MD Anderson IND Sponsor Cover Sheet	
Protocol ID	2015-0828
Protocol Title	Pilot Study Assessing the Safety and Tolerability of the Neoadjuvant Use of Durvalumab (anti-PD-L1) combined with either Tremelimumab (anti-CTLA-4) or Monalizumab (anti-NKG2A) or Oleclumab (anti-CD73) in the Treatment of Resectable Colorectal Cancer Liver or Lung Metastases
Phase	Pilot
Protocol Version	9
Version Date	1/25/2019
Protocol PI	Michael Overman
Department	GI Medical Oncology
IND Sponsor	MD Anderson Cancer Center
IND #	130,357

TITLE: Pilot Study Assessing the Safety and Tolerability of the Neoadjuvant Use of Durvalumab (anti-PD-L1) combined with either Tremelimumab (anti-CTLA-4) or Monalizumab (anti-NKG2A) or Oleclumab (anti-CD73) in the Treatment of Resectable Colorectal Cancer Liver or Lung Metastases.

Coordinating Center: *University of Texas MD Anderson Cancer Center*

Principal Investigator: Michael Overman, MD
moverman@mdanderson.org

Version: 9 dated January 25, 2019

TABLE OF CONTENTS

Page

1. OBJECTIVES

1.1. Primary Objective

Assess the safety and feasibility of adding Immune-therapy with durvalumab (MEDI4736) (anti-PD-L1) combined with either Tremelimumab (anti-CTLA-4) or Monalizumab (anti-NKG2A) or Oleclumab (MEDI9447) administered once pre-operatively and post-operatively in patients who are candidates for resection for colorectal cancer with liver or lung metastases (CRCLM).

1.2. Secondary Objectives

1. Explore the changes in various immune parameters, including PD-L1 and PD-1 expression in the tumor, over treatment and correlate with response and survival with goal of biomarker discovery.
2. Estimate the relapse-free survival (RFS) in all enrolled subjects.

2. BACKGROUND

2.1 Study Disease

2.1.1 Colon Cancer Background and Treatment Options

Colorectal cancer is the third most common cancer in the United States with an estimated 136,830 new cases and 50,310 deaths in 2014 [1]. Of new cases, 20-25% will have clinically detectable liver metastases at the time of diagnosis, and a further 40-50% of patients will eventually develop CRCLM [2]. Therefore, approximately one-third of patients will develop liver metastases within 3 years of initial diagnosis [3]. Surgery is potentially curative in the 15-20% of patients who meet criteria for resection [3-5]. As such, approximately 5,000-10,000 patients will have resectable CRCLM per year in the U.S. The definition of resectability varies, but in general resectability implies an achievable R0 surgical resection with adequate post-operative liver function [6].

For surgical candidates, complete surgical resection is associated with a 20-50% overall survival rate at 5 years [7-9]. For solitary CRCLM, the 5-year survival rate with surgery alone has been reported to be as high as 50%-71% [10]. Risk factors for survival after CRCLM identified in a meta-analysis of 60 studies include: node positive primary, CEA level, extra-hepatic disease, poor tumor grade, positive surgical margin, >1 liver metastasis, and >3cm diameter of the liver metastasis [11].

Unfortunately, 75% of resected patients ultimately recur, and there is an opportunity to improve this outcome with adjuvant therapy [12]. Aside from careful patient selection, many adjuvant and neo-adjuvant treatment strategies have been studied in an effort to improve outcomes. In a meta-analysis of 2 large clinical trials, adjuvant 5-FU plus leucovorin demonstrated a trend toward improved progression free survival (PFS) (p=0.059) and improved OS (p=0.046) [13]. In EORTC Intergroup trial 40983, FOLFOX4 was given for 6 cycles before and 6 cycles after hepatic resection. There was an absolute 8.1%

improvement in 3-year PFS from 28.1% to 36.2% (p=0.041) in the intention-to-treat population [14]. Eighty-three percent of randomized patients in both surgical and neo-adjuvant arms advanced to surgery, achieving an R0 resection. Despite the high number of patients being able to undergo R0 surgical resection, this approach does not confer a survival benefit. Post-operative hepatic arterial infusion (HAI) is performed in some high-volume, specialized academic centers, and survival when combined with 5-FU is superior to 5-FU alone (10 year survival 41% vs. 28%) [15]. However, HAI use is not a widely used strategy, especially in the community setting, and in general, there remains an urgent need to improve upon existing therapies.

FOLFOX chemotherapy is used in both an adjuvant setting for resected stage III and selected high-risk stage II colorectal cancer (CRC) patients. It was shown in a large, prospective, randomized phase III trial to be superior to infusional 5-FU in the adjuvant setting (MOSAIC [16]). FOLFOX is also a standard first line treatment option for patients with metastatic CRC with median PFS of 8 months [17]. Bevacizumab, a monoclonal antibody targeting VEGFR, is often added to FOLFOX in the up-front metastatic setting as it confers a progression free survival benefit [18]. Irinotecan has also been studied in the adjuvant setting with 5-FU. However, when added to the historical standard, 5-FU, in the adjuvant setting, irinotecan-based chemotherapy offered no benefit [19-21].

As there is wide practice pattern variation in the number of cycles varying from 2 to 10 cycles and exact type of chemotherapy (FOLFOX/Bev, FOFLOX, FOLFIRI, FOLFOXIRI, or FOLFIRI/cetuximab) that is given prior to CRC liver resection this study will not require a certain type or duration of therapy prior to liver resection. In part this variation exists as patients may have multiple liver relapses and thus treatments utilized may be adjusted based upon prior chemotherapy exposure of the patient. As oxaliplatin based therapies are the most common type, in order to maintain homogeneity in patient population at least 75% of patients will be required to have had prior oxaliplatin-based neoadjuvant therapy. This approach is in line with this study design as a window study prior to liver resection where a distinct treatment modality, immune-checkpoint therapy is being explored. Following surgical resection, treating physicians may either give Durvalumab or continue the prior systemic chemotherapy that was given in the preoperative setting.

Lung metastectomy for CRC mirrors data for liver resection as no large scale prospective clinical trials have been conducted for CRC lung metastectomy. Based on retrospective clinical trials, outcomes for lung metastectomies are similar to what is seen for liver metastectomies. Recently, studies have found the integration of checkpoint blockage into the treatment of early-stage and locally advanced NSCLC is safe, tolerable, and has the potential to improve outcomes without adding substantial toxicity [22] . As an example, Forde et al performed a pilot study to examine the safety and feasibility of the use of neoadjuvant nivolumab in 21 Stage I-IIIA resectable NSCLC. The study was designed such that treatment would not be considered feasible if the probability that surgery would be delayed was 90% or more for more than 25% of the patient. Of 21 planned resections, 20

were completed and there were no surgical delays thus feasibility endpoint was met. Similarly safety end point was satisfied with minor grade 3-4 events [23].

2.1.2 **Cancer and Immune function**

The importance of the immune system in cancer development and progression has been recognized during the past decade [24]. Failure of immune surveillance of pre-neoplastic lesions and micro-metastases is a key step in cancer development. Chronically immunosuppressed individuals show higher rates of cancer. This observation led to the hypothesis that sporadic cancers among immunocompetent individuals are likely to be minimally immunogenic, allowing for passive escape from immune surveillance. Recent data suggests that this may be an oversimplification. Some sporadic tumors are highly immunogenic, but actively suppress the local immune environment through production of immunosuppressive cytokines [25]. As such, the local tumor environment is likely a highly dynamic environment where most tumors grow and metastasize through adaptive responses that modulate antitumor immunity. The complexity and redundancy of the immune system offers multiple targets that may be manipulated to maximize the body's inherent immune response to a tumor. Immune response may be augmented by directly stimulating effector cells, indirectly stimulating effectors by augmenting antigen presentation activity or co-stimulation, or by suppressing immunosuppressive factors, cells, or messages [26].

2.1.3 **Immune Checkpoint Inhibition**

Tumor-infiltrating lymphocytes (TILs) have the capacity to control the growth of many types of cancers [27]. Most tumors show infiltration by TILs, but tumors modulate the local microenvironment through expression of inhibitory molecules. Engagement of TIL cell-surface receptors with these inhibitory ligands leads to a dysfunctional immune response, causes T-cell exhaustion, and facilitates tumor progression [28, 29]. Novel monoclonal antibodies (mAbs) that block these inhibitory receptors have shown significant clinical activity across a number of tumor types [30-34]. Specifically, blockade of immune-checkpoint inhibitors such as cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), programmed cell death 1 (PD-1), and programmed cell death ligand 1 (PD-L1) have shown clinical activity not only in conventionally immune-responsive tumors such as melanoma and renal cell carcinoma but also in non-small-cell lung cancer (NSCLC) [33-35], prostate cancer [36, 37], pancreatic cancer [38], mesothelioma [39], and other solid tumors [33, 35].

2.2 **Investigational Agents-Durvalumab**

2.2.1 Durvalumab (MEDI4736) **Background**

Durvalumab also called MEDI 4736 is a human immunoglobulin G (IgG)1 kappa mAb directed against human PD-L1. Durvalumab is expressed in Chinese hamster ovary cells and

has an overall molecular weight of approximately 149 kDa. Durvalumab6 selectively binds human PD-L1 with high affinity and blocks its ability to bind to PD-1 and CD80. The fragment crystallizable (Fc) domain of durvalumab contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to the complement component C1q and the Fc gamma receptors responsible for mediating antibody-dependent cell-mediated cytotoxicity (ADCC) [40].

2.2.2 Durvalumab **Pre-Clinical Experience**

Programmed cell death 1 (CD279) is a member of the immunoglobulin superfamily of molecules involved in regulation of T-cell activation. It is found on T cells, B cells, macrophages, NK cells, dendritic cells, and mast cells. It has also been described on peripheral tissues including cardiac endothelium, lung, small intestine, keratinocytes, islet cells of the pancreas, and syncytiotrophoblasts in the placenta as well as a variety of tumor cell types [41-47]. Programmed cell death ligand 1 (CD274, B7-H1) is constitutively expressed on many hematopoietic cells, but may be upregulated in hematopoietic and non-hematopoietic cells. Regulation of PD-L1 is mediated, in part, by type I and type II interferon (IFN). Programmed cell death ligand 2 (PD-L2; B7-DC) was identified in 2001 [45, 48]. Its expression is far more restricted and is confined to hematopoietic cells. Engagement of PD-1 on T cells inhibits activation with downstream effects on cytokine production, proliferation, cell survival, and transcription factors associated with effector T-cell function [49-54].

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

- Durvalumab binds to PD-L1 and blocks its interaction with PD-1 and CD80.
- Durvalumab can relieve PD-L1-mediated suppression of human T-cell activation in vitro.
- Durvalumab inhibits tumor growth in a xenograft model via a T-cell-dependent mechanism.
- A surrogate anti-mouse PD-L1 antibody resulted in improved survival in a syngeneic tumor model as monotherapy and resulted in complete tumor regression in > 50% of treated mice when given in combination with chemotherapy.
- In the same study, anti-mouse PD-L1 antibody-treated mice were completely tumor free 3 months after tumor implantation and demonstrated long-term immunity during re-challenge.
- In a subsequent study in the same syngeneic model, the combination of an anti-mouse PD-L1 antibody and anti-CTLA-4 antibody resulted in complete tumor regression in all mice treated.
- Prevalence of PD-L1 expression on the surface of human tumors, ranging from approximately 0% to 35%, was demonstrated in a broad survey of samples derived from tumor types of interest.

The cynomolgus monkey is considered to be the only relevant nonclinical species for evaluation of local and systemic toxicities of Durvalumab. In addition, in vivo in cynomolgus monkeys, Durvalumab suppresses soluble programmed cell death ligand 1 (sPD-L1) in serum and fully occupies membrane PD-L1 on various leukocyte subsets at doses equal to or more

than 0.1 mg/kg (lowest dose tested) with a dose-related duration of suppression and occupancy.

In general, there were no Durvalumab-related adverse effects in toxicology studies conducted in cynomolgus monkeys with Durvalumab that were of relevance to humans. Adverse findings in the non-Good Laboratory Practice (GLP) pharmacokinetic (PK)/pharmacodynamic and dose range-finding study (4 doses over 5 weeks), and a GLP 4-week repeat-dose toxicity study were consistent with antidrug antibody (ADA)-associated morbidity and mortality in individual animals. The spectrum of findings, especially the clinical signs and microscopic pathology, in a single animal in the GLP, 4-week, repeat-dose study was also consistent with ADA immune complex deposition, and ADA: Durvalumab immune complexes were identified in a subsequent non-GLP, investigative immunohistochemistry (IHC) study. Similar observations have been reported by MedImmune in cynomolgus monkeys administered human mAbs unrelated to Durvalumab. Given that immunogenicity of human mAbs in nonclinical species is not generally predictive of responses in humans, the ADA-associated morbidity and mortality were not taken into consideration for the determination of the no-observed-adverse-effect level (NOAEL) of Durvalumab. Interim audited data from the dosing phase of the pivotal 3-month GLP toxicity study with Durvalumab in cynomolgus monkeys showed that subchronic dosing of Durvalumab was not associated with any adverse effects. Therefore, the NOAEL of Durvalumab in all the general toxicity studies was considered to be 100 mg/kg, the highest dose tested in these studies. In addition to the in vivo toxicology data, no unexpected membrane binding of Durvalumab to human or cynomolgus monkey tissues was observed in GLP tissue cross-reactivity studies using normal human and cynomolgus monkey tissues. Finally, in vitro cytokine release studies showed that Durvalumab and tremelimumab, either alone or in combination, did not induce cytokine release in blood from any donor.

2.2.3 Durvalumab **Clinical Experience**

Study CD-ON-MEDI4736-1108 is a Phase 1, first-time-in-human, multicenter, open-label, dose-escalation, and dose-expansion study to determine the maximum tolerated dose (MTD) or optimal biologic dose, safety, PK, immunogenicity, and antitumor activity of Durvalumab in adult subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy exists. As of 18Feb2014, a total of 198 subjects have been treated with at least 1 dose of Durvalumab (ranging from 1 to 27 doses). Of these subjects, 177 have received Durvalumab 10 mg/kg every 2 weeks (Q2W) in either the dose-escalation or dose-expansion phase. In addition, 21 subjects have been enrolled in the following dose-escalation cohorts: 4 subjects in each of the 0.1, 0.3, and 1.0 mg/kg Q2W cohorts, 3 subjects in the 3.0 mg/kg Q2W cohort, and 6 subjects in the 15 mg/kg every 3 weeks (Q3W) cohort.

In the 177 subjects who received Durvalumab 10 mg/kg Q2W, the most frequently reported treatment-emergent adverse events (TEAEs) in subjects treated with 10 mg/kg Durvalumab Q2W regardless of grade or causality (≥ 10% incidence) were fatigue (24.3%), dyspnea (17.5%), nausea (13.6%), constipation (10.7%), and decreased appetite (10.2%). The majority of TEAEs were Grades 1 or 2 in severity and manageable by the general treatment guidelines as described in the current Durvalumab study protocols. Treatment-related TEAEs (all grades) occurring in 5 or more subjects were fatigue (11.3%), nausea (5.6%), dyspnea (4.0%), diarrhea (3.4%), vomiting (3.4%), pyrexia (3.4%), and myalgia (2.8%). Serious adverse events (SAEs) reported for 3 or more subjects were dyspnea, dehydration, abdominal pain, and sepsis. For the entire study population, none of the deaths in this study were considered related to Durvalumab. As of the data cutoff date of 18Feb2014, TEAEs resulting in discontinuation of Durvalumab have been reported for 13 subjects treated with Durvalumab 10 mg/kg Q2W (subjects could have more than one TEAE resulting in discontinuation). The TEAEs seen in 2 or more subjects resulting in discontinuation of subjects were: dyspnea (4 subjects), respiratory failure (2 subjects), “progression of disease” (verbatim term, 2 subjects). In addition, 1 subject in the 0.3 mg/kg Q2W cohort discontinued Durvalumab treatment due to a TEAE of pneumonia. All were Grade 3 or higher with the exception of the event of pneumonia. None of the TEAEs resulting in discontinuation of Durvalumab were considered related to Durvalumab by the investigator. No dose-limiting toxicities (DLTs) have been reported. Partial efficacy data are available as of 18Feb2014. Of the 177 subjects treated with Durvalumab 10 mg/kg Q2W, 77 subjects had at least 1 post-baseline disease assessment. Four subjects (5.2%) had a best response of partial response (PR; unconfirmed) assessed by Response Evaluation Criteria in Solid Tumors (RECIST) guidelines v1.1 with modifications. In addition, 36 subjects (46.8%) had stable disease (SD). Twelve of the 15 subjects in the 0.1, 0.3, 1.0, and 3.0 mg/kg Q2W dose-escalation cohorts had at least 1 post-baseline disease assessment as of 18Feb2014. Four subjects had a best response of PR (3 confirmed and 1 unconfirmed) as assessed by immune-related response criteria (irRC) [30] with 2 subjects each in the 0.3- and 1.0-mg/kg cohorts.

As of 18 Feb 2014, PK and pharmacodynamic data were available for the first 32 subjects following IV dosing of Durvalumab. Durvalumab exhibited nonlinear PK likely due to saturable target-mediated clearance. Significant target engagement, as measured by sPD-L1 suppression, was observed following dosing in all subjects tested. Screening for ADA has detected positive samples from 3 of the 31 subjects tested, with evidence for an impact on PK and target suppression in 1 subject.

Study D4190C00002 is a Phase 1 study of Durvalumab in Japanese subjects with advanced solid tumors. At present, durvalumab has been administered as mono- or combination

therapy with other anti-cancer agents to more than 6000 patients as part of ongoing studies. Section 6.5 contains details on the safety profile of durvalumab monotherapy.

Further information on durvalumab safety, efficacy, and pharmacokinetics is provided in the latest Investigator Brochure (v12).

2.3 Investigational Agents-Tremelimumab

2.3.1 Tremelimumab Background

Tremelimumab (formerly CP-675,206) is a human IgG2 mAb being investigated as a cancer immunotherapeutic agent. Tremelimumab is expressed in NS0 (murine myeloma) cells and has an overall molecular weight of approximately 149 kDa. Tremelimumab is specific for human CTLA-4, with no cross-reactivity to related human proteins. Tremelimumab blocks the inhibitory effect of CTLA-4, and therefore enhances T-cell activation. Tremelimumab shows minimal specific binding to Fc receptors, does not induce natural killer (NK) ADCC activity, and does not deliver inhibitory signals following plate-bound aggregation.

2.3.2 Tremelimumab Pre-Clinical Experience

Cytotoxic T-lymphocyte-associated antigen 4 (CD152) is a cell-surface receptor expressed primarily on activated T cells. Cytotoxic T-lymphocyte-associated antigen 4 engagement on activated T cells inhibits cytokine synthesis and restricts cell proliferation [55-58]. Upon T-cell activation, CTLA-4 expression is upregulated and acts to dampen immune responses, modulating and eventually switching off T-cell activation. The natural ligands for CTLA-4 are CD80 and CD86, which are present on antigen-presenting cells (APCs). Binding of these ligands to CTLA-4 delivers a negative regulatory signal to T cells.

Tremelimumab selectively binds to human CTLA-4 and blocks binding of CD80 and CD86 and has been shown to enhance human T-cell cytokine release in response to stimulation. Both in vitro and in vivo preclinical data suggest that a range of anti-CTLA-4 mAb exposures has the potential to be efficacious, the lower end of the potentially efficacious range being a plasma concentration of approximately 10 µg/mL and the target plasma concentration being 30 µg/mL. The toxicology program conducted for tremelimumab consisted of in vivo general toxicology studies in cynomolgus monkeys for up to 6 months duration, an embryo-fetal development study in monkeys, tissue cross-reactivity studies in both monkey and human tissues, and blood compatibility studies. Overall, tremelimumab toxicities were consistent with inhibition of CTLA-4 and with clinical safety findings, and indicated that chronic clinical use of tremelimumab may lead to adverse effects on the gastrointestinal tract, skin, lymphoid organs, thyroid tissues, and hematologic systems. Clinical dose-limiting toxicity (DLT; eg, gastrointestinal effects) and non-DLT (eg, skin

rash) were appropriately identified in a chronic toxicity study in monkeys. Most toxicities were reversible or showed a trend towards reversibility.

An embryo-fetal development study was conducted in pregnant cynomolgus monkeys during the period of organogenesis. Tremelimumab administered intravenously (IV) once weekly from Days 20 to 50 of gestation at doses of 0, 5, 15, or 30 mg/kg did not elicit maternal toxicity, developmental toxicity, or teratogenicity.

2.3.3 **Tremelimumab Clinical Experience**

As of the data cutoff date of 30 Aug 2013, 15 sponsored clinical studies have been conducted as part of the tremelimumab clinical development program. Of these studies, 13 have been completed and 2 are ongoing. Tremelimumab has been administered as monotherapy to subjects participating in 10 of the 15 clinical studies, 2 of which are ongoing. In total, 973 subjects with a variety of tumor types have been treated with tremelimumab monotherapy in the completed studies. Most of these subjects had melanoma and received the tremelimumab 15 mg/kg every 90 days dosing regimen. An additional 204 subjects (as of 07 Apr 2014) have been treated in the ongoing Phase 2b mesothelioma study, D4880C00003. In addition, 116 subjects with a variety of tumor types have received tremelimumab in combination with other anticancer agents in 5 of the 15 clinical studies.

Across the clinical development program for tremelimumab a pattern of efficacy has emerged, also observed for the related anti-CTLA-4 antibody, ipilimumab, which appears to be consistent across tumor types for this class of agents. Response rates to anti-CTLA-4 antibodies are generally low, approximately 10%. However, in subjects who respond, the responses are generally durable, lasting months to years even in subjects with aggressive tumors, such as, refractory metastatic melanoma. Some subjects may have had progression of their disease early during treatment, with delayed tumor response or disease stabilization. Tremelimumab has been tested in a Phase 3 study for advanced melanoma. Although the study failed to demonstrate improved overall survival (OS; primary endpoint) following a prespecified interim futility analysis, the final analysis showed a median OS of 12.6 months in the tremelimumab arm and 10.7 months in the dacarbazine/temozolomide arm. The ongoing Phase 2b study in recurrent pleural or peritoneal malignant mesothelioma is testing an alternative dosing schedule of tremelimumab with a dose of 10 mg/kg Q4W to maximize exposure to tremelimumab while managing safety according to the established anti-CTLA-4 AE management guidelines. The 10 mg/kg Q4W regimen is also being tested in an ongoing Phase 2 investigator-sponsored study in malignant mesothelioma (NCT01655888). In clinical subjects, tremelimumab exhibits linear (dose-proportional) PK following IV infusion. The estimate of clearance, volume of distribution at steady state, and

terminal-phase half-life is 0.132 mL/h/kg, 81.2 mL/kg, and 22.1 days, respectively. These values are consistent with those of natural IgG2.

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 seems to be confined to subjects with melanoma). As of the data cutoff date of 30Aug2013, events reported in the tremelimumab monotherapy studies at a frequency > 5% and assessed by the investigator as treatment related were diarrhea (41.2%), rash (27.2%), pruritus (25.1%), fatigue (23.8%), nausea (21.9%), vomiting (13.5%), decreased appetite (11.3%), headache (7.2%), pyrexia (7.0%), abdominal pain (6.7%), and colitis (5.5%). The events of diarrhea, rash, and pruritus are considered as identified risks. Infusion-related side effects are rare. Acute renal failure was reported in subjects who received the combination of tremelimumab and sunitinib in a Phase 1 study; however, acute renal failure has not been an expected AE for single-agent tremelimumab. The incidence and/or severity of many of the AEs observed following administration of tremelimumab can be reduced by adherence to current immune-related toxicity management guidelines.

At present, tremelimumab has been administered as mono- or combination therapy with other anti-cancer agents to more than 1500 patients as part of ongoing studies. Section_contains details on the safety profile of tremelimumab monotherapy. Further information on tremelimumab safety, efficacy and pharmacokinetics is provided in the Investigator Brochure.

2.3.4 **Combination Therapy Clinical Experience**

Study D4190C00006 is a dose-escalation and dose-expansion study of Durvalumab in combination with tremelimumab in subjects with advanced NSCLC. This study explored multiple dosing schedules and established Cohort 1 Q4W as the optimal dosing schedule of the Durvalumab and tremelimumab combination. This schedule, 20 mg/kg Durvalumab + 1 mg/kg tremelimumab, will be used in this study. Subjects enrolled in the D4190000006 study at the 20 mg/kg Durvalumab + 1 mg/kg tremelimumab dose administered Q4W have cleared the dose-limiting toxicity (DLT) evaluation period without identification of an MTD. At present, the combination has been administered to more than 3000 patients using various doses and dosing schedules.

Subjects with histologically or cytologically confirmed locally advanced or metastatic NSCLC, with at least one measurable lesion, with adequate organ and marrow function, and with Eastern

Cooperative Oncology Group (ECOG) performance status of 0-1 are eligible. Subjects cannot have had more than 3 prior lines of therapy in the metastatic setting including standard of care.

2.3.5 **Potential Risks of Durvalumab + Tremelimumab in the Relevant Indication**

Overall risks

Monoclonal antibodies may target several immune checkpoint proteins. These include programmed cell death ligand 1 (PD-L1), programmed cell death-1 (PD-1) or cytotoxic T-lymphocyte antigen-4 (CTLA-4). The anticipated result is an enhanced endogenous immune responses directed against tumor cells. However, there is the likelihood for adverse effects on other tissues as a consequence of stimulating the immune system.
Adverse drug reactions most seen with the immune checkpoint inhibitor class of agents are likely an outcome of the effects of inflammatory cells on specific tissues. These are generally events with a potential inflammatory or immune mediated mechanism and which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. Almost any organ system is susceptible to these immune mediated effects, and are most commonly seen as gastrointestinal AEs such as colitis and diarrhoea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis and endocrinopathies including hypo- and hyper-thyroidism.

Durvalumab

The following are some risks associated with durvalumab: diarrhea/colitis and intestinal perforation, pneumonitis/ILD, endocrinopathies (hypo- and hyper-thyroidism, type I diabetes mellitus, hypophysitis and adrenal insufficiency) hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/pruritus/dermatitis, myocarditis, myositis/polymyositis, other rare or less frequent inflammatory events including neurotoxicities, infusion-related reactions, hypersensitivity reactions and infections/serious infections.

Please refer to the current version of the durvalumab IB for information on all identified and potential risks with the drug.

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

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (please see Section 7.7).

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

Tremelimumab

The following are some risks associated with tremelimumab monotherapy: GI effects (colitis, diarrhoea, enterocolitis and intestinal perforation), endocrine disorders (hypo and hyperthyroidism, hypophysitis and adrenal insufficiency), skin effects (rash, and pruritus), elevations in lipase and amylase and clinical manifestations of pancreatitis, other gastrointestinal events e.g. ulcerative colitis, dehydration, nausea and vomiting; hepatic events including hepatitis, and liver enzyme elevations; pneumonitis and ILD; nervous system events including encephalitis, peripheral motor and sensory neuropathies, Guillain-Barre and proximal muscle weakness; cytopenias including thrombocytopenia, anemia and neutropenia; infusion-related reactions, anaphylaxis, and allergic reactions; renal events including renal failure, acute kidney injury, nephritis, nephrotic syndrome, autoimmune nephritis and electrolyte abnormalities such as hypokalemia; autoimmune diseases including autoimmune arthritis, Sjogren's syndrome and giant cell temporal arteritis; hyperglycemia and diabetes mellitus; and pyrexia.

Please refer to the current version of the tremelimumab IB for information on all identified and potential risks with the drug.

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

Further information on these risks can be found in the current version of the tremelimumab IB.

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

Durvalumab + tremelimumab

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

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

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

In durvalumab+tremelimumab combination studies at the dose of durvalumab 20mg/kg and tremelimumab 1mg/kg AEs (all grades) reported very commonly (≥ 10% of patients) are fatigue, diarrhea, nausea, dyspnea, decreased appetite, pruritus, vomiting, anemia, constipation, cough, abdominal pain, pyrexia, back pain, arthralgia, hypothyroidism, asthenia, oedema peripheral, weight, decreased hyponatraemia and rash.
Approximately 15% of patients experienced an AE that resulted in permanent discontinuation of study drug and approximately 15% of patients experienced an SAE that was considered to be related to durvalumab and tremelimumab by the study investigator.

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

2.4 **Investigational Agents-Monolizumab**

2.4.1 **Monolizumab Background**

Monalizumab is a humanized monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4) subtype, that specifically binds and blocks the inhibitory receptor CD94/NKG2A (a heterodimer complex between CD94 and natural killer (NK) group 2 member A), which is mainly expressed on subsets of NK cells and CD8+ T cells.

The CD94/NKG2A receptor is found on peripheral NK cells and subsets T cells in healthy volunteers as well as in patients with hematologic and solid malignancies. It is also present in tumor infiltrating NK and cytotoxic T cells in a number of solid tumors (including renal cell carcinoma, non-small cell lung cancer, cancer of the tongue, breast cancer, malignant melanoma, and endometrial, ovarian and cervical cancers).

CD94/NKG2A is a receptor for human leukocyte antigen E (HLA-E), a non-classic, major histocompatibility complex (MHC), class I molecule expressed on the cell surface of most leukocytes and large variety of transformed cells (viruses infected cells, inflammatory cells and malignant cells). HLA-E is expressed or over-expressed on human leukemic blasts in acute myeloblastic leukemia (AML), acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL) patients, as well as in human solid cancers such as colon adenocarcinoma, ovarian adenocarcinoma, malignant melanoma and esophagus squamous cell carcinoma. When engaging with the ligand HLA-E, the CD94/NKG2A receptor on NK cells and CD8+ T cells transduces inhibitory signals that suppress effector functions, such as cytotoxicity. This mechanism is relevant to HLA-E expressing hematological malignancies and solid tumors.

Blockade of the inhibitory signaling mediated by CD94/NKG2A receptor has the potential of restoring the ability of peripheral and tumor-infiltrating NK cells or cytotoxic CD8+ T cells to kill HLA-E expressing tumor cells.

2.4.2 **Monolizumab Pre-Clinical Experience**

The pharmacological, pharmacokinetic (PK) and toxicological properties of monalizumab have been investigated in the nonclinical development program, which consisted of both in vitro and in vivo studies. The initial studies included selection, cloning and characterization of the drug substance, as well as examinations of the pharmacological effect of monalizumab. Species-selection studies identified the cynomolgus monkey to be the most relevant species for nonclinical assessment of monalizumab, which exhibited binding to lymphocytes only in humans and monkeys.

Monalizumab is also being developed in combination with ibrutinib in CLL, with cetuximab in Squamous Cell Carcinoma of the Head and Neck (SCCHN), and with durvalumab in various solid tumors.

Data from nonclinical studies show that B-CLL cells express HLA-E in all patients tested by immunohistochemistry (n=7) and by flow cytometry (n=12); functional data indicate that monalizumab stimulates NK cell-mediated killing of transformed B cells and of CLL malignant cells obtained from CLL patients in vitro and in vivo.

In vitro efficacy data of the combination of monalizumab and cetuximab show that: (1) monalizumab induces increased CD107 mobilization and CD137 expression on NKG2A+ NK cells suggesting the NK cell-mediated lysis of HLA-E expressing cell lines by blocking the interaction of the inhibitory receptor CD94/NKG2A with HLA-E; (2) monalizumab enhances cetuximab–mediated Antibody Dependent Cell Cytoxicity (ADCC) in concentration-dependent manner.

A nonclinical study combining NKG2A and PD-1 checkpoint inhibitors in in vivo model of PD-L1 expressing solid tumors demonstrated enhanced anti-tumor activity, supporting the rationale for the clinical trial testing the combination with monalizumab and durvalumab (anti-PD-L1).
The nonclinical safety profiling of monalizumab has not identified any safety issues. To address specific theoretical, acute safety pharmacological effects, monalizumab was tested in various human in vitro biological assays. These assays identified no non target-related or potentially target-related safety issues. No toxicities were observed in cynomolgus monkeys after 13 weeks of dosing of up to 150 mg/kg weekly. The highest dose (150 mg/kg) resulted in approximately 18 weeks of full CD94/NKG2A receptor saturation. In humans, monalizumab binds selectively to CD94/NKG2A receptors. In monkeys, monalizumab binds with equal affinity to the activating CD94/NKG2C receptor in addition to the inhibitory CD94/NKG2A receptor. This is most likely the reason why it has been impossible to observe effects comparable to those seen in human in functional in vitro assays with cynomolgus vs human cells. Further risk assessment of long-term blocking of the CD94/NKG2A receptor was therefore performed with a surrogate anti-mouse NKG2A antibody that has been used

to demonstrate in vitro anti-tumor efficacy with mouse cells. In toxicology studies, mice were dosed s.c. every second day for up to 26 weeks at doses up to 50 mg/kg. As with the cynomolgus monkey studies, the toxicity studies in mice did not identify any safety issues.

In summary, monalizumab specifically binds and blocks the CD94/NKG2A receptor expressed on subsets of NK cells and CD8+ T cells leading to increased anti-tumor activities including cytotoxicity against HLA-E expressing tumor cells without impairing normal and resting cells. Monalizumab holds promises for a future treatment of HLA-E expressing hematologic malignancies and solid tumors by activating immune-responses in different subsets of cytotoxic lymphocytes. Safety pharmacology studies have not raised any safety concerns that would preclude further progression of the clinical investigation of monalizumab in patients suffering from cancer.

2.4.3 **Monolizumab Clinical Experience**

The safety and tolerability as well as single-dose and multiple-dose pharmacokinetic (PK) and pharmacodynamic (PD) properties of monalizumab were initially investigated in patients with active rheumatoid arthritis (RA) (NN8765-3658 trial). In this first trial (completed), the maximum tested levels were 10 mg/kg during intravenous (i.v.) infusion and 4.0 mg/kg following subcutaneous (s.c.) administrations (in single and multiples doses (MD)), with a good safety profile.

Monalizumab is now being developed in patients with various hematologic malignancies and solid tumors in monotherapy or in combination with some other drugs. A total of 190 patients have been treated with monalizumab: 68 out of 92 patients in the phase 1 in RA and 122 patients in 6 hematology/oncology trials.

One study was terminated (IPH2201-201) and 5 other studies are ongoing.

- _IPH2201-201 is a monotherapy, open label single arm phase 1b/2 study, assessing the pre-operative administration of monalizumab in patients with locally advanced resectable squamous cell carcinoma of the oral cavity. This study was terminated on 26-Nov-2016 due to slow recruitment and strategic reasons and not due to any safety concerns.
- _IPH2201-202 is an open label phase 1b/2a trial of a combination of monalizumab and ibrutinib in patients with relapsed, refractory or previously untreated CLL.
- _IPH2201-203 is a phase 1b/2 trial of a combination of monalizumab and cetuximab in patients with HPV (+) and HPV (-) recurrent or metastatic SCCHN.
- _IND.221 is an Investigator Sponsored Study (ISS) conducted by the Canadian Cancer Trials Group (CCTG). This is a dose-ranging study of monalizumab in patients with gynecologic malignancies (ovarian, endometrial and cervical cancer).

- _D419NC0001 is conducted by AstraZeneca/MedImmune. This is a phase 1 in solid tumors testing the combination of durvalumab (anti-PD-L1) and monalizumab.
- _PIRAT-IPC 2015-018 is an Investigator Sponsored Study (ISS) conducted by a French anticancer institute "Paoli Calmettes Institute" in France. This is an open label phase 1 dose ranging study testing single dose of monalizumab in patients following HLA matched allogeneic hematopoietic stem cell transplantation (allo-HSCT).

2.4.3.1 **Clinical pharmacokinetics**

Final PK data of the first phase 1 study conducted with monalizumab in RA and preliminary PK data from the IND.221 trial (part 1) in gynecological malignancies are presented in the Investigator Brochure.
The pharmacokinetics of monalizumab was originally evaluated in a first phase 1 study conducted in RA. The PK of monalizumab was as expected for a monoclonal antibody that binds to a membrane-bound target, which expression is restricted to a small subset of immune cells, and which Ab does not demonstrate intracellular internalization.

The PK of monalizumab was similar in RA patients and gynecologic cancer patients (IND.221 part 1 study). In patients with gynecologic malignancies (ovarian, endometrial and cervical cancer), the PK of monalizumab was dose proportional across the entire dose range (1-10 mg/kg). There was a 1.4-2 fold accumulation of monalizumab after the administration of four intravenous doses, which was consistent with administration frequency and the half-life of 2-3 weeks seen with single dose i.v. dosing in RA patients at similar doses.

2.4.3.2 **Clinical pharmacodynamics**

Final PD data of the first phase 1 study conducted with monalizumab in RA and preliminary PD data from the IND.221 trial (part 1) in gynecological malignancies are presented in the Investigator Brochure.
In the first study conducted in RA, levels of CD94/NKG2A receptor occupancy were detectable for all patients treated with single i.v. or s.c. or multiple s.c. doses of monalizumab. Rapid (within 0.5−1 hour and 4-8 hours post i.v. and s.c. administration respectively) and high level of receptor occupancy was reached at monalizumab single i.v. dose of 0.005 mg/kg and above and at single s.c. dose of 0.1 mg/kg and above. A clear dose–response relationship was observed as increasing doses of monalizumab resulted in both increasing CD94/NKG2A receptor occupancy and increasing duration of receptor occupancy.

A high CD94/NKG2A receptor occupancy was sustained on average for 2 weeks for doses above 0.4 mg/kg after single i.v. administration and 1.1 mg/kg after single s.c. administration and for less than 10 weeks after multiple s.c. administrations at dose 4 mg/kg.
The CD94/NKG2A receptor occupancy profiles for the first 14 days after single and multiple administrations of doses of 0.005 mg/kg, 0.025 mg/kg, 0.1 mg/kg and 0.4 mg/kg of monalizumab appeared similar considering the inter-individual variability in the receptor saturation assay. In the part 1 of the IND.221 trial in gynecological

malignancies, full NKG2A saturation was achieved from the first administration (Cycle 1, D1, H2) in all the patients at all dose levels (1, 4 and 10 mg/kg, 6 patients per dose level).

2.4.3.3 **Clinical safety**

Safety data from the phase 1 trial in patients with RA were based on total of 92 patients treated with monalizumab single dose i.v. up to 10 mg/kg or single dose or multiple doses, s.c. up to 4 mg/kg or placebo (monalizumab: 68; placebo: 24). No death, no Dose-Limiting Toxicity (DLT), no Suspected Unexpected Serious Adverse Reaction (SUSAR), no grade 4 Adverse Event (AE) and no adverse event leading to treatment withdrawal were reported. No infusion related reaction or immune related disorder was observed. No Serious Adverse Event (SAE) related to study treatment was reported. Only 4 Grade 3 AEs, all considered as unrelated to the study treatment, occurred in the monalizumab treated patients. Most of the AEs were mild (142 AEs) or moderate (61 AEs) in intensity, self-limiting and manageable. The two2two most frequent AEs were nasopharyngitis and headache. Three subjects developed treatment-related Anti-Drug Antibodies (ADA) at a low titer; one was in vitro neutralizing (patient in the dose level 1.1 mg/kg single dose, i.v.), whereas the other two showed no neutralizing capacity (one patient in the dose level 0.4 mg/kg single dose and one patient in the dose level 0.4 mg/kg MD, s.c.).

In hematology/oncology trials, 122 patients have been treated up to 10 mg/kg multiple doses i.v. Most of the reported AEs were of grade 1-2. Only 9% of events are of grade 3 or higher. Sixteen (16)% of all events were considered as related to study treatment, with less than 1% related event of grade 3-4. There was no obvious dose relationship for adverse events.

The most frequent (> 5%) adverse events considered related to monalizumab were headache, asthenia/fatigue, nausea, vomiting, diarrhea, anorexia/decreased appetite, rash/erythema and myalgia. There were 4 SAEs related to study treatment: asthenia (grade 2), nausea (grade 3) combined with vomiting (grade 3), infusion related reaction (grade 2). There was no death related to treatment. In the IND.221 study in gynecological indications, six subjects developed treatment-related low ADA response at least at one time point. No impact was detected on exposure in all these patients.

The safety data obtained up to date do not change the overall safety or risk/benefit profile of monalizumab; the data support the continuation of the clinical development of monalizumab for the treatment of various malignancies as monotherapy and combination therapy.

2.4.4 Combination Therapy Clinical Experience and Rationale

On ongoing phase clinical trial (NT02671435, D419NC0001) is a phase 1 in solid tumors that has determined the recommended phase II dosing for the combination of durvalumab (anti-PD-L1) and monalizumab. This combination was shown to be safe and was expanded in cohort of CRC patients and demonstrated anti-tumor responses. As of 28-Apr-2017, 12

patients had been treated in the trial in escalation part and had received 22.5 mg,75 mg, 225 mg, or 750 mg of monalizumab q2w in combination with 1500 mg of durvalumab q4w. Another cohort of 3 patients received 750 mg of monalizumab q4w with durvalumab 1500 mg q4w. Fourteen (14) patients received 750 mg of monalizumab q2w with durvalumab 1500 mg q4w in extension part.
One hundred thirty (130) AEs were reported in 26 patients. Most of AEs were Grade 1 or 2, only 10 were Grade 3 and 2 were Grade 4 (dehydration, hyponatremia). Twenty-three (23) AEs were considered as related to monalizumab and were all Grade 1-2.

- Seven SAEs were reported in 4 patients: one grade 4 dehydration and 6 grade 3 SAEs (abdominal pain, ascites, hematochezia, pleural effusion, sepsis, hydronephrosis). None of them were related to study drug. There were no AE leading to treatment withdrawal.

- No death occurred at time of this report.

HLA-E is expressed in 81% to 82% of patients with colorectal carcinoma (internal data in file) (9). Over-expression of HLA-E correlates with a poor outcome in colorectal carcinoma (9). Binding of HLA-E to CD94/NKG2A induces inhibitory signals which suppress the cytokine secretion and direct cytotoxicity of lymphocytes against malignant cells. This mechanism may play a significant role in the immune escape of tumor cells (10), (11). NK cells overexpressing CD94/NKG2A in the peripheral blood of patients with hematological malignancies transplanted with hematopoietic cells from allogeneic donors, or infiltrating solid tumors are usually dysfunctional (12), (13), (14), (15).

By suppressing the inhibitory signal transduced by CD94/NKG2A, monalizumab enhances the anti-tumor functions, including cytolytic activity of these immune effector cells, as shown ex vivo and in vivo in several experimental models described in Section 4. Furthermore, it has to be emphasized that ADCC mediating at least partly the anti-tumor effect of cytotoxic mAbs widely used in oncology is mainly supported in human by NK cells. Interestingly cetuximab-induced ADCC on NK cells is inhibited by HLA-E expression and this inhibition can be circumvented with CD94/NKG2A blockade (16).

2.5 Investigational Agents- Oleclumab

2.5.1 **Oleclumab Background**

Oleclumab, also known as MEDI9447, is a human immunoglobulin G1 lambda (IgG1λ) mAb that is expressed in Chinese Hamster Ovary cells. It specifically binds and inhibits CD73 ectonucleotidase activity, an enzyme catalyzing adenosine and organic phosphate production from adenosine monophosphate (AMP), which leads to inhibition of T-cell receptor activation through increased extracellular adenosine. Oleclumab decreases expression of CD73 by internalizing the receptor and causing shedding of the extracellular domain. It has a triple mutation within the heavy chain constant region that decreases

immunoglobulin G (IgG) effector function, thereby resulting in an increase in anti-tumor immunity.

2.5.2 **Oleclumab Pre-Clinical Experience**

CD73 is a receptor located on tumor cells, endothelial cells and some leukocytes. Its ectonucleotidase activity allows increased extracellular adenosine which inhibits T-cell receptor activation by binding receptors and triggering cyclic AMP signaling. It thus serves a regulatory role in B and T lymphocyte function. Additionally, this activity within the tumor microenvironment creates an "immunosuppressive halo" that limits antitumor immunity, downregulates phagocytosis, and increases pro-angiogenic factors, among other effects . Binding of oleclumab to the N-terminal domain of CD73 causes non-competitive inhibition by preventing structural conversion to the active, closed state.

Oleclumab has shown the following activity in non-clinical studies (see Investigator's Brochure):

- After incubation of human mammary carcinoma (MDA-MB-231) with Oleclumab, assessment by flow cytometry demonstrated 73% reduction in cell surface expression of CD73, suggesting shedding or internalization of the molecule after drug binding (Report ONC94470002).
- In human in vitro studies, Oleclumab impedes dephosphorylation of AMP and conversion to adenosine by CD73 was decreased in a dose dependent manner.
- In vitro models exhibit anti-CD73 antibody binding to CD73 can limit production of adenosine and the regulatory effect on T-cell function.
- Balb/C, syngeneic, CT26 colon carcinoma tumor model mice demonstrated >= 50% inhibition of tumor growth from day 7 – day 16 with intraperitoneal treatment of Oleclumab.
- In the same study, tumors harvested after day 16 showed Oleclumab inhibits myeloid-derived suppressor cells (MDSCs), which have demonstrated suppression of anti-tumor immunity. anti-mouse PD-L1 antibody-treated mice were completely tumor free 3 months after tumor implantation and demonstrated long-term immunity during re-challenge.
- In a subsequent study in the same syngeneic murine model, the combination of Oleclumab and anti-PD-1 treated animals produced 60% tumor-free mice, compared to 10% tumor-free animals in receiving monotherapy.
- In another study using MC38-OVA and 4T1.2 pre-clinical mouse models, Oleclumab showed syngergistic effect with anti-CTLA4, demonstrated by increased antigen-specific CD8+ T cell infiltration within tumors of mice receiving combination therapy.

In general, there were no Oleclumab-related adverse effects in toxicology studies conducted in CD-1 [ICR] mice that were of relevance to humans. Adverse findings in the Good Laboratory Practice (GLP)-compliant repeat dose toxicity study on cynomolgus monkeys (Oleclumab once weekly via a 30-minute IV infusion for 5 weeks), showed no adverse changes on clinical or anatomic pathology parameters during the dosing or recovery phases. Therefore, the no-observed-adverse-effect level (NOAEL) of Oleclumab in

all the general toxicity studies was considered to be 300.7 mg/kg, the highest dose tested in these studies. GLP tissue cross-reactivity study conducted on human tissue cryosections showed predicted diffuse immunoreactivity of Oleclumab as CD73 is present in most tissues. In the monotherapy dose-escalation phase study, NOAEL in cynomolgus monkeys was noted at 300 mg/kg.

2.5.3 **Oleclumab Clinical Experience**

The ongoing multicenter, open-label, dose-escalation, dose-expansion study with oleclumab (D6070C00001) is a first-time-in-human, phase 1 study, used to model the agent's pharmacokinetics, pharmacodynamics, and clinical safety profile. It was administered as a single agent or in combination with durvalumab in adults with selected advanced solid tumors. There were 42 and 24 subjects enrolled in the monotherapy and combination therapy dose escalation phases, respectively, which were completed by the data cut-off on 09 January 2018. The dose-expansion phase of the study, with combination therapy, is ongoing. There are 50 subjects enrolled with diagnoses of CRC (n=21), pancreatic adenocarcinoma (n=25), and epidermal growth factor receptor mutant (EGFRm) non-small cell lung cancer (NSCLC) (n=4).

2.5.3.1 **Clinical Pharmacokinetics**

As of the 09 Nov 2017 data cut-off, preliminary population PK was modelled by means of the nonlinear mixed-effects modelling approach (NONMEM). Data was used from 97 subjects after receiving 5, 10, 20, and 40 mg/kg Q2W IV doses of Oleclumab as monotherapy (N=40) or combination therapy with durvalumab at 10 mg/kg (N=57). Outcomes demonstrated PK that was dose-dependent (non-linear) and congruent with target-mediated clearance of the antibody, thus rates of Oleclumab elimination was faster at lower doses than higher doses. In the same study, there was similar steady-state PK concentrations and general between-patient variability during simulations for body weight-based and fixed dosing regimens. Fixed dose of 1500 mg or 3000 mg Q2W of Oleclumab for an average body weight of 75 mg/kg is comparable to 20 mg/kg or 40 mg/kg Q2W, respectively. Simulations to predict Oleclumab concentration profiles recommend 3000 mg Q2W or first four doses at 3000mg Q2W followed by 3000 mg Q4W for maintenance dose.

2.5.3.2 **Clinical Pharmacodynamics**

No new pharmacodynamics data is available as of 09 Nov 2017 since the last IB update. Assessment of target engagement demonstrates IV administration of Oleclumab monotherapy or combination therapy serves to completely suppress free soluble CD73 in serum.

Summary of Clinical Safety: Oleclumab Monotherapy

There were 39 (92.9%) and 23 (54.8%) subjects reporting >= 1 TEAE and treatment-related TEAE, respectively with no significant trends among dosing groups. Fatigue (38.1%), anemia, abdominal pain, and dyspnea (21.4%) were the most frequently reported TEAEs while fatigue (16.7%), nausea (9.5%), and anemia (9.5%) were the most frequently reported treatment-related TEAE.

Grade 3 or 4 TEAEs were experienced by 19 subjects (45.2%). The most common (>1 subject) were ascites (11.9%), acute kidney injury (4.8%), hyperglycemia (4.8%), and hyponatremia (4.8%).

The only treatment-emergent SAE effect reported by more than one subject was ascites (7.1%); no treatment-related SAE were reported.

Three subjects required discontinuation due to AEs during the dose-escalation phase, none were treatment related. Two subjects were in the 10 mg/kg treatment group and experienced a Grade 3 event ascites and Grade 4 event metastasis to the central nervous system. One subject in the 20mg/kg group developed Grade 4 pulmonary embolism.

Three deaths were reported during the study which were not related to treatment. One subject in the 20 mg/kg dose group experienced a Grade 5 treatment-emergent SAE of small intestinal obstruction. Two subjects had deaths due to disease under study treatment (one subject in each of the 20 mg/kg and 40 mg/kg dose group)

2.5.4 **Combination clinical therapy experience and rationale: Oleclumab and Durvalumab**

The dose expansion phase of the study D6070C00001 with combination therapy of Oleclumab and durvalumab is ongoing. The overall objective response rates (ORR) (confirmed and unconfirmed) for Oleclumab 40 mg/kg + durvalumab 10 mg/kg dose-expansion was 7.1% (95% CI; 1.5%, 19.5%). The CRC and PANC cohorts had ORR (confirmed and unconfirmed) of 4.8% (95% CI: 0.1%, 23.8%) and 10.0% (95% CI: 1.2%, 31.7%), respectively. The overall disease control rate (DCR) was 16.7% (95% CI: 7.0%, 31.4%) in the Oleclumab 40 mg/kg + durvalumab 10 mg/kg dose-expansion group. This included 3 subjects in the CRC cohort; 2 stable disease (SD) and 1 partial response (PR). The DCR in the CRC and PANC cohorts was 14.3% (95% CI; 3.0%, 36.3%) and 20.0% (95% CI; 5.7%, 43.7%), respectively.

Among the subjects treated with combination therapy, 91.9% experienced >= 1 TEAE without clinically significant patterns emerging across all combination therapy dose groups. The most frequent ones (reported in >=15% of total subjects) were fatigue (25.7%), abdominal pain, constipation, and vomiting (16.2%). Treatment-related TEAE was

experienced by 47.3%. The most frequent (reported in >=5% total subjects) were fatigue (13.5%); increased AST, diarrhea, and pyrexia (8.1%); increased blood ALP (6.8%); and increased ALT, decreased appetite and vomiting (5.4%).

Grade 3 or 4 severity TEAE were found in 52.7% of total subjects. The most common (in >2 subjects) were increased ALP (8.1%); anemia, increased ALT, AST and GGT (5.4%); pulmonary embolism, increased bilirubin, abdominal pain and ascites (4.1%). Treatment-related TEAE of Grade 3 or 4 severity were the following: anemia, thrombocytopenia, increased lipase, hyponatremia, headache and dyspnea reported in one subject each; hepatitis, increased ALT and ALP in two subjects each; and AST increase in three subjects.

Treatment-emergent SAE were reported in 44.6% of total subjects. The most common (>2 subjects) were abdominal pain and ascites (4.1%). Treatment-related SAE occurred in 5.4% of total subjects: anemia, thrombocytopenia and abdominal pain reported in one subject; hepatitis reported by two subjects.

TEAEs resulting in permanent discontinuation of treatment occurred in 10.8% of the subjects receiving combination therapy. Treatment-related TEAEs resulting in permanent discontinuation occurred in 4.1% of this population.

During the study, six deaths were reported in subjects receiving combination therapy, none related to the study treatment. The following is a brief summary:

- One subject in the Oleclumab 20 mg/kg + durvalumab 10 mg/kg dose group experienced Grade 5 SAE of renal failure.
- One subject in the Oleclumab 40 mg/kg + durvalumab 10 mg/kg dose group developed a new extrahepatic biliary obstruction due to a new mass with ensuing clinical deterioration.
- One subject with CRC in the expansion cohort experienced fatal SAE of pneumonia
- One subject in the PANC cohort developed Grade 5 SAE of vomiting.
- One subject in the CRC cohort experienced Grade 5 SAE of respiratory failure.
- One subject in the CRC cohort experienced fatal pneumonitis.

2.6 **Rationale**

Colorectal cancer is potentially curable at a metastatic stage, provided the metastases can be resected surgically. A meaningful subset of patients is able to undergo resection with expected long term survival of ~20%. Efforts to improve survival, including chemotherapy, have

only had a modest benefit on relapse-free but not overall survival. New approaches are needed to improve the outcomes in this patient population. Harnessing the immune system via immune checkpoint blockade has already increased survival in many solid malignancies and is the standard of care in advanced melanoma. Checkpoint blockade has the potential of increasing survival when given pre-operatively in the case of resectable CRCLM.

Single agent blockade, with anti-CTLA-4, anti-PD-1, or anti-PD-L1, has not demonstrated robust responses in metastatic colorectal cancer in phase I studies with the exception of PD-1 blockade in patients with tumors that demonstrate microsatellite instability (MSI-high). However, the combination of anti-CTLA-4 with anti-PD-1, which operate to enhance the immune response at different levels and, in general, have non-overlapping effects on the immune system, has led to a nearly 50% response rate in metastatic melanoma. In a CT26 BALB/c mouse CRC pre-clinical model, the combination of tremelimumab and Durvalumab led to disease regression and long term disease control, whereas each individual agent did not. As single agents, both tremelimumab and Durvalumab have been shown to be safe in humans with metastatic solid tumors [61, 62]. The combination has demonstrated encouraging safety and efficacy profiles in a Phase 1b study of patients with advanced NSCLC [63]Based on the pre-clinical efficacy and the established safety profile, the combination of tremelimumab and Durvalumab may offer enhanced survival when used pre-operatively prior to CRCLM resection. The addition of Durvalumab as a single agent post-operatively may counteract immune surveillance inhibition and prevent CRC recurrence.

One of the major research questions in immunotherapy—and checkpoint inhibitor therapy in particular—is establishing why only a subset of patients responds. Early data point to overall mutation burden as a key factor. More research is needed in this area to help delineate biomarkers of response and, ultimately, to choose the best candidates for what can be toxic therapy. A pre-operative approach will allow biomarker discovery and validation as tissue will be available before and after the therapy is given. MD Anderson—through the Immune Platform—has the capability and expertise to optimize such discovery.

As of 6-1-2018 this clinical trial (2015-0828) has enrolled 18 patients of which 2 screen failed, 2 have been treated but not yet reached the point of surgical resection, and 14 patients have undergone therapy and reached the point of surgical liver resection. Eleven of these 14 patients, 79%, have undergone liver resection, which is similar to the historical rate of 80%, and demonstrates this neoadjuvant approach to be safe. Treatment toxicity did not preclude any patient from undergoing surgery, with the reasons for non-surgery being progression in two patients and underlying prior chemotherapy induced liver toxicity in one patient. Grade 3/4 reported toxicities were fatigue (n=1), thromboembolic event (n=1), lipase elevation (n=1) and AST/ALT increase (n=3). Given the demonstrated safety of this approach we have amendment the protocol to evaluate the safety of other novel immune therapy combinations and thus, this study will explore the safety of three immunotherapy based approaches all utilizing durvalumab

as the consistent agent. In part, the rationale for exploring additional combinations rests upon the early clinical signals of activity with these other immune therapy agents in solid cancer and especially colorectal cancer. In addition, at this time after 15 patients enrolled, the safety of such a preoperative immune therapy approach has been determined. The translational knowledge gained from the combination of durvalumab and tremilimumab has clearly demonstrated T-cell activity with this combination occurs and, at present, greater knowledge gained from the translational aspects of this clinical trial will be best optimized by exploring additional immune therapy combinations prior to liver resection.

The rationale for the addition of cohorts B and C,patients with resectable CRC with liver or lung metastasis receiving durvalumab+oleclumab or durvalumab+monalizumab, respectively (refer to Section 5 for detailed definition of all cohorts), are discussed above in detail. In brief, we hypothesize that targeting CD73 and NKG2A will be safe in the neoadjuvant setting and will have the ability to generate anti-tumor immune responses that can provide successful eradication of minimal residual disease following surgical resection of metastatic disease. In particular for cohort B, the CD73 antibody, oleclumab can mitigate the inhibition of T-cell activation by extracellular adenosine in conjuncture with durvalumab. By curtailing the effector function of CD73 on the immune system, there will be enhanced anti-tumor activity. We anticipate that oleclumab will enhance the immunological response and enable T-cell functioning within the tumor environment to help to control minimal residual disease following surgical resection. For cohort C, binding of HLA-E to CD94/NKG2A induces inhibitory signals which suppress the cytokine secretion and direct cytotoxicity of lymphocytes against malignant cells. HLA-E is expressed in 81% to 82% of patients with colorectal carcinoma representing a common target and active mechanism of immune escape. We hypothesize that monalizumab in conjuncture with durvalumab will be safe and generate an immunological response to CRC and that this activation of T-cells will help to control minimal residual disease following surgical resection.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed colorectal cancer with liver or lung metastases deemed resectable by a liver or thoracic surgeon, respectively (resectability may involve the use of ablative techniques to some but not all liver or lung metastases). Patients with a primary colorectal tumor that is planned for surgical resection are eligible. In addition patients with nonspecific lung lesions (lesions that are uncertain to be metastases given their small size, defined here as <1cm) are eligible.

3.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$10 mm with spiral CT scan. See Section 11 for the evaluation of measurable disease.

3.1.3 All lines of prior therapy accepted. Subjects with prior hepatic or extra-hepatic resections of metastatic disease will be included.

3.1.4 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of tremelimumab, oleclumab, or monalizumab in combination with durvalumab in patients <18 years of age, children are excluded from this study.

3.1.5 Life expectancy of greater than 6 months.

3.1.6 ECOG performance status ≤1 (Karnofsky ≥70%; see Appendix1).

3.1.7 Patients must have normal organ and marrow function as defined below:

- leukocytes	≥3,000/mcL
- absolute neutrophil count	≥1,500/mcL
- platelets	≥100,000/mcL
- total bilirubin	< 1.5 X institutional normal limits (subjects with known Gilbert syndrome are eligible with total bilirubin < 3.0 mg/dL)
- Hemoglobin	≥9g/dL
- AST(SGOT)/ALT(SGPT)	≤ 3 X institutional upper limit of normal
- creatinine	within normal institutional limits
OR	
- creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

3.1.8 Known or ordered molecular testing for MSI, BRAF, and KRAS status.

3.1.9 Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply: Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy). Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

3.1.10 Ability to understand and the willingness to sign a written informed consent document.

3.1.11 Weight ≥35kg (required for flat dose-based administration of study agents)

3.2 **Exclusion Criteria**

3.2.1 Prior chemotherapy < 2 weeks prior to study drug treatment and treatment related adverse events that have not recovered to baseline or grade 1 (alopecia excluded). Prior radiation therapy <4weeks prior to study drug treatment (excluding short course radiation for rectal primaries).

3.2.2 Patients may not be receiving any other investigational agents.

3.2.3 Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:
--Patients with vitiligo or alopecia
--Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
--Any chronic skin condition that does not require systemic therapy
--Patients without active disease in the last 5 years may be included but only after consultation with the study physician
--Patients with celiac disease controlled by diet alone

3.2.4 Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. The following are exceptions to this criterion:

- Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)
- Systemic corticosteroids at physiologic doses not to exceed <<10 mg/day>> of prednisone or its equivalent
- Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

3.2.5 Prior exposure to T cell checkpoint inhibitor therapies for colorectal cancer, including durvalumab and tremelimumab, monalizumab, oleclumab.

3.2.6 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, interstitial lung disease, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.7 Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.

3.2.8 History of active primary immunodeficiency

3.2.9 Women who are pregnant, which includes women with a positive pregnancy test at enrollment or prior to the administration of study medication, or breastfeeding are not allowed on study.

3.2.10 Receipt of a live vaccine within 30 days of study entry

3.2.11 Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
---Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
---Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab may be included only after consultation with the Study Physician.

3.2.12 Any concurrent chemotherapy, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non–cancer-related conditions (e.g., hormone replacement therapy) is acceptable.

3.2.13 Major surgical procedure within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.

3.2.14 History of allogenic organ transplantation.

3.2.15 Known active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), **hepatitis B** (known positive HBV surface antigen (HBsAg) result), **hepatitis C**, or **human immunodeficiency virus** (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

3.2.16 Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab and tremelimumab or durvalumab and oleclumab or durvalumab and monalizumab combination therapy.

3.2.17 For cohort B only (durvalumab and oleclumab), patients with a recent (within three months) myocardial infarction, stroke, transient ischemic attack or thromboembolism are not eligible.

4. REGISTRATION PROCEDURES

This is a single institution study.

5. TREATMENT PLAN

5.1 Study Design and Duration

This study is an open-label, single center trial assessing the safety and feasibility of using perioperative neoadjuvant and adjuvant immune-therapy for resectable liver or lung metastases.

Cohort A will consist of neoadjuvant tremelimumab 75 mg IV flat dose and durvalumab 1500 mg IV flat dose. Adjuvant therapy will consist of 4 monthly doses of durvalumab 1500mg IV.

Cohort B will consist of neoadjuvant oleclumab 3000 mg IV flat dose followed by durvalumab 1500 mg IV flat dose. Adjuvant therapy will consist of 4 months of oleclumab every two weeks at 3000 mg IV flat dose and durvalumab every 4 weeks at 1500 mg IV flat dose. On days oleclumab and durvalumab are both administered, oleclumab will be given first (see Section 8.1.4).

Cohort C will consist of neoadjuvant durvalumab 1500 mg IV flat dose then Monalizumab 750mg IV flat dose. Adjuvant therapy will consist of 4 months of durvalumab 1500 mg IV flat dose and monolizumab 750 mg, both administered every four weeks.

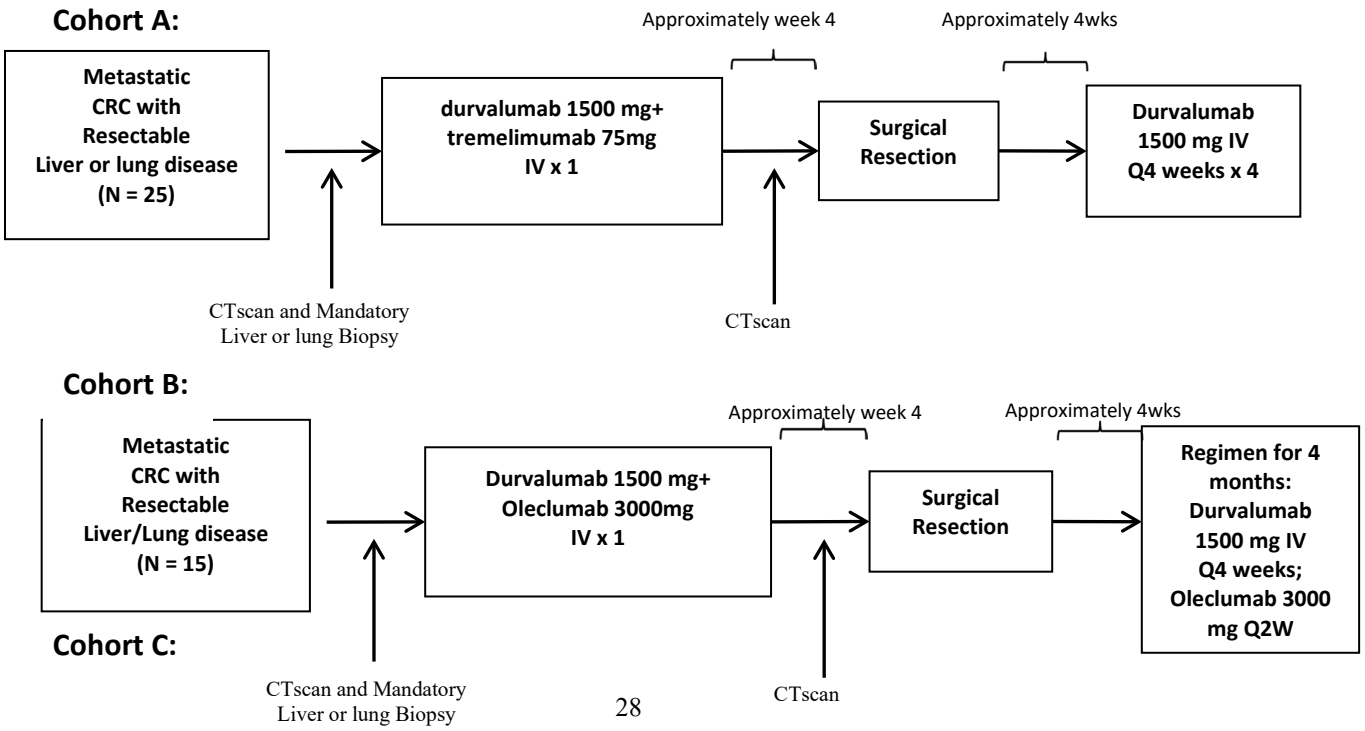
Cohort A has been enrolling since the study initiation and will enroll up to 25 patients. At the time of amendment activation initially opening, cohort B may enroll 5 patients followed by 5 patient enrollment for cohort C. Enrollment will continue in this alternating manner with approximately 5 patient blocks at a time for these cohorts. Enrollment may be adjusted based on Medimmune/MD Anderson determined priorities and drug availability. Cohort B and C will each be 15 patients.

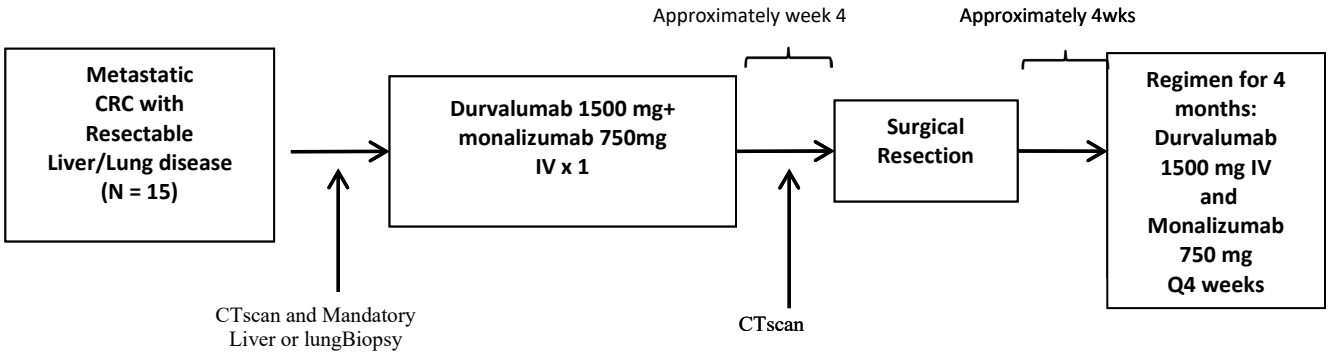
Lung or liver resection will be scheduled approximately 3-weeks after the infusion of the immunotherapeutic agents. Completing up to 4 months of chemotherapy after surgical resection instead of immunotherapy (durvalumab for cohort A, durvalumab/oleclumab for cohort B, or durvalumab/monalizumab for cohort C) continuation is an option depending on the preferences of the treating physician/patient (i.e., subjects can opt out of the planned post-operatively immuntherapy). Post-operative therapy will be either chemotherapy per physician/patient choice or 4months of immunotherapy. As synchronous primary lesions are allowed in this study, the appropriate clinical care as determined by the treating multidisciplinary team for addressing the primary lesion will be allowed. Though primary resection on clinical trial prior to liver resection will not be allowed, primary resection may be simultaneous with liver resection or occur after liver resection. In addition as short course radiation therapy (5 days) is often employed for rectal primaries this will be allowed in this clinical trial as long as radiation therapy is ≥1 week from first dose of study treatment. Factoring the occurrence of potential immune mediated AEs prior to resection, an allowance of a 3-10 weeks from neoadjuvant therapy administration will be permitted to complete metastatic and/or primary resection

As the mechanism of action of immunotherapy should not impact wound healing, patients may start adjuvant therapy as early as 4 weeks after resection, per treating physician discretion, provided they have achieved adequate status after surgery (ex. Resolution of post-operative concerns). Post-operative therapy thus can begin between 4weeks to 12 weeks post-operatively. However, if patients require >12weeks for postoperative recovery they will not be allowed to initiate adjuvant immunotherapy.

The study design schematic is below.

Study Schematic





5.1.1 Screening visit.

If a patient is thought to be a potential candidate for the trial, then he/she can be offered participation and, if agreeable, will undergo screening procedure outlined below from D-14 to D-1. Previously conducted HIV, PT/PTT, and hepatitis testing within 30 days does not need to be repeated and will be acceptable for screening purposes (tests performed at outside laboratories as standard of care testing will be accepted).

Table 5.1-1: Screening Procedural Outline

Procedure	Screening Visit From D-14 to D-1	Notes
Eligibility Assessments		
Informed Consent (IC)	X	Original IC in screening for protocol participation;
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose.
Surgical Evaluation to determine resectability	X	
Medical History	X	
Tumor Tissue Sample	X	Confirm diagnosis of colorectal adenocarcinoma
MSI Status	X	If not done or not available, then MSI status may be obtained either from archived tissue or at hepatic resection.
Determine KRAS Mutation Status	X	If not done or not available, then KRAS mutation status may be obtained either from archived tissue or at hepatic resection.

Table 5.1-1: Screening Procedural Outline		
Procedure	**Screening Visit From D-14 to D-1**	**Notes**
Determine BRAF Mutation Status	X	If not done or not available, then BRAF mutation status may be obtained either from archived tissue or at hepatic resection.
Prior Medications	X	Prior exposure to checkpoint inhibitor therapy excluded
ECOG Performance Status	X	Within 14 days prior to first dose
Safety Assessments		
Physical Examination	X	
Vital Signs & Oxygen Saturation	X	Including BP, HR, temperature and oxygen saturation by pulse oximetry (at rest). Obtain vital signs at the screening visit and within 72 hours prior to first dose.
Physical Measurements	X	Height and Weight. Within 14 days prior to first dose
Assessment of Signs and Symptoms	X	Within 14 days prior to first dose
ECG	X	Within 14 days prior to first dose.
Concomitant Medication Collection	X	Within 14 days prior to first dose
Laboratory Tests	X	CBC w/differential and platelet count, Chemistry panel including: LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, Glucose, CEA, amylase, lipase, TSH, Free T4, Free T3, within 14 days prior to first dose
HIV, hepatitis, PT/PTT laboratory tests	X	HIV Ab, Hepatitis B surface antigen (HBV sAg), and hepatitis C antibody (HCV Ab) or Hepatitis C RNA (HCV RNA) or PT/PTT within 30 days prior to first dose
Pregnancy Test (WOCBP only)	X	Serum or urine to be done at screening visit and repeated within 72hours of first dose of study therapy
Efficacy Assessment		
Baseline Tumor Imaging Assessment	X	CT of the C/A/P or MRI of the liver within 28 days of signing of informed consent.

5.1.2 Treatments

Management of and dose modifications in response to adverse events related to study medications are outlined in section 7.7, below.

5.1.2.1 Cohort A:

Tremelimumab

Tremelimumab is a human IgG2 anti-CTLA-4 mAb. It will be given at a dose of 75 mg IV over 1 hour in an outpatient setting beginning week 1 of the trial. No premedications are needed. This drug will only be used as neo-adjuvant therapy. In the post-resection portion of the study, Cohort A will only receive Durvalumab according to its schedule (see tables 10.1, 10.2, 10.3). Pharmaceutical details and preparation are given in section 8.

Durvalumab

Durvalumab, a human IgG1κ mAb directed against PD-L1, and with reduced binding to C1q and the Fcγ receptors. It will be given immediately following tremelimumab beginning week 1 at a dose of 1500 mg IV over 1 hour. No premedications are needed. Pharmaceutical details and preparation are given in section 8.

5.1.2.2 Cohort B

Oleclumab

Oleclumab, a human IgG1λ mAb that selectively binds to and inhibits CD 73, will be administered following Durvalumab. Please note duvalumab will always be given first. Oleclumab will be given in an outpatient setting at a dose of 3000 mg IV fixed dose over one hour. Pharmaceutical details and preparation are given in section 8.

Durvalumab

Durvalumab, a human IgG1κ mAb directed against PD-L1, and with reduced binding to C1q and the Fcγ receptors. It will be given immediately before Oleclumab beginning week 1 at a dose of 1500 mg IV over 1 hour. No premedications are needed. Pharmaceutical details and preparation are given in section 8.

5.1.2.3 Cohort C

Monalizumab is a mAb of the IgG_4 subtype that specifically binds and blocks the inhibitory receptor CD94/NKG2A for HLA-E, potentially restoring the ability of peripheral and tumor infiltrating NK cells or cytotoxic CD8+ T-cells to kill HLA-E expressing tumor cells. It will be administered following Durvalumab infusion at a dose of 750mg. Pharmaceutical details and preparation are given in section 8

Durvalumab

Durvalumab will be given immediately following monalizumab beginning week 1 at a dose of 1500 mg IV over 1 hour. No premedications are needed. Pharmaceutical details

and preparation are given in section 8.

5.1.3 Treatment and Follow Up visits

Once enrolled on trial, he/she will have the following visits/events. The study calendar is in section 10 outlines schedule of treatments and assessments. Treatment will not commence until at least 2 weeks from prior systemic chemotherapy. Patients may undergo screening during this time or after two weeks. There is no maximum time from prior chemotherapy till immune-therapy treatment.

PREOPERATIVE SCHEDULE

Refer to Table 10.1 for the preoperative schedule of visits, assessments and treatments for all cohorts.

Note, due to the variation in recovery from surgical resection, weeks will restart following surgical resection when Durvalumab is administered.

POST-OPERATIVE SCHEDULE

Refer to Table 10.2 for cohort A post-operative schedule and Table 10.3 for cohort B and C post-operative schedule.

5.2 General Concomitant Medication and Supportive Care Guidelines

No formal drug interaction studies have been performed with either experimental agent. However, as an antibody, it is not expected to cause significant interaction with medications metabolized by the cytochrome P450 system.

Permitted concomitant medications

Table 5.2.1. Supportive medications

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (e.g., acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted

Excluded concomitant medications

Table 5.2.2. Prohibited concomitant medications

Prohibited medication/class of drug:	Usage:
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [e.g., by local surgery or radiotherapy])

Prohibited medication/class of drug:	Usage:
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding <<10 mg/day>> of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	*Should not be given concomitantly, or used for premedication prior to the I-O infusions. The following are allowed exceptions:* • *Use of immunosuppressive medications for the management of IP-related AEs,* • *Use in patients with contrast allergies.* • *In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.* *A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of* non-immunotherapy related events experienced by *the patient (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc).*
Drugs with laxative properties and herbal or natural remedies for constipation	Should be used with caution through to 90 days after the last dose of tremelimumab during the study
Sunitinib	Should not be given concomitantly or through 90 days after the last dose of tremelimumab (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib)
EGFR TKIs	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
Live attenuated vaccines	Should not be given through 30 days after the last dose of investigational agents (including SoC)
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor

Blood donation

Patients should not donate blood while participating in this study, or for at least 180 days following the last infusion of durvalumab or tremelimumab.

Reproductive Guidelines

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

Female patient of child-bearing potential

Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception (Table 5.2.3) from the time of screening and must agree to continue using such precautions for 180 days after the last dose of durvalumab + oleclumab or durvalumab + monalizumab combination therapy or 90 days after the last dose of durvalumab monotherapy. Non-sterilized male partners of a female patient must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

Male patients with a female partner of childbearing potential

Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from screening through 180 days after receipt of the final dose of durvalumab + oleclumab or durvalumab + monalizumab combination therapy or 90 days after receipt of the final dose of durvalumab monotherapy. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.
Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table 5.2.3).

Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

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

Highly effective methods of contraception, defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are

described in (Table 5.2.3). Note that some contraception methods are not considered highly effective (e.g., male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 5.2.3. Highly effective methods of contraception (<1% failure rate)

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

[a] This is also considered a hormonal method

5.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

X Disease recurrence

X Intercurrent illness that prevents further administration of treatment,

X Unacceptable adverse events(s),

X Patient decides to withdraw from the study, or

X General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.4 **Duration of Follow Up**

Patients may be followed for up to 2 years from liver surgery or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Note after one year of follow-up without recurrence schedule of follow-ups can be adjusted according to standard of care. This will take precedence over the study calendar.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose modifications for adverse events are per section 7.7.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.1 **Definition of Adverse Events**

The International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) E6(R1) defines an AE as:

> Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's preexisting condition. An abnormal laboratory finding (including ECG finding) that requires medical intervention by the investigator, or a finding judged by the investigator as medically significant should be reported as an AE. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine red blood cells increased). Abnormal laboratory values that are not, in the investigator's opinion, medically significant and do not require intervention should not be reported as AEs.

Adverse events may be treatment emergent (ie, occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product. Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.

7.2 **Definition of Serious Adverse Events**

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

7.3 **Definition of 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 supporting company. An AESI may be serious or non-serious. The rapid reporting of AESIs 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 ±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. An immune-mediated adverse event (imAE) is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the Investigator has any questions in regards to an event being an imAE, the Investigator should promptly contact the Study Physician.

AESIs observed include:

- Fatigue / asthenia
- Pyrexia
- Diarrhea / Colitis

- Pneumonitis / Interstitial lung disease (ILD)
- ALT/AST increases / hepatitis / hepatotoxicity
- Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- Endocrinopathies (i.e. events of hypophysitis, hypopituitarism adrenal insufficiency, diabetes insipidus, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase , increased serum amylase)
- Other inflammatory responses that are rare with a potential immune-mediated aetiology include, but are not limited to, myocarditis, pericarditis, and uveitis.
- AESI specifically related to Oleclumab (cohort B) include)::
    - Cardiac chest pain, transient ischemic attack, and thromboembolism

      These are of interest due to the drug's risk of arterial calcifications, arterial ischemic disorder and thrombosis.
    - Edema

      Oleclumab has potential risk of increased microvascular permeability, thus edema (pulmonary, peripheral, etc.) is considered an AESI. In the case of >= Grade 3 edema, doses should be omitted and therapy may be discontinued at the discretion of the investigator.
    - Immune complex disease

      This may occur when human-anti-human antibodies are produced as a response to humanized mAb, resulting in formation and deposition of immune complexes in blood vessels, joints and glomeruli leading to symptomatic diseases (vasculitis, glomerulonephritis, arthritis, serum sickness, etc.). Subjects will be monitored clinically and with labs. If subjects experience a suspected immune-complex related AE, with confirmed presence of ADAs treatment will be discontinued and the condition will be managed based on standard of care.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs.
Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab and tremelimumab Investigator's Brochures. Additional information on the anticipated AE's for duvalumab + monalizumab combination therapy is noted in the current version of the monalizumab Investigator's Brochure (v.6). More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification

and Toxicity Management Guidelines (see Section 7.7). These guidelines have been prepared by the supporting company to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

If new or worsening pulmonary symptoms (e.g. dyspnea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see Table 7.7.1) will be applied. The results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, hematological parameters etc) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

7.3.1 **Hepatic Function Abnormality**

Hepatic function abnormality meeting the definition of Hy's law (ie, any increase in ALT or AST to greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN) is considered an AESI. 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 (eg, cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product. Guidelines for management of subjects with hepatic function abnormality are outlined in section 7.7.

7.3.2 **Pneumonitis**

Adverse events of pneumonitis are also of interest for the supporting company, as pneumonitis has been observed with anti-PD-1 mAbs (but not with anti-PD-L1 mAbs). Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended. Guidelines for management of subjects with pneumonitis are outlined in Section 7.7.

7.3.3 **Infusion Reactions**

Adverse events of infusion reactions (also termed infusion-related reactions) are of special interest to the supporting company and are defined, for the purpose of this protocol, as all AEs occurring from the start of the study treatment infusion up to 48 hours after the infusion start time. For all infusion reactions, the eCRF should be completed as instructed in Section, 7.4 and all SAEs should be reported to MedImmune Patient Safety as described in Section 7.5.

7.3.4 **Hypersensitivity Reactions**

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy[35]. 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 (immunoglobulin E-mediated) and anaphylactoid reactions against the mAb, 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, urticaria, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness. Guidelines for management of subjects with hypersensitivity (including anaphylactic reaction) and infusion-related reactions are outlined in Section 7.7.

7.3.5 **Gastrointestinal Disorders**

Diarrhea/colitis is the most commonly observed treatment emergent SAE. In rare cases colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome if not properly managed. Diarrhea/colitis in subjects receiving tremelimumab should be managed as per Tremelimumab Guidelines for the Management of Diarrhea and Colitis (Appendix 2).

7.4 **Recording of Adverse Events**

Adverse events will be recorded on the eCRF (Protocol Data Management System/Clinical Oncology Research System - PDMS/CORe) using a recognized medical 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 MedImmune Patient Safety. See Section 7.2 for the definition of SAEs. If an AE evolves into a condition that meets the regulatory definition of “serious,” it will be reported on the SAE Report Form. Infusion of biological products is commonly associated with infusion-related reactions.

Anaphylaxis and infusion-related reactions have some common manifestations and may be difficult to distinguish from each other. Infusion-related reactions are commonly observed during or shortly after the first time exposure to therapeutic mAbs delivered through intravenous infusion. These reactions are less common following subsequent exposures. Unlike infusion-related reactions, anaphylaxis is a rare event, usually occurring after subsequent exposure to an antigen, and it is most commonly accompanied by severe systemic skin and/or mucosal reactions. The investigator is advised to carefully examine symptoms of adverse reactions observed during or shortly after exposure to Durvalumab and tremelimumab, and consider the above mentioned facts prior to making a final diagnosis.

Reactions occurring at the time of or shortly after subsequent infusions of investigational product are to be judged by the investigator at his/her own discretion. For the Investigator’s convenience and in order to facilitate consistency in judgments, a copy of the National

Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) guidance for anaphylaxis diagnosis is provided in Appendix 3.

7.4.1 **Time Period for Collection of Adverse Events**

Adverse events will be collected from time of signature of informed consent, enrollment, randomization, throughout the treatment period and including the follow-up period of 90 days after the last dose of Durvalumab post-operatively. Serious adverse events will be recorded from the time of informed consent signature through 90 days after the last dose of Durvalumab.

7.4.2 **Follow-up of Unresolved Adverse Events**

Any possible/probably/definite treatment-related SAEs that are unresolved at the subject's last AE assessment or other assessment/visit as appropriate in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF.

7.5 Serious Adverse Event Reporting (SAE) for M.D. Anderson-sponsored IND Protocols

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- 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 that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 90 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 90 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the IND Office guidelines, and Institutional Review Board policy.

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III

Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

7.5.1 Reporting of Serious Adverse Events

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 first protocol intervention through 90 days after the last dose of durvalumab or until the initiation of alternative anticancer therapy. The investigator is 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 eSAE 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 eSAE report must be emailed 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 ***eSAE*** 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-16-11821)

***** 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:*** AEMailboxClinicalTrialTCS@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. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

7.6 **Other Events Requiring Immediate Reporting**

7.6.1 **Overdose and Death**

7.6.1.1 Overdose

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol. Any overdose of a study subject with the investigational product, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event If the overdose results in an AE, the AE must also be recorded on the AE eCRF. Even when an overdose does not automatically make an AE serious, it will be reported to the IND Office through the eSAE application within the supporting company required reporting period. If the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be reported as an SAE (see Section 7.4 and Section 7.5). The investigator will use clinical judgment to treat any overdose.

7.6.1.2 Death

All deaths that occur during the study, or within the protocol-defined 90-day post-last dose of durvalumab + tremelimumab safety follow-up period must be reported to AstraZeneca as follows:

- Death that is clearly the result of disease progression should be documented but should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to AstraZeneca as a SAE within **24 hours**. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as a SAE.

7.6.2 **Hepatic Function Abnormality**

Adverse events of hepatic function abnormality of special interest to the supporting company are defined as any increase in ALT or AST to greater than 3 × ULN **and concurrent** increase in bilirubin to greater than 2 × ULN (ie, Hy's law cases). Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. In the event of hepatic function abnormality where the etiology is unknown, timely follow-up investigations and inquiries should be initiated by the investigational site, based on medical judgment, to make an informed decision regarding the etiology of the event.

If the underlying diagnosis for the hepatic function abnormality is known (including progression of pre-existing disease such as primary or metastatic malignancy), the diagnosis

should be recorded as an AE/SAE. If the underlying diagnosis for the hepatic function abnormality remains unknown, the term "hepatic function abnormal" should be used to report the AE/SAE. Hepatic function abnormality of unknown etiology, or which is considered attributable to investigational product, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to AstraZeneca Patient Safety, even if the event is considered to be non-serious (see Section 7.5 for contact information). The investigator will review the data with the medical monitor. The investigator should then use clinical judgment to establish the cause based on local standard of care and follow the subject by conducting testing as clinically indicated.

If, after appropriate workup, in the opinion of the investigator, the underlying diagnosis for the abnormality remains unexplained, or is considered attributable to investigational product, permanent discontinuation of dosing for the study subject should be considered. Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the supporting company. If the etiology of the event remains unconfirmed and/or is considered related to investigational product, a prompt cumulative review of safety data and the circumstances of the event in question will be conducted and assessed by the AstraZeneca safety review committee (or equivalent) to determine whether continued dosing of current study subjects and/or study entry should be interrupted, whether the protocol will be modified, or whether the study will be discontinued permanently. Review and approval by the AstraZeneca safety review committee (or equivalent) is required for resumption of subject dosing or study entry in the event that the study is interrupted. Where applicable, regulatory authorities IRBs/IECs will be notified of any actions taken with the study.

7.6.3 **Pregnancy**

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- Pregnancy discovered before the study patient has received any study drugs.
- Pregnancy of a female partner of male patient, providing there is no restriction of male patient fathering a child.

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

Male patients should refrain from fathering a child or donating sperm during the study and 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.
Pregnancy of the patient's partner is not considered to be an AE. However, 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 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 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 patient's 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.

7.6.4 **Pneumonitis**

Adverse events of pneumonitis are required to be reported ***within 24 hours of knowledge of the event*** to AstraZeneca Patient Safety

7.7 **<u>Management of Study Medication Related Toxicities</u>**

Adjustments for the trial drugs will follow the guidelines and recommendations noted below. Based on the mechanism of action of Durvalumab, tremelimumab, oleclumab, and monalizumab leading to T-cell activation and proliferation, the occurrence of irAEs that are either overlapping or greater than each of these drugs when used as monotherapy is possible. Potential irAEs may be similar to those seen with the use of ipilimumab, nivolumab, or the combination thereof and may include [31, 34, 35, 64]:

- Gastrointestinal events including colitis, 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 hyper and hypothyroidism
- Hepatitis including autoimmune hepatitis, and increased serum alanine aminotransferase and aspartate aminotransferase
- Pancreatitis including autoimmune pancreatitis, and lipase and amylase

Elevation (reported in Tremelimumab).
• Respiratory tract events including pneumonitis and interstitial lung disease
• Nervous system events including encephalitis, peripheral motor and sensory neuropathies, Guillain-Barre and myasthenia gravis (the latter reported with combination of tremelimumab and Durvalumab)
• Cytopenias including thrombocytopenia, anemia and neutropenia
• Infusion-related reactions, anaphylaxis, and serious allergic reactions
• Headache, fatigue, and pyrexia
• Serious infections
•Immune complex disease.

Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (eg, infection or PD), an immune-related etiology should be considered for signs or symptoms of enterocolitis, pneumonitis, dermatitis, hepatitis, neuropathy, and endocrinopathy. In addition to the treatment modifications shown in Table 7.7.1 it is recommended that management of irAEs follow the guidelines outlined for ipilimumab [65]. These guidelines recommend the following:

1. Subjects should be evaluated to identify any alternative etiology.
2. In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered to be immune-related.
3. Symptomatic and topical therapy should be considered for low-grade events.
4. Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.
5. More potent immunosuppressives should be considered for events not responding to systemic steroids (eg, infliximab, mycophenolate, etc).

If the investigator has any question in regards to an AE being an irAE, the investigator should immediately contact the medical monitor. Treatment modifications will not be required for AEs that are clearly not attributed to Durvalumab, tremelimumab, oleclumab or Monalizumab (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant.

Dose reductions of Durvalumab, tremelimumab, oleclumab or Monalizumab are not permitted.

Treatment modifications may be required for Durvalumab, tremelimumab, monalizumab, and oleclumab in the event of treatment-related toxicity. General guidelines regarding treatment modification are provided in Table 7.7.1 for all cohorts. In addition, management guidelines for adverse events of special interest (AESI) are detailed in Section 7.3. All toxicities will be graded according to NCI CTCAE v4.03 for cohort A and CTCAE v5.0 for cohorts B and C (CTCAE v5.0 is referenced in Table 7.7.1). In case of doubt, the investigator should consult with the medical monitor.

Table 7.7.1 Dosing Modification and Toxicity Management Guidelines

Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (Use for all Cohorts)

1 November 2017 (CTCAE Version 5.0)

General Considerations

Dose Modifications		Toxicity Management
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v5.0 . In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/study regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing		It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table: – It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. – Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. – Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events. – For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Some events with high likelihood for morbidity and/or mortality – e.g., myo-carditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper). – More potent immunosuppressives such as TNF inhibitors (e.g., infliximab) (also refer to the individual sections of the imAEs for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines
Grade 1	No dose modification	
Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per Investigator or treating physician's clinical judgement. 3. Doses of prednisone are at ≤10 mg/day or equivalent.	
Grade 3	Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below.	
Grade 4	Permanently discontinue study drug/study regimen.	

Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (Use for all Cohorts)

1 November 2017 (CTCAE Version 5.0)

General Considerations

Dose Modifications	Toxicity Management
Note: For Grade ≥3 asymptomatic amylase or lipase levels, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).	– when these events are not responding to systemic steroids. – With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. – Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version5.0)	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider Pulmonary and Infectious disease consult.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If still no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version5.0)	Dose Modifications	Toxicity Management
			antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[a] – Consider pulmonary and infectious disease consult. – Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious disease consult; consider, as necessary, discussing with study physician. – Hospitalize the patient. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks' dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Diarrhea/Colitis	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression,

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version5.0)	Dose Modifications	Toxicity Management
			other medications, or 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; mild increase in ostomy output compared to baseline) (Colitis: asymptomatic; clinical or diagnostic observations only)	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
	Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day; moderate increase in ostomy output compared to baseline; limiting instrumental ADL) (Colitis: abdominal pain; mucus or blood in stool)	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version5.0)	Dose Modifications	Toxicity Management
			– If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks[a]. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3 diarrhea: stool frequency of ≥7 over baseline per day; hospitalization indicated; severe increase in ostomy compared to baseline; limiting self care ADL Grade 4 diarrhea: life threatening consequences; urgent intervention indicated) (Grade 3 colitis: severe abdominal pain, peritoneal signs; Grade 4 colitis: life-threatening	**Grade 3** Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. **Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – 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 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g., infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version5.0)	Dose Modifications	Toxicity Management
	consequences, urgent intervention indicated)		
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. Refer to CTCAEv5 for criteria of each grade	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	Grade 1 ())	• No dose modifications. • If it worsens, then treat as Grade 2 event.	**For Grade 1:** – Continue LFT monitoring per protocol.
	Grade 2 ()	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to Grade ≤1 in 1 to 2 days, consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional work up and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version5.0)	Dose Modifications	Toxicity Management
			guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3:) (Grade 4:)	**For Grade 3:** For elevations in transaminases ≤8 × ULN, or elevations in bilirubin ≤5 × ULN: • Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.[b] **For Grade 4:** Permanently discontinue	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (i.e., mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Perform hepatology consult, abdominal workup, and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version5.0)	Dose Modifications	Toxicity Management
		study drug/study regimen.	
Nephritis or renal dysfunction (elevated serum creatinine) Refer to CTCAEv5 – Renal and urinary disorders	**Any Grade**	**General Guidance**	**For Any Grade:** – Consult with nephrologist. – Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections). – 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 to 1.5 × baseline; > ULN to 1.5 × ULN)	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
	Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent (>3 to 5 days) or worsens, promptly start

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version5.0)	Dose Modifications	Toxicity Management
		after completion of steroid taper.	prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – 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 × baseline; >3.0 to 6.0 × ULN; Grade 4: serum creatinine >6.0 × ULN)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – 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 PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Rash (excluding bullous skin	**Any Grade** (refer to NCI CTCAE	**General Guidance**	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus).

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version5.0)	Dose Modifications	Toxicity Management
formations)	v5.0 for definition of severity/grade depending on type of skin rash)		– IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED.**
	Grade 1	No dose modifications.	**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 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days,	**For Grade 3 or 4:** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version5.0)	Dose Modifications	Toxicity Management
		then permanently discontinue study drug/study regimen. **For Grade 4:** Permanently discontinue study drug/study regimen.	antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v5.0 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version5.0)	Dose Modifications	Toxicity Management
	Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until patient is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the	**For Grade 2 (including those with symptomatic endocrinopathy):** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version5.0)	Dose Modifications	Toxicity Management
		following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	– Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement.	**For Grade 3 or 4:** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version5.0)	Dose Modifications	Toxicity Management
		3. Doses of prednisone are ≤10 mg/day or equivalent.	consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v5.0 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). – Perform symptomatic treatment with neurological consult as appropriate. –
	Grade 1	No dose modifications.	**For Grade 1:** – See "Any Grade" recommendations above.
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or 4. Study drug/study regimen can be resumed once event	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Obtain neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (e.g., IV IG).

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version5.0)	Dose Modifications	Toxicity Management
		improves to Grade ≤1 and after completion of steroid taper.	
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consider, as necessary, discussing with study physician. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., IV IG). – Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis) Refer to CTCAEv5 for grade criteria	**Any Grade**	**General Guidance**	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version5.0)	Dose Modifications	Toxicity Management
			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. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 1	No dose modifications.	**For Grade 1:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult.
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version5.0)	Dose Modifications	Toxicity Management
			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 IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 3 or 4 (severe or life-threatening events):** – Consider, as necessary, discussing with study physician. – Recommend hospitalization. – Monitor symptoms and obtain neurological consult. *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version5.0)	Dose Modifications	Toxicity Management
		For Grade 4: Permanently discontinue study drug/study regimen.	○ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. ○ If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* ○ It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. ○ Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** − The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. − Consider, as necessary, discussing with the study physician. − Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version5.0)	Dose Modifications	Toxicity Management
			– Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)
	Grade 1 (asymptomatic with laboratory (e.g., BNP) or cardiac imaging abnormalities)	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 (no definitive findings):** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. - Consider using steroids if clinical suspicion is high.
	Grade 2, 3 or 4 (Grade 2: Symptoms with mild to moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical	- If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version5.0)	Dose Modifications	Toxicity Management
	hemodynamic support))	drug/study regimen.	guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Myositis/Polymyositis ("Poly/myositis")	**Any Grade**	**General Guidance**	**For Any Grade:** − Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. − If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. − Consider, as necessary, discussing with the study physician. − Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version5.0)	Dose Modifications	Toxicity Management
			electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
	Grade 1 (mild pain)	- No dose modifications.	**For Grade 1:** − Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. − Consider Neurology consult. − Consider, as necessary, discussing with the study physician.
	Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	Hold study drug/study regimen dose until resolution to Grade ≤1. - Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2:** − Monitor symptoms daily and consider hospitalization. − Obtain Neurology consult, and initiate evaluation. − Consider, as necessary, discussing with the study physician. − If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant − If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day − If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version5.0)	Dose Modifications	Toxicity Management
			refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (severe pain; limiting self-care ADLs)	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** - Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether patient may require IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Table 7.7.1 (cont.) Infusion-related Reactions

Severity Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade:** – Manage per institutional standard at the discretion of investigator. – Monitor patients for signs and symptoms of infusion-related reactions (eg, fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (eg, generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For 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 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.	**For Grade 1 or 2:** – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. – Consider premedication per institutional standard prior to subsequent doses. – Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Manage severe infusion-related reactions per institutional standards (eg, IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

PCP ; PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

CTCAE Common Terminology Criteria for Adverse Events; IM Intramuscular; IV Intravenous; NCI National Cancer Institute.

Table 7.7.1 Non-immune-mediated Reactions

Severity Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (ie, events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the IND Medical Monitor.).	Treat accordingly, as per institutional standard.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."

AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.

8. PHARMACEUTICAL INFORMATION

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

8.1 **Identity of Investigational Products**

MedImmune will provide the investigators with investigational product using designated distribution centers (Table 8.1).

Table 8.1 Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
Durvalumab	MedImmune	Supplied as a vialed liquid solution containing 500 mg (nominal) Durvalumab per vial. The solution contains 50 mg/mL Durvalumab 26 mM histidine/histidine HCl,

		275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, at pH 6.0
Tremelimumab	MedImmune	Formulated at a nominal concentration of 20 mg/mL in 20 mM histidine/histidine HCl, 222 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, and 0.27 mM EDTA, pH 5.5.
OLECLUMAB (liquid)	MedImmune	Oleclumab is supplied as a sterile liquid product. It is formulated at 50 mg/mL in 25 mM histidine/histidine hydrochloride, 240 mM sucrose, 0.03% (w/v) polysorbate 80, pH 6.0.
Monalizumab	Merck (Drug substance), Rentschler (Drug Product)	Monalizumab is supplied as 100mg/vial as a lyophilized powder in a 10 mL vial. Additional ingredients are L-Histidine buffer, sucrose for tonicity/stability, polysorbate 80 for surfactant, hydrogen chloride for pH adjustment, and sodium hydroxide for pH adjustment.

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Commercially available IV bags containing 0.9% (weight per volume [w/v]) saline or 5% (w/v) dextrose will be supplied by the site. Upon completion of the study, copies of investigational product accountability records will be returned to MedImmune. All unused investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune according to the investigational site policy. Both investigational products should be kept in a secure place at 2°C to 8°C (36°F to 46°F) and must not be frozen.

8.1.1 **Investigational Product Inspection**

Investigational products will be supplied to the site in vials in coded kits. Each kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each vial within the carton). Each vial selected for dose preparation should be inspected. If there are any defects noted with the investigational product(s), the investigator and site monitor should be notified immediately. Refer to the Product Complaint section (8.1.6) for further instructions.

8.1.2 Investigational Agents

Durvalumab

The doses of durvalumab will be a flat dose. This prescription is based on an expectation of similar pharmacokinetic exposure and variability to weight-based dosing. If a patients' weight drops below 30 kg, then therapy must be held until the weight returns to 30 kg or more.

Durvalumab will be given at a dose of 1500 mg IV flat dose per 4 week cycle.

Durvalumab will be supplied as a 500 mg/vial concentrate solution for infusion after dilution. The solution contains 50 mg/mL Durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% (w/v) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10.0 mL. If there are any defects noted with the investigational product, the investigator and site monitor should be notified immediately. Refer to the Product Complaint section (section 8.1.6) for further instructions.

Tremelimumab

The dose of tremelimumab will be a flat doses. This prescription is based on an expectation of similar pharmacokinetic exposure and variability to weight-based dosing. If a patients' weight drops below 30 kg than therapy must be held until the weight returns to 30 kg or more.

Tremelimumab will be given at a flat dose of 75 mg IV once pre-operatively along with Durvalumab.

Tremelimumab is supplied as a sterile IV solution for infusion after dilution, filled in 20 mL clear glass vials with a rubber stopper and aluminum seal. Each vial contains 20 mg/mL (with a nominal fill of 20.0 mL accounting to 400 mg/vial) of tremelimumab, in an isotonic solution at pH 5.5. During the inspection if the solution is not clear or any turbidity, discoloration, or particulates are observed, notify your site monitor and store the vial(s) in QUARANTINE at refrigerated (2ºC to 8ºC) temperature for drug accountability and potential future inspection.

Oleclumab

Liquid product:
The product is supplied as a sterile liquid product in a 10R glass vial at nominal fill volume of 10.0 mL, with each vial containing 500 mg (nominal) of active investigational product. This is formulated at 50 mg/mL in 25 mM histidine/histidine hydrochloride, 240 mM sucrose, 0.03% (w/v) polysorbate 80, pH 6.0. The drug is intended for IV administration following dilution into commercially available 0.9% (w/v) saline.

Oleclumab will be given at a flat dose of 3000 mg IV with durvalumab.

If there are any defects noted with the investigational product, the investigator and site monitor should be notified immediately. Refer to the Product Complaint section (section 8.1.6) for further instructions.

Monalizumab

Monalizumab is supplied as a 100 mg/vial lyophilized powder in a 10 mL vial. Vials of the drug product should be reconstituted in 1.1 mL of sterile water for injection. After reconstitution, the concentration of the active ingredient monalizumab in the solution is

100 mg/mL, and 1 mL can be drawn from the vial. The reconstituted drug product is a clear to slightly opalescent and colorless to slightly yellow liquid, essentially free of visible particles and with a pH of 6.0.

Monalizumab will be given at a flat dose of 750 mg IV with durvalumab.

If there are any defects noted with the investigational product, the investigator and site monitor should be notified immediately. Refer to the Product Complaint section (section 8.1.6) for further instructions.

8.1.3 **Dose Preparation Steps**

Durvalumab (MEDI4736)
No incompatibilities between Durvalumab and polyvinylchloride or polyolefin IV bags have been observed. Total in use storage time from needle puncture of Durvalumab vial to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). If the in-use storage time exceeds these limits, a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded. The infusion solution in the prepared final IV bag should be equilibrated to room temperature prior to administration.

A dose of 1500mg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter.

Preparation of Durvalumab and preparation of the IV bag are to be performed aseptically by the investigational product manager or qualified personnel using the following steps:

1. Select 3 vials of investigational product required to prepare the subject's dose.
2. Add 30 mL of durvalumab (ie, 1500mg of durvalumab to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. The bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

Tremelimumab

Tremelimumab does not contain preservatives and any unused portion must be discarded. Preparation of tremelimumab and preparation of the IV bag are to be performed aseptically. Total in-use storage time from needle puncture of the product vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2ºC to 8°C (36ºF to 46°F). If storage time exceeds these limits, a new dose must be prepared from new vials. The infusion solution in the prepared final IV bag should be equilibrated to room temperature prior to administration.

For dose preparation steps, the following ancillary items are required:

• IV bags of 0.9% (w/v) saline or 5% (w/v) dextrose. IV bags can be made of polyvinylchloride (PVC) or polyolefin.
• IV infusion lines should contain a 0.22 or 0.2-µm in-line filter.
• Syringes and needles.

The investigational product manager or qualified personnel will be responsible for preparing the IV doses using the following steps:

1. Select one vial of investigational product required to prepare the subject's dose.
2. Add 3.8 mL (ie,75 mg of tremelimumab, with the dose volume rounded to the nearest tenth mL) to the IV bag. The IV bag size should be selected such that the final concentration is within 0.10 to 10 mg/mL. Gently mix the solution in the bag by inverting up and down to ensure homogeneity of the dose in the bag.

Oleclumab (based on protocol D6010C00005)

The Oleclumab (MEDI9447) doses must be prepared by the investigator's or site's designated investigational product manager using aseptic technique.
Total time from needle puncture of the Oleclumab (MEDI9447) 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 preparation time exceeds the time limits a new dose must be prepared from new vials. Oleclumab (MEDI9447) does not contain preservatives, and any unused portion must be discarded.

No incompatibilities between Oleclumab (MEDI9447) and polyvinylchloride or polyolefin bags have been observed.

Dose of 3000 mg will be administered using an IV bag containing 0.9% (w/v) saline, with a final Oleclumab (MEDI9447) concentration ranging from 1.5 to 30 mg/ml, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Add 60.0 mL (ie, 3000 mg dose) of Oleclumab (MEDI9447) to the IV bag. The IV bag size should be selected such that the final concentration is within 1.5 to 30 mg/mL. Mix the bag gently to ensure homogeneity of the bag.

Monalizumab

The dose of monalizumab for administration must be prepared by the investigators or site's designated investigational product manager using aseptic technique.

Slowly add 1.1 mL of sterile Water for Injection by tilting the vial to one side such that the liquid stream is directed along the vial wall and not directly onto the lyophilized cake. Gently swirl the solution until all solids are dissolved. DO NOT SHAKE OR VIGOROUSLY AGITATE THE VIAL. Visually inspect the solution to ensure that the entire content of the lyophilized cake is completely reconstituted. The reconstituted solution should appear clear to opalescent. A thin layer of bubbles on the surface of the liquid is normal.

Monalizumab should be protected from direct sunlight during preparation and handling. Total time from start of reconstitution to the start of monalizumab administration must be no longer than 4 hours and the temperature must be kept lower than 25°C. No freezing is allowed.

No incompatibilities between monalizumab and polyethylene, polypropylene, and polyvinyl chloride have been observed.

Add 7.5 mL (750 mg) of monalizumab to the IV bag containing 100 to 500 mL of 0.9% saline. A total of 750 mg will be delivered through a 0.2- or 0.22-μm polyether sulfone in-line filter (ethylhexyl-phthalate free). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

8.1.4 **Treatment Administration**

The first day of dosing is considered Day 1.

For cohort A tremelimumab will be administered first; the durvalumab infusion will start approximately 1 hour (maximum 2 hours) after the end of the tremelimumab infusion. Standard infusion time for each is approximately 60 minutes In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

For cohort B, oleclumab will be infused with standard infusion time of approximately 60 minutes. The drug will be administered at room temperature (approximately 20 to 25°C) by controlled infusion into a peripheral or central vein. Standard infusion time for Oleclumab (MEDI9447) is 1 hour; however, if there are interruptions during infusion, the total allowed time should not exceed 4 hours at room temperature. If this duration is met, then the remainder of the dose should be abandoned and should not be completed with a second prepared dose. On days where both oleclumab and durvalumab are administered, durvalumab infusion will start no less than 15 minutes after the end of Oleclumab infusion. Standard infusion time for durvalumab is 1 hour; however, if there are interruptions during the infusion, the total allowed time should not exceed 8 hours at room temperature.

Do not co-administer other drugs through the same infusion line.

Flush the IV line with a volume of IV diluent 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.

For cohort C durvalumab will be infused first with standard infusion time of approximately 60 minutes. In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

Each dose of intravenous investigational product should be administered using the following guidelines:

1. Investigational product(s) must be administered at room temperature by controlled infusion into a peripheral vein or central line. Prior to the start of the infusion, ensure that the bag contents are at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.

2. A physician must be present at the site or immediately available to respond to emergencies during all administrations of investigational product(s). Fully functional resuscitation facilities should be available. Investigational product(s) must not be administered via IV push or bolus but as an IV infusion. The entire content of each IV bag will be infused using an infusion pump.

3. The infusion lines should be attached only at time of use. Lines used for infusion during dose administration will need to be equipped with 0.22- or 0.2-µm in-line filters. Tremelimumab, Durvalumab, Oleclumab, or Monalizumab solution should not be infused with each other or with other solutions or medications in the same infusion line.

4. The entire contents of the IV bag should be administered as an IV infusion for approximately 1 hour. Some investigational product may remain in the IV line after the infusion has completed. Fifteen to 30 mL of IV solution should be added to the infusion bag after the investigational product has been administered to flush the line. The infusion rate should not be changed unless necessary to manage acute reactions. Document if the line was not flushed.

8.1.5 **Monitoring of Dose Administration**

Subjects will be monitored prior to, during, and after infusion of Durvalumab, Tremelimumab, Oleclumab and Monalizumab.

Refer to Table 10.4 for monitoring schedule for vitals during dose administration for all cohorts.

In the event of Grade ≤ 2 infusion-related reaction, the infusion rate of Durvalumab, Tremelimumab, Oleclumab or monalizumab may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. In subjects experiencing Grade ≤ 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate.

Primary prophylaxis against infusion-related reactions is not permitted during this study in order to avoid obscuring a potential safety signal and enable a future assessment regarding whether premedications should be required for all subjects in future studies. However, at the discretion of the investigator, secondary prophylaxis (ie, prevention of infusion-related reaction following initial episode) is appropriate and will be permitted. Acetaminophen and/or an antihistamine (eg, 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, treatment with Durvalumab, tremelimumab, Oleclumab and monalizumab will be discontinued.

As with any mAb, allergic reactions to dose administration are possible. Therefore, 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.

8.1.6 **Reporting Product Complaints**

Any defects with the investigational product must be reported *immediately* to the MedImmune Product Complaint Department by the site with further notification to the site monitor. All defects will be communicated to MedImmune and investigated further with the Product Complaint Department. During the investigation of the product complaint, all investigational product must be stored at labeled conditions unless otherwise instructed. MedImmune contact information for reporting product complaints:

Email: productcomplaints@medimmune.com
Phone: +1-301-398-2105
+1-877-MEDI-411 (+1-877-633-4411)
Fax: +1-301-398-8800
Mail: MedImmune, LLC
Attn: Product Complaint Department
One MedImmune Way

Gaithersburg, MD 20878, USA

8.1.7 **Additional Study Medications**

No other study medications are specified for use in this clinical protocol.

8.1.8 **Labeling**

Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. Label text will be translated into local languages, as required.

8.1.9 **Storage**

Store Durvalumab, tremelimumab, Oleclumab and monalizumab at 2°C to 8°C (36°F to 46°F). Do not freeze.

8.1.10 **Treatment Compliance**

Investigational product is administered by study site personnel, who will monitor compliance.

8.1.11 **Accountability**

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to MedImmune. All unused investigational product will be returned to MedImmune-authorized depot or disposed of upon authorization by MedImmune.

9. CORRELATIVE/SPECIAL STUDIES

9.1 **Laboratory Correlative Studies**

All correlative studies will be performed by the Immune Platform at MD Anderson except for PD-L1 staining/status. Studies in the study cohorts may include, but are not limited to, identification of relevant immunologic biomarkers and CMS typing. Samples include tumor biopsy samples prior to checkpoint inhibitor therapy and resection specimens after surgery. Peripheral blood samples will be collected in red top tubes at the time points outlined in section 5 and in the study calendar in section 10. We will be attempting to uncover biomarkers associated with safety and relapse-free survival. These will be uncovered by quantifying:

1. Pre- and post-immune checkpoint inhibitor therapy effect on T-effector cell populations; CD4 subsets; T-regulatory populations; B cell populations; dendritic and macrophage populations.

2. Pre- and post-immune checkpoint inhibitor therapy on functional assays related to Teff cells.
3. Immunologic markers obtained in peripheral blood versus those obtained at the tissue level.
4. Immunologic biomarkers obtained in the tissue and peripheral blood correlated with safety, feasibility, and progression free survival.

These will be reported via:

1. Graphical displays will be used to display all biomarker data a baseline and follow-up. Transformation will be used as needed prior to hypothesis testing and estimating summary statistics. We will use a paired t test to determine if there is a difference in pre- and post-immune checkpoint inhibitor therapy in T-effector cell populations; T-regulatory populations; CD4 subsets; B cell populations; dendritic and macrophage populations.
2. We will use scatterplots to demonstrate correlation between immunologic markers obtained in peripheral blood versus those obtained at the tissue level. A Pearson correlation will be estimated to describe the level of association.

10. STUDY CALENDAR AND SCHEDULES

Table 10.1 Study Calendar from Enrollment until Surgical Resection

TIME PERIOD	Screening	Wk 1	Wk 4**	Comment
	within 14 days	+/-3d	3 - 10 weeks**	
PROCEDURE				
Cohort A: Tremelimumab + Durvalumab		X		
Cohort B: Durvalumab + Oleclumab		X		
Cohort C: Durvalumab + Monalizumab		X		
Liver/lung resection			X	
Clinic Visit	X	X	X	
Physical Examination	X	X	X	
Vital Signs	X	X	X	Including BP,HR, temperature. Obtain vital signs
Review of Concomitant Medication	X	X	X	
Laboratory	X	X	X	CBC w/differential and platelet count,LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, glucose)
CEA lab		X	X	
HIV and hepatitis and PT/PTT	X (within 30 days allowed)			HIV, hepatits B and C testing and PT/PTT
Specialized laboratory tests	X		X	Lipase, amylase, TSH, FT4
Pregnancy test (WOCBP only)	X	X		Serum or urine pregnancy test to be done within 72 hours prior to first dose.
ECOG PS	X	X	X	see appendix 1
Adverse Events Assessment	X		X	Per CTCAE v4.03 for Cohort A and v5.0 for Cohorts B and C
CT C/A/P with IV contrast with tumor measurements	X (within 30 days)		X	
Immunogenicity Assessment (special lab)		X	X	
Liver biopsy (tumor)	X			
Immuno- genicity Assessments, Peripheral Blood	12 red top tubes of blood with 5ml each will be collected for immunological assessment. See section 5.1.3 (up to 4 missed blood draws are allowed)			
**Factoring the occurrence of potential immune mediated adverse eventsprior to resection, an allowance of 3 -10 weeks after the administration of neoadjuvant therapy will be permitted to complete metastatic and/or primary resection.				

CEA: Carcioembryonic Antigen; ECOG PS: Eastern Cooperative Oncology Group Performance Status; TSH: Thyroid stimulating hormone; FT4: Free T4; WOCBP: Women of child bearing potential; CT C/A/P: CT scan chest, abdomen and pelvis

Table 10.2 Post-Resection Study Calender for Cohort A (**Durvalumab + Tremlimumab)**

(Week 1 begins the day Durvalumab treatment is given)

TIME PERIOD	Post-operative evaluation	Wk	Wk	Wk	Wk	Wk	Comment
		1	**5**	**9**	**13**	every **4months**	
	(0.5-2wks post surgery)	+/-3d	+/-7d	+/-7d	+/-7d	+/-6 weeks	
PROCEDURE							
Durvalumab		X	X	X	X		If patient requires >12 weeks for postop recovery, they will not be initiated on adjuvant immunotherapy
Clinic Visit	X	X	X	X	X	X	
Physical Examination	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	Including BP, HR, temperature
Review of Concomitant Medication	X	X	X	X	X		
Laboratory	X	X	X	X	X	X	CBC w/differential and platelet count,LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, glucose)
CEA	X			X		X	
TSH/FT4	X			X			
Lipase/amylase	X						
Immunogenicity Assessments, Peripheral Blood	X				X	X (at first visit only)	

Pregnancy test (WOCBP only)		X	As indicated clinically				Serum or urine pregnancy test to be done within 72 hours of dose
ECOG PS	X	X	X	X	X		see appendix 1
Adverse Events Assessment	X	X	X	X	X		Per CTCAE v4.03 for Cohort A and v5.0 for Cohorts B and C
CT C/A/P with IV contrast with tumor measurements					X	X	
Immunogenicity Assessments, Peripheral Blood	Up to 12 tubes of blood with 5ml each will be collected for immunological assessment. For specific details see laboratory manual (up to 4 missed blood draws are allowed)						
	CEA: Carcioembryonic Antigen; ECOG PS: Eastern Cooperative Oncology Group Performance Status; TSH: Thyroid stimulating hormone; FT4: Free T4; WOCBP: Women of child bearing potential; CT C/A/P: CT scan chest, abdomen and pelvis Toxicity 30 day f/u can happen 30 days (+/-2 weeks) after last treatment dose and this can be done by phone call. Note after one year of follow-up without recurrence schedule of follow-ups can be adjusted according to standard of care. This will take precedence over the study calendar.						

Table 10.3 Post-Resection Study Calender for **Cohorts (B and C)**

TIME PERIOD	Post-operative evaluation	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Comment
		1 (same day as Durvalumab)	**3**	**5**	**7**	**9**	**11**	**13**	**15**	every **4months**	
	(0.5-2wks post surgery)	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-6 weeks	
PROCEDURE											
Durvalumab		X		X		X		X			If patient requires >12 weeks for postop recovery, they will not be initiated on adjuvant immunotherapy
Olecluma b (cohort B)		X	X	X	X	X	X	X	X		
Monalizumab (cohort C)		X		X		X		X			
Clinic Visit		X	X	X	X	X	X	X	X	X	
Physical Examination		X	X	X	X	X	X	X	X	X	
Vital Signs		X	X	X	X	X	X	X	X	X	Including BP, HR,

											temperature
Review of Concomitant Medication		X	X	X	X	X	X	X	X		
Laboratory		X	X	X	X	X	X	X	X	X	CBC w/differential and platelet count,LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, glucose)
CEA	X								X	X	
TSH/FT4	X			X		X		X			
Lipase/amylase	X										
Immunogenicity Assessments, Peripheral Blood	X			X				X		X (at first visit only)	
Pregnancy test (WOCBP only)		X	As indicated clinically								Serum or urine pregnancy test to be done within 72 hours of dose
CT C/A/P with IV contrast with tumor measurements								X		X	
ECOG PS		X		X		X		X			see appendix 1
Adverse Events Assessment		X	X	X	X	X	X	X	X		Per CTCAE v4.03 for Cohort A and v5.0 for Cohorts B and C
Immunogenicity Assessments, Peripheral Blood	Up to 12 tubes of blood with 5ml each will be collected for immunological assessment. For specific details see laboratory manual (up to 4 missed blood draws are allowed)										

	CEA: Carcioembryonic Antigen; ECOG PS: Eastern Cooperative Oncology Group Performance Status; TSH: Thyroid stimulating hormone; FT4: Free T4; WOCBP: Women of child bearing potential; CT C/A/P: CT scan chest, abdomen and pelvis Toxicity 30 day f/u can happen 30 days (+/-2 weeks) after last treatment dose and this can be done by phone call. Note after one year of follow-up without recurrence schedule of follow-ups can be adjusted according to standard of care. This will take precedence over the study calendar.

Table 10.4 Collection Times for Vitals During Treatment Period

Treatment Arm	Durvalumab			Tremelimumab			Oleclumab			Monolizumab		
	Pre-dose	**During**	**EOI**	**Pre-dose**	**During**	**EOI**	**Pre-dose**	**During**	**EOI**	**Pre-dose**	**During**	**EOI**
Cohort A	Within 30 mins	N/A	Within 15 mins	Within 30 mins	Q15 mins	Within 5, 30 and 60 mins	N/A	N/A	N/A	N/A	N/A	N/A
Cohort B	Within 30 mins	N/A	Within 15 mins	N/A	N/A	N/A	Within 30 mins	None	Within 15 mins	N/A	N/A	N/A
Cohort C	Within 30 mins	N/A	Within 15 mins	N/A	N/A	N/A	N/A	N/A	N/A	Within 30 mins	N/A	Within 5, and 30
All Cohorts will require an additional 2-hour observation period for **Dose-1** of each drug. This will not be required for subsequent doses unless the subject experiences an infusion reaction. Note: exact times for vital signs are approximate.												

11. MEASUREMENT OF EFFECT

RECIST 1.1 will be used to identify measurable disease on baseline CT scans. Tumor measurements will be made upon restaging CT scans prior to surgery. Further imaging will be performed according to the study outline in section 5 and study calendar in section 10. No tumor measurements will take place post-operatively as the goal of therapy is no evidence of disease. Suspected first site of recurrence should be biopsied to confirm CRC recurrence unless interval imaging demonstrates clear growth / progression.

11.1.1. **Definitions**

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of enrollment.

Evaluable for recurrence. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for recurrence. These patients will have their response classified according to the definitions stated below.

11.1.2 **Disease Parameters**

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

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 10 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

11.1.3 **Methods for Evaluation of Measurable Disease**

CT will be used for all evaluations.

11.1.4 **Response Criteria**

Subjects will be monitored for recurrence, not response, and thus no formal response criteria will be employed.

11.1.5 **Relapse-Free Survival**

Relapse-Free Survival is defined as the time from surgical excision of CRCLM to evidence of definite recurrence, as determined by the treating physician.

12. DATA REPORTING REQUIREMENTS / STUDY AND DATA MANAGEMENT

12.1 **Training of Study Site Personnel**

Before the first subject is entered into the study, a MedImmune representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilized.

The principal investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved. The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

12.2 **Monitoring of the Study**

During the study, a MedImmune representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed.
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts).
- Ensure withdrawal of informed consent to the use of the subject's biological samples isreported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The MedImmune representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

12.2.1 **Source Data**

Refer to the Clinical Study Agreement for location of the source data.

12.2.2 **Study Agreements**

The principal investigator at each/the center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between MedImmune and the principal investigator must be in place before any study-related procedures can take place, or subjects are enrolled.

12.2.3 **Archiving of Study Documents**
The investigator follows the principles outlined in the Clinical Study Agreement.

12.3 <u>Study Timetable and End of Study</u>
An individual subject will be considered to have completed the study if the subject was followed through the DLT-evaluation period or experienced a DLT during the DLT-evaluation period (for subjects in the dose-exploration phase) or the subject completed at least 1 on-treatment disease evaluation (for subjects in dose-expansion phase) regardless of the number of doses of investigational product that was received. The end of the study ("study completion") is 5 years after the final subject is enrolled or the date the study is closed by the sponsor, whichever occurs first.

12.4 <u>Data Management</u>
Data management will be performed according to the Data Management Plan.
A Web Based Data Capture system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

13. STATISTICAL CONSIDERATIONS

13.1 Endpoints

1. Primary Endpoints

- Feasibility will be assessed by whether or not the patient successfully goes to surgery following the planned treatments, scans, and biopsy.
- Safety will be assessed by CTCAE version 4.03 for cohort A and 5.0 for cohorts B and C.

2. Secondary Endpoints

- Various immune parameters
- Response - irRECIST
- Overall survival (OS) measured from the date of study entry until death from any cause
- Relapse-free survival (RFS) from the date of study entry until relapse or death from any cause

13.2 **Sample Size Justification**

Sample sizes of 15 and 25 patients, are driven by safety and feasibility endpoints. The selection of 25 patients in cohort A ensures that if the trial continues to full size, a posterior 95% credible interval (ci) of surgery received will be (0.62, 0.92), assuming that the proportion of patients successfully getting to surgery is 80%, with a prior of beta(1.2, 0.8) and 20 patients getting to surgery. Cohorts B and C will enroll 15 patients, which will ensure that a posterior 95% credible interval (ci) of surgery received will be (0.57, 0.94), assuming that the proportion of patients successfully getting to surgery is 80%, with a prior of beta(1.2, 0.8) and 12 patients getting to surgery. The smaller number in cohorts B and C are due to feasibility constraints of accrual rate and overall trial budget. We expect to enroll approximately 25 patients in Cohort A by the time this protocol revision is approved.

In order to ensure a homogenous population clinical trial will require that at least 66% of patients have pre-treatment with either no chemotherapy or oxaliplatin-based chemotherapy. The use and type of per-operative therapy prior to enrollment in this clinical trial will be monitored.

13.3 Interim Monitoring

A Bayesian sequential monitoring design[66, 67] will be used to monitor the trial for surgery and toxicity rates. Generally, interim analyses will begin after 3 patients become evaluable, and will then be performed continuously to ensure that patients are exhibiting reasonable toxicity and surgery rates to continue the trial. Specific rules are in each subsection below. Since 1-2 patients are expected to be enrolled each month, monitoring data will be kept up-to-date and the tables below checked prior to consenting each patient once the 3rd patient in each cohort has been on study 4 weeks after the first dose of Durvalumab. Enrollment will not need to wait for the previous patient to become evaluable, but the rules will be checked for all evaluable patients before consenting each patient. This includes a risk of 1-2 patients entering on the study beyond the designed stopping rules, which is considered a reasonable risk. If accrual occurs faster than 1-2 patients per month, this practice will be reconsidered. All calculations for stopping boundaries and operating characteristics were performed in Multc Lean Desktop v2.1.

Patients will be evaluable once they have received the first dose of Durvalumab/tremilimumab, durvalumab/oleclumab or durvalumab/monalizumab and have then had 8 weeks time to go to surgery. If surgery has not occurred by 8 weeks then for monitoring these patients will have been considered not to have gone to surgery even if they do after 8 weeks. Patients will be allowed up to 12 weeks to complete surgical resection. If surgical resection is not done within 12 weeks from then patient will be removed from clinical trial

13.3.1 Interim Analyses for Futility per cohort

For futility, the trial will be stopped early if $Pr[\theta_S < 0.60 \mid data] > 0.90$, where θ_S denotes the proportion of patients who successfully receive surgery. That is, given the outcomes from the patients who have already been evaluated, if it is determined that there is a more than 90% chance that the surgery rate is 60% or less, the trial will be stopped for futility. Assuming a prior distribution of θ_S of ~beta(1.2, 0.8) for this experimental treatment against a constant 60%, pre-defined stopping boundaries corresponding to this probability criterion are provided in the following table. Once 3 patients have been enrolled in a cohort, follow the instructions in this table according to the schedule described above.

If there are this many (or more) patients whose surgery status is determined	Stop if there are this many or fewer patients who received surgery	If there are this many (or more) patients whose surgery status is determined	Stop if there are this many or fewer patients who received surgery
3	0	15*	6
5	1	17	7
7	2	19	8
9	3	20	9
11	4	22	10
13	5	24	11

* Cohorts B and C will stop at 15 patients regardless of the number of patients who received surgery

Three patients will be accrued first. If 0 of the 3 patients receive surgery in a given cohort as scheduled, the cohort should be stopped and the treatment will be declared as not feasible for this population. If there is at least 1 patient with surgery, the next patient will be entered in the study, unless the trial needs to stop according to the toxicity boundaries below. Check continuously as described above for sufficient surgery rate assuming the trial does not stop for toxicity first. The operating characteristics for futility and toxicity are summarized below the toxicity rules.

13.3.2 Interim Analyses for Toxicity

Under the same model described for futility, toxicities will be monitored assuming a prior probability of toxicity following Beta(0.6,1.4) in the current treatment arm against a constant rate of 0.30. Based on a previous study, we assume that a 15% rate of toxicity events would be acceptable and a 30% rate of toxicity would be unacceptable. [68] For trial monitoring and decisions about future trials, extreme toxicities (TOX) will be defined as any grade 3 or higher adverse event that is possibly, probably, or definitely related to any therapy received on this protocol and occur between the first dose of Durvalumab and surgery (or 4 weeks after that dose if the patient does not receive surgery as scheduled) with the following exception. Any grade 3 adverse event that is

potentially treatable with steroids will only count as an extreme toxicity if it does not improve to grade 2 or better within 2 weeks. Grade 3 nausea or vomiting that responds to anti-emetics within 72 hours and asymptomatic grade 3 or 4 lipase or amylase elevations will not count as TOX. The trial will be terminated if Prob(Θ_{TOX} > 0.30 | data) > 0.9, where Θ_{TOX} is the proportion of patients experiencing a TOX event. Following this rule, the trial will be terminated according to the following table once the first 3 patients are evaluable.

If there are this many patients (or more) with TOX	3	4	5	6	7	8	9	10	11
Stop the cohort if there are this many (or fewer) patients who are evaluable (have TOX or completed 4 weeks after first Durvalumab dose without TOX)	3	7	9	12	14	17*	20	22	25*

* Always stop with 25 patients in Cohort A, but if 11 or more patients have TOX, then this treatment regimen is too toxic for further use. Always stop at 15 patients in Cohorts B and C, but if 8 or more patients have TOX, then this regimen is too toxic for further use.

Three patients in each cohort will be accrued first. If 3 of the 3 patients have TOX, stop that cohort and the treatment will be declared as too toxic for that cohort. If there is at least 1 patient with surgery without TOX, the next patient will be entered in the study, unless the trial needs to stop according to futility boundaries above. Check continuously as described above for toxicity assuming the trial does not stop for futility first. The operating characteristics for the combined futility and toxicity are summarized in the following table

The operating characteristics for the combined futility and toxicity based on Multc Lean are shown in the following table, assuming that toxicity and surgery rates are independent.

		Stop if Prob(Θ_{TOX} > 0.30 | data) > 0.90 or Prob (θ_S < 0.60 | data) > 0.90					
		Cohort A (N=25)			Cohorts B and C (N=15)		
True Toxicity Rate	True Surgery Rate	Pr(stop early)	Mean Number of Patients	Median (25^{th} %ile, 75^{th} %ile)	Pr(stop early)	Mean Number of Patients	Median (25^{th} %ile, 75^{th} %ile)
0.10	0.50	0.59	16.2	19 (7, 25)	0.43	11.4	15 (7, 15)
0.20	0.50	0.62	15.6	17 (7, 25)	0.46	11.1	15 (7, 15)
0.30	0.50	0.69	13.9	12 (5, 25)	0.55	10.3	12 (5, 15)
0.40	0.50	0.83	11.2	7 (4, 19)	0.69	8.9	7 (4, 15)
0.50	0.50	0.94	8.3	6 (4, 11)	0.84	7.3	6 (4, 11)
0.10	0.60	0.27	20.8	25 (20, 25)	0.21	13.2	15 (15, 15)

0.20	0.60	0.32	20.0	25 (15, 25)	0.25	12.8	15 (15, 15)
0.30	0.60	0.46	17.6	25 (7, 25)	0.37	11.8	15 (7, 15)
0.40	0.60	0.69	13.7	11 (5, 25)	0.57	10.1	11 (5, 15)
0.50	0.60	0.90	9.6	7 (4, 12)	0.78	8.1	7 (4, 12)
0.10	0.70	0.09	23.5	25 (25, 25)	0.08	14.3	15 (15, 15)
0.20	0.70	0.14	22.5	25 (25, 25)	0.12	13.9	15 (15, 15)
0.30	0.70	0.31	19.8	25 (12, 25)	0.27	12.7	15 (12, 15)
0.40	0.70	0.61	15.2	15 (6, 25)	0.50	10.8	15 (6, 15)
0.50	0.70	0.87	10.4	7 (4, 16)	0.74	8.6	7 (4, 15)
0.10	0.80	0.02	24.6	25 (25, 25)	0.02	14.8	15 (15, 15)
0.20	0.80	0.08	23.6	25 (25, 25)	0.07	14.3	15 (15, 15)
0.30	0.80	0.27	20.6	25 (20, 25)	0.22	13.1	15 (15, 15)
0.40	0.80	0.59	15.8	17 (7, 25)	0.47	11.1	15 (7, 15)
0.50	0.80	0.86	10.7	7 (4, 16)	0.73	8.8	7 (4, 15)

13.3.3 Interim Analyses for Toxicity Post Surgery Immune-therapy

Under the same model described for futility and toxicity above, toxicities on immune-therapy after surgery will be monitored assuming an a priori probability of toxicity following Beta(0.4,1.6) in the current treatment against a constant rate of 0.20. For trial monitoring and decisions about future trials, extreme toxicities (TOXpost) will be defined as any grade 3 or higher adverse event that is possibly, probably, or definitely related to any therapy received on this protocol and occur after surgery between the first dose of adjuvant immune-therapy and the final dose received (up to 12 weeks) with the following exception. Any grade 3 adverse event that is potentially treatable with steroids will only count as an extreme toxicity if it does not improve to grade 2 or better within 2 weeks. Grade 3 nausea or vomiting that responds to anti-emetics within 72 hours and asymptomatic grade 3 or 4 lipase or amylase elevations will not count as TOXpost. The trial will be terminated if Prob(TOXpost > 0.20 | data) > 0.9. Following this rule, the trial will be terminated according to the following table once the first 3 patients are evaluable.

If there are this many patients (or more) with TOXpost	2	3	4	5	6	7	8
Stop the cohort if there are this many (or fewer) patients who are evaluable (have TOXpost or completed 4 weeks after first adjuvant immune-therapy dose without TOXpost)	3	6	9	13	17	21	25*

* Only patients who successfully have surgery and begin treatment with immune-therapy will be included. The table goes to 25 patients as the maximum of possible patients.

Three patients in each cohort will be accrued first. If 2 of the 3 patients have TOXpost, stop this portion of the trial and the adjuvant treatment will be declared as too toxic for this population. Check continuously as described above for toxicity. The operating characteristics (OCs) for this stopping rule for are summarized in the following table assuming all 25 or 15 patients in each cohort receive surgery and start adjuvant immune-therapy. Since we do not expect all 25 or 15 patients to enter this portion of the study, the OCs are slightly over-estimated.

	Stop if Prob(TOXpost > 0.20 | data) > 0.90					
	Cohort A (N=25)			Cohorts B and C (N=15)		
True Toxicity Rate	Pr(stop early)	Mean Number of Patients	Median (25^{th} %ile, 75^{th} %ile)	Pr(stop early)	Mean Number of Patients	Median (25^{th} %ile, 75^{th} %ile)
0.05	0.01	24.8	25 (25, 25)	0.01	14.9	15 (15, 15)
0.10	0.04	24.2	25 (25, 25)	0.04	14.6	15 (15, 15)
0.20	0.25	20.8	25 (24, 25)	0.20	13.1	15 (15, 15)
0.30	0.62	15.2	16 (5, 25)	0.47	10.8	15 (5, 15)
0.40	0.89	9.9	6 (3, 15)	0.73	8.3	6 (3, 15)

13.4 Analysis Plan

Primary endpoint: Each combination regimen will be considered feasible if at least 80% of patients successfully undergo surgery. It will be infeasible if fewer than 60% of patients can undergo surgery. If the successful surgery rate is between 60% and 80%, then consideration will be given to toxicity, clinical outcome measures, and immune changes to determine whether this regimen warrants further investigation. The 95% posterior credible interval will be calculated for proportion of patients undergoing surgery. Adverse events will be tabulated.

Additional analyses: Demographic and patient baseline disease characteristics will be summarized for all patients. Descriptive tables and figures will be presented for immune markers. Overall (OS) and relapse-free survival (RFS) will be calculated and plotted by Kaplan-Meier methods[69]. Relationships between baseline characteristics, immune markers, and outcomes (response, OS, or RFS) will be explored with logistic or Cox[70] models as patient numbers allow. No formal hypotheses will be tested, but results will be used to design the next formal trial if toxicity and feasibility are reasonable for further investigation.

The Investigator is responsible for completing a futility/toxicity summary report, and submitting it to the IND Office Medical Affairs and Safety Group, for review and approval. This should be submitted after the first 3 evaluable patients per cohort, have surgery or 4 weeks after the first dose of immune-therapy, whichever comes first, and

every 2 to 4 evaluable patients thereafter, according to the schedule described in the toxicity/futility monitoring tables.

On every summary submission, futility information about previous reported patients will need to be updated to week eight.

A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

REFERENCES

1. Siegel, R., et al., *Cancer statistics, 2014.* CA Cancer J Clin, 2014. **64**(1): p. 9-29.
2. Scheele, J., et al., *Resection of colorectal liver metastases.* World J Surg, 1995. **19**(1): p. 59-71.
3. Adam, R. and E. Vinet, *Regional treatment of metastasis: surgery of colorectal liver metastases.* Ann Oncol, 2004. **15 Suppl 4**: p. iv103-6.
4. Parkin, D.M., et al., *Global cancer statistics, 2002.* CA Cancer J Clin, 2005. **55**(2): p. 74-108.
5. Leporrier, J., et al., *A population-based study of the incidence, management and prognosis of hepatic metastases from colorectal cancer.* Br J Surg, 2006. **93**(4): p. 465-74.
6. Ismaili, N., *Treatment of colorectal liver metastases.* World J Surg Oncol, 2011. **9**: p. 154.
7. Choti, M.A., et al., *Trends in long-term survival following liver resection for hepatic colorectal metastases.* Ann Surg, 2002. **235**(6): p. 759-66.
8. Abdalla, E.K., et al., *Improving resectability of hepatic colorectal metastases: expert consensus statement.* Ann Surg Oncol, 2006. **13**(10): p. 1271-80.
9. Gallagher, D.J., et al., *Response to neoadjuvant chemotherapy does not predict overall survival for patients with synchronous colorectal hepatic metastases.* Ann Surg Oncol, 2009. **16**(7): p. 1844-51.
10. Aloia, T.A., et al., *Solitary colorectal liver metastasis: resection determines outcome.* Arch Surg, 2006. **141**(5): p. 460-6; discussion 466-7.
11. Kanas, G.P., et al., *Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors.* Clin Epidemiol, 2012. **4**: p. 283-301.
12. Nordlinger, B., et al., *Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie.* Cancer, 1996. **77**(7): p. 1254-62.
13. Mitry, E., et al., *Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials.* J Clin Oncol, 2008. **26**(30): p. 4906-11.
14. Nordlinger, B., et al., *Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial.* Lancet Oncol, 2013. **14**(12): p. 1208-15.
15. Kemeny, N.E. and M. Gonen, *Hepatic arterial infusion after liver resection.* N Engl J Med, 2005. **352**(7): p. 734-5.
16. Andre, T., et al., *Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial.* J Clin Oncol, 2009. **27**(19): p. 3109-16.
17. Tournigand, C., et al., *FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study.* J Clin Oncol, 2004. **22**(2): p. 229-37.
18. Haller, D.G., et al., *Potential regional differences for the tolerability profiles of fluoropyrimidines.* J Clin Oncol, 2008. **26**(13): p. 2118-23.
19. Saltz, L.B., et al., *Irinotecan fluorouracil plus leucovorin is not superior to fluorouracil plus leucovorin alone as adjuvant treatment for stage III colon cancer: results of CALGB 89803.* J Clin Oncol, 2007. **25**(23): p. 3456-61.

20. Van Cutsem, E., et al., *Randomized phase III trial comparing biweekly infusional fluorouracil/leucovorin alone or with irinotecan in the adjuvant treatment of stage III colon cancer: PETACC-3.* J Clin Oncol, 2009. **27**(19): p. 3117-25.
21. Ychou, M., et al., *A phase III randomised trial of LV5FU2 + irinotecan versus LV5FU2 alone in adjuvant high-risk colon cancer (FNCLCC Accord02/FFCD9802).* Ann Oncol, 2009. **20**(4): p. 674-80.
22. Puri, S., M. Chatwal, and J.E. Gray, *Anti PD-L1 combined with other agents in non-small cell lung cancer: combinations with non-immuno-oncology agents.* Expert Rev Respir Med, 2017. **11**(10): p. 791-805.
23. Forde, P.M., et al., *Neoadjuvant PD-1 Blockade in Resectable Lung Cancer.* N Engl J Med, 2018. **378**(21): p. 1976-1986.
24. Hanahan, D. and R.A. Weinberg, *Hallmarks of cancer: the next generation.* Cell, 2011. **144**(5): p. 646-74.
25. Shields, J.D., et al., *Induction of lymphoidlike stroma and immune escape by tumors that express the chemokine CCL21.* Science, 2010. **328**(5979): p. 749-52.
26. Monti, S., et al., *Molecular profiling of diffuse large B-cell lymphoma identifies robust subtypes including one characterized by host inflammatory response.* Blood, 2005. **105**(5): p. 1851-61.
27. Gooden, M.J., et al., *The prognostic influence of tumour-infiltrating lymphocytes in cancer: a systematic review with meta-analysis.* Br J Cancer, 2011. **105**(1): p. 93-103.
28. Baitsch, L., et al., *The three main stumbling blocks for anticancer T cells.* Trends Immunol, 2012. **33**(7): p. 364-72.
29. Crespo, J., et al., *T cell anergy, exhaustion, senescence, and stemness in the tumor microenvironment.* Curr Opin Immunol, 2013. **25**(2): p. 214-21.
30. Wolchok, J.D., et al., *Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria.* Clin Cancer Res, 2009. **15**(23): p. 7412-20.
31. Hodi, F.S., et al., *Improved survival with ipilimumab in patients with metastatic melanoma.* N Engl J Med, 2010. **363**(8): p. 711-23.
32. Robert, C., et al., *Ipilimumab plus dacarbazine for previously untreated metastatic melanoma.* N Engl J Med, 2011. **364**(26): p. 2517-26.
33. Brahmer, J.R., et al., *Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates.* J Clin Oncol, 2010. **28**(19): p. 3167-75.
34. Topalian, S.L., et al., *Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer.* New England Journal of Medicine, 2012. **366**(26): p. 2443-2454.
35. Brahmer, J.R., et al., *Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer.* New England Journal of Medicine, 2012. **366**(26): p. 2455-2465.
36. Harzstark, A.L. and E.J. Small, *Castrate-resistant prostate cancer: therapeutic strategies.* Expert Opin Pharmacother, 2010. **11**(6): p. 937-45.
37. Slovin, S.F., et al., *Ipilimumab alone or in combination with radiotherapy in metastatic castration-resistant prostate cancer: results from an open-label, multicenter phase I/II study.* Ann Oncol, 2013. **24**(7): p. 1813-21.
38. Royal, R.E., et al., *Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma.* J Immunother, 2010. **33**(8): p. 828-33.
39. Calabro, L., et al., *Tremelimumab for patients with chemotherapy-resistant advanced malignant mesothelioma: an open-label, single-arm, phase 2 trial.* Lancet Oncol, 2013. **14**(11): p. 1104-11.

40. Oganesyan, V., et al., *Structural characterization of a human Fc fragment engineered for lack of effector functions.* Acta Crystallogr D Biol Crystallogr, 2008. **64**(Pt 6): p. 700-4.
41. Hamanishi, J., et al., *Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer.* Proc Natl Acad Sci U S A, 2007. **104**(9): p. 3360-5.
42. Inman, B.A., et al., *PD-L1 (B7-H1) expression by urothelial carcinoma of the bladder and BCG-induced granulomata: associations with localized stage progression.* Cancer, 2007. **109**(8): p. 1499-505.
43. Ishida, M., et al., *Differential expression of PD-L1 and PD-L2, ligands for an inhibitory receptor PD-1, in the cells of lymphohematopoietic tissues.* Immunol Lett, 2002. **84**(1): p. 57-62.
44. Keir, M.E., et al., *PD-1 and Its Ligands in Tolerance and Immunity.* Annual Review of Immunology, 2008. **26**(1): p. 677-704.
45. Latchman, Y., et al., *PD-L2 is a second ligand for PD-1 and inhibits T cell activation.* Nat Immunol, 2001. **2**(3): p. 261-8.
46. Nakanishi, J., et al., *Overexpression of B7-H1 (PD-L1) significantly associates with tumor grade and postoperative prognosis in human urothelial cancers.* Cancer Immunol Immunother, 2007. **56**(8): p. 1173-82.
47. Thompson, R.H., et al., *Costimulatory B7-H1 in renal cell carcinoma patients: Indicator of tumor aggressiveness and potential therapeutic target.* Proc Natl Acad Sci U S A, 2004. **101**(49): p. 17174-9.
48. Tseng, S.Y., et al., *B7-DC, a new dendritic cell molecule with potent costimulatory properties for T cells.* J Exp Med, 2001. **193**(7): p. 839-46.
49. Bennett, F., et al., *Program death-1 engagement upon TCR activation has distinct effects on costimulation and cytokine-driven proliferation: attenuation of ICOS, IL-4, and IL-21, but not CD28, IL-7, and IL-15 responses.* J Immunol, 2003. **170**(2): p. 711-8.
50. Carter, L., et al., *PD-1:PD-L inhibitory pathway affects both CD4(+) and CD8(+) T cells and is overcome by IL-2.* Eur J Immunol, 2002. **32**(3): p. 634-43.
51. Fife, B.T. and J.A. Bluestone, *Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways.* Immunol Rev, 2008. **224**: p. 166-82.
52. Freeman, G.J., et al., *Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation.* J Exp Med, 2000. **192**(7): p. 1027-34.
53. Nurieva, R., et al., *T-cell tolerance or function is determined by combinatorial costimulatory signals.* EMBO J, 2006. **25**(11): p. 2623-33.
54. Saunders, P.A., et al., *PD-L2:PD-1 involvement in T cell proliferation, cytokine production, and integrin-mediated adhesion.* Eur J Immunol, 2005. **35**(12): p. 3561-9.
55. Krummel, M.F. and J.P. Allison, *CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation.* J Exp Med, 1995. **182**(2): p. 459-65.
56. Walunas, T.L., et al., *Pillars article: CTLA-4 can function as a negative regulator of T cell activation. Immunity. 1994. 1: 405-413.* J Immunol, 2011. **187**(7): p. 3466-74.
57. Brunner, M.C., et al., *CTLA-4-Mediated inhibition of early events of T cell proliferation.* J Immunol, 1999. **162**(10): p. 5813-20.
58. Greenwald, R.J., et al., *CTLA-4 regulates induction of anergy in vivo.* Immunity, 2001. **14**(2): p. 145-55.
59. Hay, C.M., et al., *Targeting CD73 in the tumor microenvironment with MEDI9447.* Oncoimmunology, 2016. **5**(8): p. e1208875.
60. Geoghegan, J.C., et al., *Inhibition of CD73 AMP hydrolysis by a therapeutic antibody*

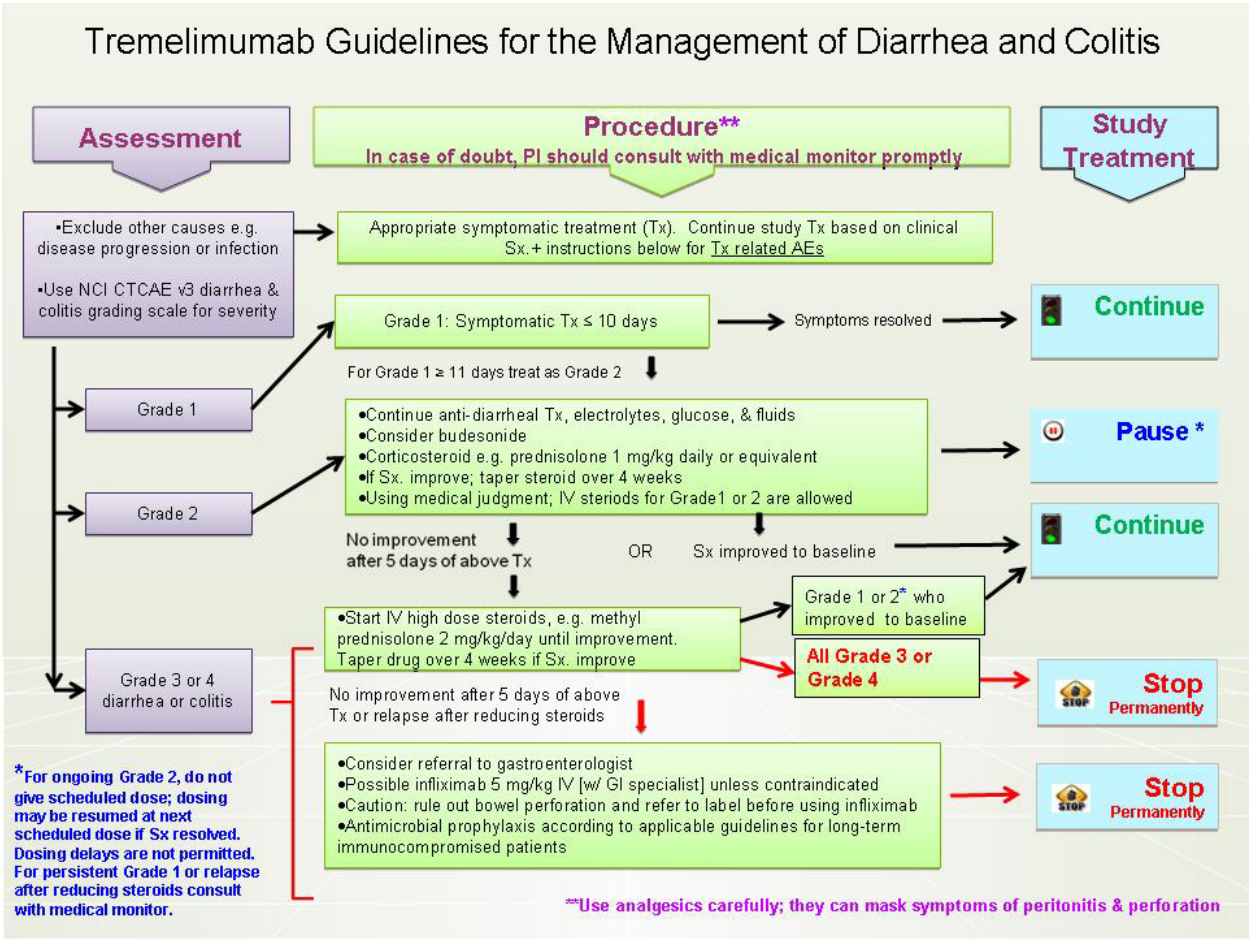
with a dual, non-competitive mechanism of action. MAbs, 2016. **8**(3): p. 454-67.
61. Pardoll, D.M., *The blockade of immune checkpoints in cancer immunotherapy.* Nat Rev Cancer, 2012. **12**(4): p. 252-64.
62. Antonia, S., et al., *Clinical Activity and Safety of MEDI4736, an Anti-programmed Cell Death Ligand-1 (PD-L1) Antibody, in Patients with NSCLC*, in *European Society for Medical Oncology (ESMO) Meeting*. 2014: Madrid, Spain.
63. Antonia, S., et al., *A Phase 1 Open-label Study to Evaluate the Safety and Tolerability of MEDI4736, an Anti-programmed Cell Death-ligand 1 (PD-L1) Antibody, in Combination with Tremelimumab in Patients with Advanced Non-small Cell Lung Cancer (NSCLC)*, in *European Society of Medical Oncology (ESMO) Meeting*. 2014: Madrid, Spain.
64. Wolchok, J.D., et al., *Nivolumab plus ipilimumab in advanced melanoma.* N Engl J Med, 2013. **369**(2): p. 122-33.
65. Weber, J.S., K.C. Kahler, and A. Hauschild, *Management of immune-related adverse events and kinetics of response with ipilimumab.* J Clin Oncol, 2012. **30**(21): p. 2691-7.
66. Thall, P.F., R.M. Simon, and E.H. Estey, *Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes.* Stat Med, 1995. **14**(4): p. 357-79.
67. Thall, P.F. and H.G. Sung, *Some extensions and applications of a Bayesian strategy for monitoring multiple outcomes in clinical trials.* Statistics in Medicine, 1998. **17**(14): p. 1563-1580.
68. Zimmitti, G., et al., *Greater complexity of liver surgery is not associated with an increased incidence of liver-related complications except for bile leak: an experience with 2,628 consecutive resections.* J Gastrointest Surg, 2013. **17**(1): p. 57-64; discussion p 64-5.
69. Kaplan, E.L. and P. Meier, *Nonparametric estimator from incomplete observations. . J Am Stat Assoc* 1958. **53**: p. 457-481.
70. Cox, D.R., *Regression Models and Life-Tables.* Journal of the Royal Statistical Society Series B-Statistical Methodology, 1972. **34**(2): p. 187-+.
71. Panel, N.I.-S.E., et al., *Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel.* J Allergy Clin Immunol, 2010. **126**(6 Suppl): p. S1-58.

APPENDIX 1

Performance Status Criteria

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

APPENDIX 2


Tremelimumab Guidelines for the Management of Diarrhea and Colitis
Assessment
Procedure**
In case of doubt, PI should consult with medical monitor promptly
Study Treatment
•Exclude other causes e.g. disease progression or infection
•Use NCI CTCAE v3 diarrhea & colitis grading scale for severity
Appropriate symptomatic treatment (Tx). Continue study Tx based on clinical Sx.+ instructions below for Tx related AEs
Grade 1
Grade 2
Grade 3 or 4 diarrhea or colitis
Grade 1: Symptomatic Tx ≤ 10 days
Symptoms resolved
Continue
For Grade 1 ≥ 11 days treat as Grade 2
•Continue anti-diarrheal Tx, electrolytes, glucose, & fluids
•Consider budesonide
•Corticosteroid e.g. prednisolone 1 mg/kg daily or equivalent
•If Sx. improve; taper steroid over 4 weeks
•Using medical judgment; IV steriods for Grade1 or 2 are allowed
Pause *
No improvement after 5 days of above Tx
OR
Sx improved to baseline
Continue
•Start IV high dose steroids, e.g. methyl prednisolone 2 mg/kg/day until improvement. Taper drug over 4 weeks if Sx. improve
Grade 1 or 2* who improved to baseline
All Grade 3 or Grade 4
Stop Permanently
No improvement after 5 days of above Tx or relapse after reducing steroids
•Consider referral to gastroenterologist
•Possible infliximab 5 mg/kg IV [w/ GI specialist] unless contraindicated
•Caution: rule out bowel perforation and refer to label before using infliximab
•Antimicrobial prophylaxis according to applicable guidelines for long-term immunocompromised patients
Stop Permanently
*For ongoing Grade 2, do not give scheduled dose; dosing may be resumed at next scheduled dose if Sx resolved. Dosing delays are not permitted. For persistent Grade 1 or relapse after reducing steroids consult with medical monitor.
**Use analgesics carefully; they can mask symptoms of peritonitis & perforation

Appendix 3
National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network guidance for Anaphylaxis Diagnosis

The NIAID and FAAN define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death [71]. They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to > 95% of all cases of anaphylaxis (for all 3 categories).

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips, tongue, uvula)
AND AT LEAST ONE OF THE FOLLOWING:
a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline.