with durvalumab + tremelimumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the A<;traZeneca/Medl mmune Patient Safety or designee using the designated Safety a-mailbox. If the overdose results in an AE, the AE must also be recorded as an AE.

Study recording period and follow-up for adverse events and serious adverse events

Adverse events and serious adverse events will be recorded frCJTl time of signature of informed consent, throughout the treatment period and including the follow-up period (90 days after the last dose of durvalumab or tremelimumab).

During the course of the study aIIAEs and SAEs should be proactively followed up for each subject. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

If a subject discontinues from treatment for reasons other than disease progression, and therefore continues to have tumor assessments, drug or procedure-related SAEs must be captured until the patient is considered to have confirmed PD and will have no further tumor assessments.

The investigator is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 90 days after the last dose of durvalumab or tremelimumab or until the initiation of alternative anticancer therapy. The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

The investigator and/or sponsor must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AstraZeneca. A copy of the MedWatch/AdEERs report must be faxed to AstraZeneca at the time the event is reported to the FDA It is the responsibility of the sponsor to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

* A *cover page* should accompany the *MedWatch/AdEERs* form indicating the following:

- "Notification from an Investigator Sponsored Study"
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number (ESR-15-11668

* Sponsor must also indicate, either in the SAE report or the cover page, the *causality* of events *in relation to all study medications* and if the SAE is *related to disease progression,* as determined by the principal investigator.

* *Send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox:* AE MailboxClinicalTrialTCS@astrazeneca.com

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the FDA

Serious adverse events that do not require expedited reporting to the FDA still need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

11.2 Other events requiring reporting

Overdose

An overdose is defined as a subject receiving a dose of durvalumab + tremelimumab in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study subject with durvalumab + tremelimumab, with or without asscx;iated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the sponsor and AstraZeneca/Med Immune Patient Safety or designee using the designated Safety e-mailbox. If the overdose results in an AE, the AE must also be recorded as an AE. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE. There is currently no specific treatment in the event of an overdose of durvalumab or tremelimumab. The investigator will use clinicaljudgment to treat any overdose.

Hepatic function abnormality

Hepatic function abnormality (as defined in Section 11.3.) in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to the sponsor and AstraZeneca/Med Immune Patient Safety using the designated Safety a-mailbox (see above for contact information), unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study subject will be based on the clinical judgment of the investigator.

- If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor and AstraZeneca/Med Immune.

Pregnancy

Maternal exposure

If a patient becomes pregnant during the course of the study, the IPs should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform the appropriate AstraZeneca representatives within 1 day, i.e., immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

Paternal exposure

11/ele patients should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of durvalumab + tremelimumab canbination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period.

Pregnancy of the patient's partner is not considered to be an AE. I-lowever, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 90 days after the last dose should, if possible, be followed up and documented.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patienfs partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

11.3 Durvalumab + tremelimumab 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 and rapid communication by the investigator to the sponsor. AA AESI may be serious or non-serious. The rapid reporting of AES Is allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

AESIs for durvalumab and 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 are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. AA immune-related adverse event (irAE) is defined as an adverse event 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 irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

If the Investigator has any questions in regards to an adverse event (AE) being an irAE, the Investigator should promptly contact the Study Physician.

AESIs observed with durvalumab and tremelimumab include:

- Colitis
- Pneumonitis
- *M..*T/AST increases / hepatitis / hepatotoxicity
- Neuropathy / neuromuscular toxicity (i.e. events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barre, and myasthenia gravis)

- Endocrinopathy (i.e. events of hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism)
- Dermatitis
- Nephritis
- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase, increased serum amylase)

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab and tremelimumab Investigator Brochure. For durvalumab and tremelimumab, AESIs will comprise the following:

Pneumonitis

AEs of pneumonitis are also of interest for AstraZeneca, as pneumonitis has been observed with use of anti-PD-1 mAbs (but not with anti-PD-L 1 mAbs). Initial work-up should include a high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended. Guidelines for the management of patients with immune-related AEs (irAEs) including pneumonitis are provided in Appendix A

Infusion reactions

AEs of infusion reactions (also termed infusion-related reactions) are of special interest to AstraZeneca and are defined, for the purpose of this protocol, as all AEs occurring fran the start of IP infusion up to 48 hours after the infusion start time. For all infusion reactions, SAEs should be reported to AstraZeneca Patient safety as described in Section 11.1.

Hypersensitivity reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L 1 and anti-PD-1 therapy (Brahmer et al, 2012.). As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of mAbs can be caused by various mechanisms, including acute anaphylactic (lgE-mediated) and anaphylactoid reactions against the mAbs and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting, and unresponsiveness. Guidelines for the management of patients with hypersensitivity (including anaphylactic reaction) and infusion-related reactions are provided in Append ix A

Hepatic function abnormalities (hepatotoxicity)

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

Gastrointestinal disorders

Diarrhea/colitis is the most commonly observed treatment emergent SAE when tremelimLJTiab is used as monotherapy. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome if not properly managed. Guidelines on management of diarrhea and colitis in patients receiving tremelimumab are provided in Appendix A

Endocrine disorders

Immune-mediated endocrinopathies include hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism. Guidelines for the management of patients with immune-mediated endocrine events are provided in Appendix A

Pancreatic disorders

Immune-mediated pancreatitis includes autoimmune pancreatitis, and lipase and amylase elevation. Guidelines for the management of patients with immune-mediated pancreatic disorders are provided in Appendix A

Neirotoxicity

Immune-mediated nervous system events include encephalitis, peripheral motor and sensory neuropathies, Guillain-Barre, and myasthenia gravis. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Appendix A

Nephritis

Immune-mediated nephritis includes autoimmune nephritis, renal dysfunction, and elevated serum creatinine. Guidelines for the management of patients with immune-mediated nephritis events are provided in Appendix A

Immune-related adverse events

Based on the mechanism of action of durvalumab and tremelimumab leading to T-cell activation and proliferation, there is a possibility of observing irAEs during the conduct of this study. Potential irAEs may be similar to those seen with the use of ipilimumab, BMS-936558 (anti-PD-1 mAb), and BMS-936559 (anti-PD-L1 mAb} and may include immune-mediated enterocolitis, dermatitis, hepatitis (hepatotoxicity), pneumonitis, and endocrinopathies (Hodi et al 2010, Brahmer et al 2012, Topalian et al 2012.). These AEs are inflammatory in nature and can affect any organ. With anti-PD-L1 and anti-CTLA-4 combination therapy, the occurrence of overlapping or increasing cumulative toxicities that include irAEs could potentially occur at higher frequencies than with either durvalumab or tremelimumab monotherapy. Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or PD), an immune-related etiology should be considered for signs or symptoms of enterocolitis, dermatitis, pneumonitis, hepatitis, and endocrinopathy. In addition to the dose modification guidelines provided in Appendix A, it is recommended that irAEs are managed according to the general treatment guidelines outlined for ipilimumab (Weber et al 2012.). These guidelines recommend the following:

- Patients should be evaluated to identify any alternative etiology.

- In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered immune related.
- Symptomatic and topical therapy should be considered for low-grade events.
- Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.
- IVore potent immunosuppressives should be considered for events not responding to systemic steroids (e.g., infliximab or mycophenolate).

If the Investigator has any questions in regards to an *PE* being an ir/IE, the Investigator should immediately contact the Study Physician.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

For the purposes of this study, patients will be evaluated for response every 2 cycles (approximately 8 weeks), or as clincially indicated if interim toxicity occurs mandating cancer staging re-assessment. RECIST 1.1 criteria will be used.

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

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

II/RI scans

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

Measurability of Tumor Lesions

Tumor lesions will be categorized as follows:

- **Measurable Lesions** - M.lst be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
    - 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm)
    - 10 mm caliper measurement by clinical exam (when superficial)
    - Malignant lymph nodes are considered pathologically enlarged and measurable, a lymph node must be <!: 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

- **Nonmeasurable Lesions** - Nonmeasurable lesions are defined as all other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with <!: 10 to < 15 mm short axis). Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardia! effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

- **Target Lesions** • All lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

- **Non-target Lesions** • It is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., "multiple enlarged peMc lymph nodes· or "multiple liver metastases")

Response Criteria

Evaluation of Target Lesions

- **Complete Response** • Disappearance of all target lesions. Ally pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm (the sum may not be "O" if there are target nodes).

- **Partial Response** • *At.* least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

- **Progressive Disease** • *At.* least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression.)

- **Stable Disease**-Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

Evaluation of Non-target Lesions

- **Complete Response** • Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

- **Non-complete response/Non-progressive disease** • Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

- **Progressive Disease** • Unequivocal progression of existing non-target lesions will be defined as the overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. In the absence of measurable disease, change in non-measurable disease comparable in magnitude to the increase that would be required to declare PD for

measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large,' an increase in lymphangitic disease from localized to widespread.

Appearance of New Lesions

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

Evaluation of Overall Response

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

Table 12 Evaluation of Overall Response

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

- Not evaluable is dEi1ned as eitha-when no *a* only asumet *c:l* las10n rreasIJ"ell'Snts are rrede at an assess111Bnt.

13.1 CRITERIA FOR REMOVAL FROM STUDY

In the absence of treatment delays due to adverse event(s), or serious toxicity or complications, treatment may continue until one of the following criteria applies:

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

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

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

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

After the end of treatment, each subject will be followed for 28 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up, for 2 years or until study closes. After documented disease progression each subject will be followed by telephone (unless not otherwise following up at Memorial Hospital) for overall survival until death, withdrawal of consent, the end of the study, or 2 years.

14.0 BIOSTATISTICS

The primary endpoint of this trial is the response rate in CRC treated with RT plus durvalumab and tremelimumab (cohort 1) or ablation plus durvalumab and tremelimumab (cohort 2). Based on historical controls, 1/20 responses may be observed in a non-radiated or non-ablated lesion with these current therapies and we consider a response rate S5% as unacceptable (Overman, Kopetz et al. 2016). A two-stage Simon's optimal design will be employed to test the null hypothesis that the true response rate is S5% versus the alternative hypothesis that the true response rate is at least 25% with type I and II error rates of 10% each. Each cohort will be evaluated separately for this purpose. Patients will be considered evaluable if they have received at least one dose of durvalumab and/or tremelimumab and undergone ablation/RT. Response will be determined only in disease that is not ablated or radiated. In the first stage, we will accrue 9 patients in each cohort. If 0 objective tumor responses (PR or CR) are observed among the 9 subjects treated in a cohort, then subject enrollment will be terminated in that cohort. If at least 1 response is observed among the 9 subjects treated in a cohort, then the study will be expanded to enroll a total of 24 treated subjects in that cohort. In the likelihood that we observe at least one response in each of the 9 subjects treated in stage 1 of the two cohorts, it will be at the discretion of the investigators which cohort to expand based on pharmacodynamic data (such as circulating CEA, changes in composition/activation status of lymphocyte subsets present in peripheral blood mononuclear cell preparations or tumor immunohistochemistry analysis, and/or circulating cytokines/ chemokines). The cohort to be expanded will enroll an additional 15 patients for a total of 24 treated subjects. *At.* the end of the study, if 2 or less objective tumor responses are observed in the expanded cohort, then the study will be considered not worthy of further investigation in that particular cohort. If at the end of the study <!3 tumor responses per RECIST 1.1 are observed in the expanded cohort, then further investigation of durvalumab and tremelimumab plus RT and/or durvalumab and tremelimumab plus ablation will be considered worthwhile.

Secondary outcomes, including toxicity, the additional measures of efficacy and exploratory objectives will be summarized by cohort.

The study will complete when all subjects have either progressed or discontinued from the study for other reasons. This study requires accrual of a minimum of 18 subjects and up to a maximum of 33 subjects if one cohort is expanded to the second stage. The accrual time is estimated to be 9 months to 2 years for both cohorts.

Antitumor Activity

Assessmen1s of antitumor activity will be based on the ORR, PFS, and OS. Response Evaluation Criteria in Solid Tumors guidelines (v1.1) (Eisenhauer, Therasse et al. 2009).

The ORR is defined as the proportion of subjec1s CR or PR based on RECIST criteria. The exact 95% CI of ORR will be estimated using the binomial distribution. Progression-free survival will be measured from the start of treatment with durvalumab and tremelimumab until the documentation of disease progression or death due to any cause, whichever occurs first. Progression-free survival will be censored on the date of last tumor assessment documenting absence of tumor progression for subjects who are still alive prior to data cutoff, dropout, or the initiation of alternate anticancer treatment. Subjects having no tumor assessmen1s after the start of treatment with durvalumab and tremelimumab will have PFS censored on the first date of treatment with durvalumab and tremelimumab. These patients will be counted as non responders and considered evaluable. Progression-free survival will be evaluated using the Kaplan-lv'eier method (Kaplan and Meier, 1958). Overall survival will be determined as the time from the start of treatment with durvalumab and tremelimumab until death. For subjects who are alive at the end of study or lost to follow-up, OS will be censored on the last date when subjects are known to be alive. The OS will be evaluated using the Kaplan-lv'eier method. Progression free survival at 1 and 2 years will be estimated by the Kaplan-lv'eier.

Safety and Tolerability Analyses

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

Biomarker Analysis

Exploratory research studies will be done to evaluate the effect of this therapy will be perfonmed using research blood draws and tumor biopsies at baseline, week 1 and at week 4.

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

The pharmacodynamic effect of durvalumab and tremelimumab and RT or ablation on markers in peripheral blood, such as ICOS, HI.A-DR, PD-1, CTL.A-4; and, serum proteins, such as CXCL9;

CXCL10, will be assessed by summary statistics, and investigated graphically to explore patterns of change over time, i.e.: pretreatment, then week 2, week 4 and week 8.

In addition, the relationship of TIL changes and tumor marker expression with measures of peripheral blood markers will be summarized descriptively.

Associations between the markers and response by RECIST will be explored.

Fisher's exact test will be employed to assess associations between categorical variables while Spearman's rank correlation will be used for continuous variables. Wilcoxon signed rank test will be used to test for differences in continuous expression tumor markers between pre- and post-treatment specimens while 11/k:Nemar's test will be used to assess these relationships for binary markers.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for PatienUSubject Eligibility.

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

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

15.3 Randomization

NIA

16.1 DATA MANAGEMENT ISSUES

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

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

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and

protocolcompliance audits may be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety M>nitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety M>nitoring of Clinical Trials", which can be found at http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC DSM Plans can be found on the MSKCC Intranet at http://mskweb5.mskcc.org/intranet/ assets/ tables/content/359689/Data safetv%20M>nitoring07.pdf

17.1 PROTECTION OF HUMAN SUBJECTS

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

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

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

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

Costs: The patient will be responsible for the costs of standard medical care, including, CT scans, all drug administration fees and all hospitalizations, even for ccrnplications of treatment. Durvalumab and tremelimumab will be supplied to patients by MedImmune/ Atstra Zeneca at no cost. Patients will not be responsible for the costs of blood procurement obtained for research purposes or the cost for obtaining the tumor biopsy for research purposes.

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

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

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

17.1 Privacy

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

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- 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

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 90-days after the participant's last investigational treatment or intervention.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mslu:c.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mslu:c.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

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

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

For IND/IDE protocols:
The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office

17.2.1

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to MedImmune/ Ac>tra Zeneca product, must be reported within 5 calendar days to the MSKCC Safety Office.

Non-serious Even1s of Clinical Interest will be forwarded to 1\11edImmune/ Ac>tra Zeneca Global Safety andwill be handled in the saTie mainer as SAEs.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to MedImmune/ Astra Zeneca product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to MedImmune/ Astra Zeneca.

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRS/PB-approved consent form indicating their consent to participate. This consent form mee1s the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

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

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

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

19.0 REFERENCES

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.20.0 APPENDICES

APPENDIX *A:*.	Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions
APPENDIX B:	Requisition For Blood Specimens
APPENDIX C:	Requisition For Tumor Specimens

Appendix A Dosing Modification and Toxicity Management Guidelines for Inmune-mediated, Infusion Related, and Non Inmune-mediated Reactions

The following table is a guide to the management of immune-related toxicity, and is subject to physician discretion.

Table A Immune-Mediated Reactions

	Dose Modifications	Toxicity Management
Immune-related Adverse Events (Overall Manageme nt For toxicities not noted below)	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 v4.03. In addition to the criteria for penmanent 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 S10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing.	It is recommended that management of irAEs follow the guidelines presented in this table – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, infections, etc.) – In the absence of a clear alternative etiology, all events should be considered potentially immune related. – 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 – 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 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. – Discontinuation of study drug is not mandated for Grade 3 / Grade 4 inflammatory reactions attributed to
	Grade 1 No dose modification Grade 2 • Hold study drug/study regimen dose until grade 2 resolution to s Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date • Study drug/study treatment can be resumed at the next scheduled dose once event stabilizes to grade s1 and 5-7 days have passed after completion of steroid taper • Patients with endocrinopathies who may require prolonged or continued steroid replacement can be	

Appendix A Dosing Modification and Toxicity Management Guidelines for Inmune-mediated, Infusion Related, and Non Inmune-mediated Reactions

The following table is a guide to the management of immune-related toxicity, and is subject to physician discretion.

		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 judgment, and 3) Doses of prednisone are at less than or equal to 10mg/day or equivalent.	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
	Grade 3	Depending on the individual toxicity, may permanently discontinue study drug/study regimen. Please refer to guidelines below	
	Grade 4	Permanently discontinue study drug/study regimen	
	Note: For Grade 3 and above asymptomatic amylase or lipase levels hold study drug/regimen and if complete work up shows no evidence of pancreatitis, may continue or resume study drug/regimen		

Appendix A Dosing Modification and Toxicity Management Guidelines for Irrmune-mediated, Infusion Related, and Non Irrmune-mediated Reactions

Event	Event Grade (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Pneumonitis/ ILD	Ally Grade		• Ivlonitor 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) • Ivlonitor 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 s Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then the decision to reinitiate study drug/regimen at next scheduled treatment date will be based upon treating physician's clinical judgment • Study drug/study treatment can be resumed at the next scheduled dose once event stabilizes to grade S1 and 5-7 davs	For Grade 2 (Mild to Moderate New Symptoms) • Ivlonitor symptoms daily and consider hospitalization • Promptly start systemic steroids (e.g., prednisone 1-2mg/kg/day 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 methylprednisone at 2-4/g/kg/day, promptly start immunosuppressive therapy such as TNF inhibiters (e.g. infliximab at 5mg/kg every 2 weeks). Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using

Appendix A Dosing Modification and Toxicity Management Guidelines for Irrmune-mediated, Infusion Related, and Non Irrmune-mediated Reactions			
Event	**Event Grade (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
		have passed after completion of steroid taper	infliximab • Once improving, gradually taper steroids over weeks and consider prophylactic antibiotics, antifungal or anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 28 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 AOL; oxygen indicated; Grade 4: life threatening respiratory compromise, urgent intervention indicated [e.g. tracheostomy or intubation])	Penmanently discontinue study drug/study regimen	For Grade 3 or 4 (severe or new symptoms, newiWorsening hypoxia, life threatening • Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent • Obtain pulmonary and infectious disease consult • 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 improving, gradually taper steroids over 28 days and consider prophylactic antibiotics, antifungals and in particular, anti PCP treatment (please refer to current NCCN auidelines for treatment of cancer-

[1] ASCO Educational Book 2015 "Managing Imnmne Checkpoint Blocking Anubody 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"

Appendix A Dosing Modification and Toxicity Management Guidelines for Irrmune-mediated, Infusion Related, and Non Irrmune-mediated Reactions			
Event	**Event Grade (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			related infections (Category 28 recommendation)'
Diarrhea/ Enterocolitis	Ally Grade		• Monitor for symptoms that may be related to diarrhea/enterocol itis (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 day)	No dose modification	For Grade 1 diarrhea : • Close monitoring for worsening symptoms • Consider symptomatic treatment including hydration, electrolyte 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	• Hold study drug/study regimen until resolution to s Grade 1 • If toxicity worsens	For Grade 2 diarrhea: • Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g.,

[4] ASCO Educational Book 2015 "Managing Imnnme Checkpoint Blocking Antibody Side Effects" by Michae! Postow MD

Appendix A Dosing Modification and Toxicity Management Guidelines for Irrmune-mediated, Infusion Related, and Non Irrmune-mediated Reactions			
Event	**Event Grade (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	day)	then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date • Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade S1 and 5-7 days have passed after completion of steroid taper	American Dietetic Association colitis diet), and loperamide and/or budesonide • 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, 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, prompUy start immunosuppressives such as infliximab at 5mg/kg once every 2 weeks). **Caution:** Important to rule out bowel perforation and refer to inftiximab label for general guidance before using inftiximab • Consult study physician if no resolution to s Grade 1 in 3-4 days • Once improving, gradually taper steroids over :!:28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])

[5] ASCO Educational Book 2015 Michael Postow MI "Managing mmune Checkpoint Blocking Antibody Side Effecis

Appendix A Dosing Modification and Toxicity Management Guidelines for Irrmune-mediated, Infusion Related, and Non Irrmune-mediated Reactions			
Event	**Event Grade (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 3 or 4 diarrhea (Grade 3: stool frequency of 7 over baseline per day; Grade 4: life threatening consequences)	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 improving, gradually taper steroids over 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
Hepatitis (Elevated LFTs)	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) • **Infliximab should not be used for management of Immune Related Hepatitis**
	Grade 1 (AST or ALT > ULN to 3 times ULN and/or TB > ULN to 1.5 times ULN)	• No dose modification • If it worsens, treat as Grade 2 event	For Grade 1 AST or ALT and/or TB elevation • Continue LFT monitoring per protocol

Appendix A Dosing Modification and Toxicity Management Guidelines for Irrmune-mediated, Infusion Related, and Non Irrmune-mediated Reactions			
Event	**Event Grade (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 2 (AST or ALT > 3 to 5 times ULN and/or TB >1.5-3.0 times ULN)	• Hold Study drug/study regimen dose until grade 2 resolution to s Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If improves to baseline then treat at next scheduled treatment date • Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade s1 and 5-7 days have passed 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 s Grade 1 in 1-2 days, discuss with study physician. • If event is persistent (> 3-5 days) or worsens, pranptly start prednisone 1-2mg/kg/day or IV equivalent. • If still no improvement within 3-5 days despite 1-2mg/kg/day of prednisone or M equivalent, consider additional workup and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. • If still no improvement within 3-5 days despite 2-4mg/kg/day of IV methylprednisolone, prompUy start immunosuppressives (mycophenolate mofetil}[6] . Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** • Once improving, gradually taper steroids over :!:28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
	Grade 3 (AST or ALT >5-20 times ULN and/or TB > 3.0-10 times ULN	• For elevations in transaminases s 8 x ULN, or elevations in bilirubin s 5 x ULN • Hold study drug/study regimen dose until resolution to s Grade 1 or baseline	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

[6] ASCO Educational Book 2015 "Managirg Immune Checkpoint Blocking Antibody Side Effecis" , by Mchael Poslow MD

Appendix A Dosing Modification and Toxicity Management Guidelines for Irrmune-mediated, Infusion Related, and Non Irrmune-mediated Reactions			
Event	**Event Grade (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
		• Resume study drug/study regimen administration at the next scheduled dose if elevations downgrade s Grade 1 or baseline within 14 days • PermanenUy discontinue study drug/study regimen if the elevations do not downgrade to s Grade 1 or baseline within 14 days • For elevations in transaminases > 8 x ULN or elevations in bilirubin > 5 x ULN, discontinue study drug/study regimen • PermanenUy discontinue study drug/study regimen for any case meeting Hy's law criteria (ALT > 3x ULN + bilirubin > 2x ULN without initial findings of cholestasis (i.e. elevated alkaline P04) and in the absence of any alternative cause'	methylprednisolone IV or equivalent , promptly start treatment with immunosuppressive therapy (mycophenolate mofetil) Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** • Hepatology consult, abdominal workup, and imaging as appropriate. • Once improving, gradually taper steroids over <!:28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
	Grade 4 (AST or ALT > 20 times ULN and/or TB > 1O times ULN)	Permanently discontinue study drug/study regimen	

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

Appendix A Dosing Modification and Toxicity Management Guidelines for Irrmune-mediated, Infusion Related, and Non Irrmune-mediated Reactions			
Event	**Event Grade (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
Nephritis or Renal Dysfunction (Elevated Serum Creatinine)	Ally Grade		• Consult with Nephrologist • tvlonitor 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 1 [Serum Creatinine > 1-1.5X baseline; > ULN to 1.5X ULN]	• No dose modification • If toxicity worsens, depending on the severity, treat as Grade 2 or Grade 3 or 4	For Grade 1 elevated creatinine: • tvlonitor serum creatinine weekly and any accompanying symptom • If creatinine returns to baseline, resume its regular monitoring per study protocol. • 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 s Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date • Study drug/study regimen can be resumed at the next	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, prompUy start prednisone 1 to 2 mg/kg/day or IV equivalent • If event is not responsive within 3-5 davc: or worsens desoite orednisone at

Appendix A Dosing Modification and Toxicity Management Guidelines for Irrmune-mediated, Infusion Related, and Non Irrmune-mediated Reactions			
Event	Event Grade (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		scheduled dose once event stabilizes to grade s1 for 5-7 days have passed after completion of steroid taper	1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4mg/kg/day started. • Once improving gradually taper steroids over <!:28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 28 recommendation]). • When event returns to baseline, resume study drug/study regimen 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)	PenmanenUy 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 improving, gradually taper steroids over 0!:28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 28 recommendation]
Rash (excluding Bullous skin fonmations	Ally Grade (Please refer to NCI CTCAE version 4.03 for definition of		• 11/bnitor for signs and symptoms of dermatitis (rash and pruritus) • **IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED AND

Appendix A Dosing Modification and Toxicity Management Guidelines for Irrmune-mediated, Infusion Related, and Non Irrmune-mediated Reactions			
Event	**Event Grade (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	severity/ grade depending on type of skin rash)		**STUDY DRUG DISCONTINUED****
	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 s Grade 1 or baseline • If toxicity worsens then treat as Grade 3 • If toxicity improves then resume administration at next scheduled dose • Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade s1 and 5-7 days have passed 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, discuss with study physician and promptly start systemic steroids prednisone 1-2 mg/kg/day or IV equivalent • Consider skin biopsy if persistent for >1-2 weeks or recurs
	Grade 3	• Hold study drug/study regimen until resolution to s Grade 1 or baseline • If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to s Grade 1or baseline within 30	For Grade 3 or 4: • Consult dermatology • PrompUy initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent • Consider hospitalization • 11/bnitor extent of rash [Rule of Nines] • Consider skin biopsy (preferably more than 1) as clinically feasible.

Appendix A Dosing Modification and Toxicity Management Guidelines for Irrmune-mediated, Infusion Related, and Non Irrmune-mediated Reactions

Event	Event Grade (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		days, then penmanenUy discontinue Study drug/study regimen	• Once improving, gradually taper steroids over 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 28 recommendation]) • Discuss with Study Physician
	Grade 4	Penmanently discontinue study drug/study regimen	
Endocrinopathy (e.g. hyperthyroidism, hypothyroidism, hypopituitarism, adrenal insufficiency, etc.)	Any Grade (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity)		• Consult Endocrinologist • 11/bnitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension and weakness. • Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infections, etc.) • 11/bnitor and evaluate thyroid function tests: TSH, free T_3 and free T_4 and other relevant endocrine labs depending on suspected endocrinopathy. • 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 1 (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade 1)	No dose modification	For Grade 1: (including those with asymptomatic TSH elevation) • 11/bnitor patient with appropriate endocrine function tests • If TSH < 0.5X LLN, or TSH >2X ULN or consistenUy out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider endocrinology consult.

Appendix A Dosing Modification and Toxicity Management Guidelines for Irrmune-mediated, Infusion Related, and Non Irrmune-mediated Reactions			
Event	**Event Grade (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 2 (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity 2)	• For Grade 2 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until subject is clinically stable • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date • Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade s1 and 5-7 days have passed 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 judgment, and 3) doses of prednisone are at less than or equal to 1Omg/day or equivalent.	For Grade 2: (including those with symptomatic endocrinopathy} • Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids • Initiate hormone replacement as needed for management • Evaluate endocrine function, and as clinically indicated, consider pituitary scan • For patients with abnormal endocrine work up, except for those with isolated hypothyroidism, consider short-term, corticosteroids (e.g., 1-2mg/kg/day methylprednisolone or IV equivalent) and prom pt initiation of treatment with relevant hormone replacement (e.g. Levothyroxine, hydrocortisone, or sex hormones). • Once improving, gradually taper steroids over 8 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 28 recommendation]) • For patients with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated.

Appendix A Dosing Modification and Toxicity Management Guidelines for Irrmune-mediated, Infusion Related, and Non Irrmune-mediated Reactions			
Event	**Event Grade (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 3 or 4 (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity 3 or 4)	• For Grade 3 or 4 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled • Resume study drug/study regimen administration if controlled at the next scheduled dose • Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade s1 and 5-7 days have passed after completion of steroid taper	For Grade 3 or 4: • Consult endocrinologist • Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids • Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent • Administer hormone replacement therapy as necessary. • For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity • Once improving, gradually taper immunosuppressive steroids over weeks and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 28 recommendation]) • Discuss with study physician
Immune mediated Neurotoxicity (to include but not limited to limbic encephalitis . autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	Any Grade (Depending on the type of neurotoxicity , refer to NCI CTCAE version 4.03 for defining the CTC grade/severity		• 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) • Symptomatic treatment with neurological consult as appropriate

Appendix A Dosing Modification and Toxicity Management Guidelines for Irrmune-mediated, Infusion Related, and Non Irrmune-mediated Reactions			
Event	**Event Grade (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 1	No dose modifications	See "Arly Grade" recommendations above.
	Grade 2	• For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to s Grade 1 • For sensory neuropathy/neuropathi c pain, consider holding study drug/study regimen dose until resolution to s Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date • Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade s1 and 5-7 days have passed after completion of steroid taper	• Discuss with the study physician • Obtain Neurology Consult • Sensory neuropathy/neuropathi c pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.) • Promptly start systemic steroids prednisone 1-2mg/kg/day or IV equivalent • If no improvement within 3-5 days despite 1-2mg/kg/day prednisone or IV equivalent consider additional workup and prom pUy treat with additional immunosuppressive therapy (e.g. MG}
	Grade 3	• Hold Study drug/study regimen dose until resolution to s Grade 1 • PermanenUy discontinue Study drug/study regimen if Grade 3 irAE does not resolve to s Grade 1 within 30 days.	For Grade 3 or 4: • Discuss 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
	Grade 4	Permanently discontinue	

Appendix A Dosing Modification and Toxicity Management Guidelines for Irrmune-mediated, Infusion Related, and Non Irrmune-mediated Reactions			
Event	**Event Grade (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
		study drug/study regimen	with additional immunosuppressants (e.g. IVIG} • Once stable, gradually taper steroids over weeks
Immune-mediated peripheral neuromotor syndromes, such as Guillain-Barre and Myasthenia Gravis	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 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 and medications, etc.). 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 r""uirina treatment

Appendix A Dosing Modification and Toxicity Management Guidelines for Irrmune-mediated, Infusion Related, and Non Irrmune-mediated Reactions			
Event	**Event Grade (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			should be started with IVIG and followed by plasmapheresis if not responsive to MIG
	Grade 1	No dose modification	• Discuss 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 unless the symptoms are very minor and stable
	Grade 2	• Hold study drug/study regimen dose until resolution to s Grade 1 • Permanently discontinue study drug/study regimen if it does not resolve to s Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	• Discuss 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 • Sensory neuropathy/neuropathi c pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.) *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Illlyasthenia Gravis. 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 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:*

Appendix A Dosing Modification and Toxicity Management Guidelines for Irrmune-mediated, Infusion Related, and Non Irrmune-mediated Reactions

Event	Event Grade (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			o 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 MG and followed by plasmapheresis if not responsive to IVIG.
	Grade 3	• Hold study drug/study regimen dose until resolution to s Grade 1 • PermanenUy discontinue Study drug/study regimen if Grade 3 irAE does not resolve to s 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: • Discuss with study physician • Recommend hospitalization • I\Ilonitor 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 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:* • 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 MG and followed by plasmapheresis if not responsive to IVIG
	Grade 4	Permanently discontinue study drug/study regimen	

Appendix A Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions

Table B. 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
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}

Appendix A	Dosing Modification and Toxicity Management Guidelines for Inmune-mediated, Infusion Related, and Non Irrmune-mediated Reactions

Table C. Non-inmune Mediated Reactions
(Note: *If is* 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 adjustment	Treat accordingly as per institutional standard
2	Hold study drug/study regimen until resolution to s Grade 1 or baseline	Treat accordingly as per institutional standard
3	Hold study drug/study regimen until resolution to s Grade 1 or baseline For AEs that downgrade to s Grade 2 within 7 days or resolve to s Grade 1 or baseline within 14 days, resume study drug/study regimen administration at next scheduled dose. 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 would be based on accompanying clinical signs/symptoms and as per Investigator's clinical judgment and in consultation with the sponsor)	Treat accordingly as per institutional standard

.APPENDIX B: REQUISITION FOR BLOOD SPECIMENS

Phase II Study to Assess the Efficacy of Durvalumab and Tremelirrumab Plus Radiotherapy or Ablation in Patients with Metastatic Colorectal Cancer

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

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

Single Arm Phase II Study to Assess the Efficacy of Durvalumab and tremelimumab Plus Radiotherapy or Ablation in Metastatic Colorectal Cancer Patients

A) Section A: Patient information (To be completed by RSA)	**B) Section B: Sample information** (To be checked off by RSA)
Patient initials: _____ Patient study ID#: _____ Site: _____	[] Baseline: 5 Core Biopsies [] Week 1: 5 Core Biopsies [] Week 4: 5 Core Biopsies [] Routine Procedure: 5 Cores or divided tumor
C) Section C: Sample Collection information (To be completed by physician or designee) Obtained By: _____ Procedure: _____ Date/ Time: _____	Sample Collection Instructions: 1. Cores # 1, 3, 5: Place into formalin (3-5 cc) 2. Cores # 2, 4: Place in sterile Nunc tube and snap freeze in liquid nitrogen 3. *Core #_: Place in RPM/ (5 cc)* *[If tissue remains, collect/ process as for core #5]*
D) Section D: Storage/Processing information (To be completed by laboratory personnel) Lab ID#: _____ Received by: _____ Date/Time: _____	Sample Storage/ Processing Instructions 1. Cores # 1, 3, 5: Store at 4-8°C 2. Cores # 2, 4: Store at -70 to -80°C 3. *Core #_: Process immediate/y for isolation of tumor infiltrating lymphocytes.*
E) Section E: Sanple shipping information (To be completed by laboratory personnel) Sent by: _____ Date/Time: _____ Received by: _____ Date/Time: _____	Sample shipping Instructions Ship samples 1, 3, and 5 at room temperature; samples 2 and 4 on dry ice, attention:

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