A Phase II, open label, clinical trial of pre-surgical and adjuvant treatment of recurrent Glioblastoma with Tremelimumab and Durvalumab (MEDI4736) alone and in combination to determine immunologic changes from treatment

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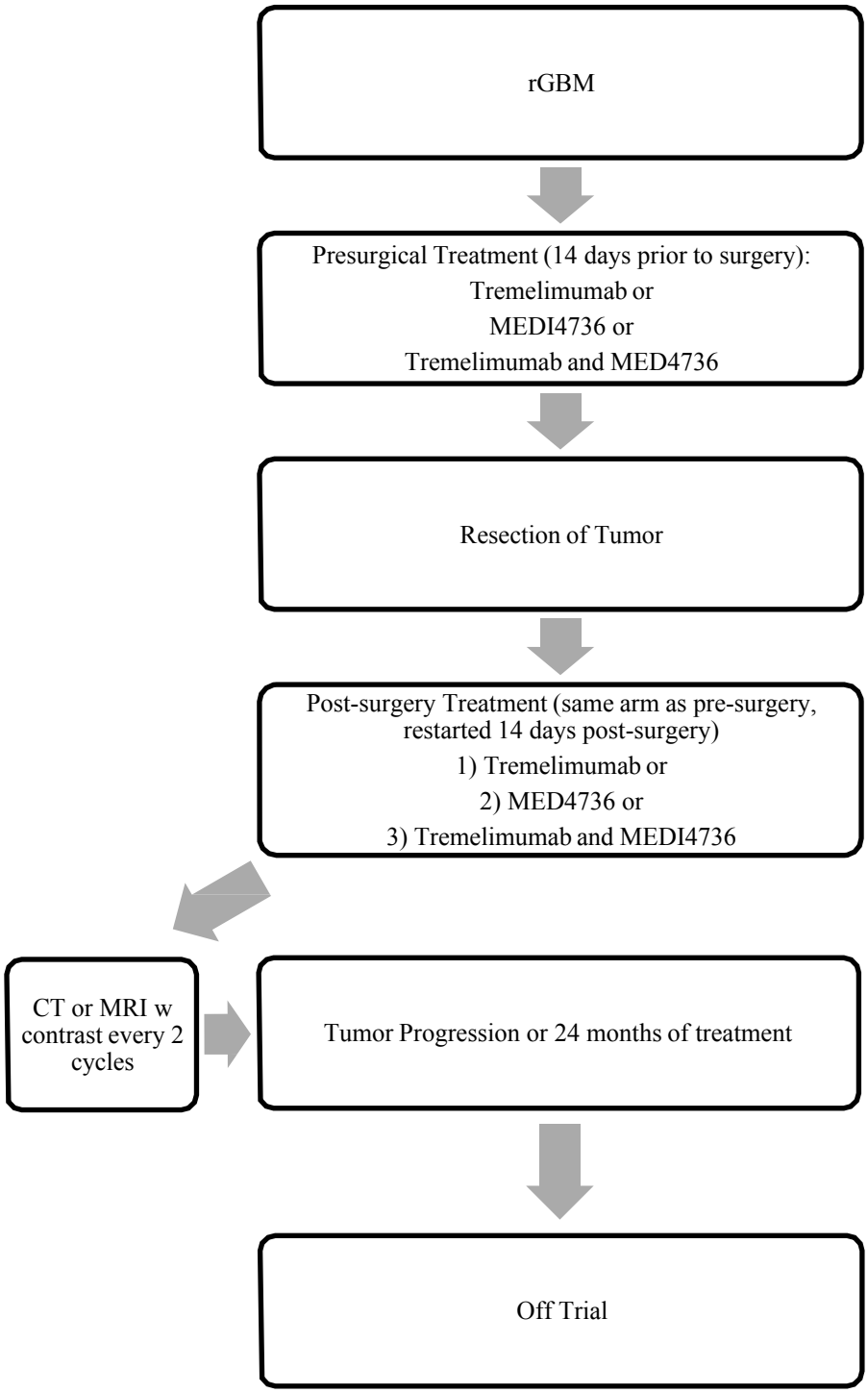
LIST OF ABBREVIATIONS

AE	Adverse Event
AChE	Acetylcholine esterase
ADA	American Dietetic Association
ADL	Activities of Daily Living
AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
ALP	Alkaline phosphatase
AST	Aspartate Aminotransferase
aPTT	Activated Partial Thromboplastin Time
ASCO	American Society of Clinical Oncology
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
FT4	Free Thyroxine
GI	Gastrointestinal
H&PE	History & Physical Exam
INR	International Normalized Ratio
irAE	Immune- Related Adverse Event
IRR	Infusion Related Reaction
IDS	Infectious Disease Service
ILD	Interstitial Lung Disease
IM	Intramuscular
IV	Intravenous
IVIG	Intravenous Immunoglobulin
KPS	Karnofsky Performance Status
LFT	Liver Function Test
LLN	Lower Limit of Normal MTD
	Maximum Tolerated Dose
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
ORR	Overall Response Rate or Objective Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PCP	Pneumocystis Pneumonia
PD	Progressive Disease
PFS	Progression Free Survival
PO (or p.o.)	Per os/by mouth/orally
PR	Partial Response
PT	Prothrombin time
PTT	Partial Thromboplastin Time
RT	Radiotherapy
RANO	Response Assessment in Neuro-Oncology
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase

TB	Total Bilirubin
TMZ	Temozolomide
TNF	Tumor Necrosis factor
TFTs	Thyroid function tests
TSH	Thyroid Stimulating Hormone
ULN	Upper limit of normal
WBC	White Blood Cells

STUDY SCHEMA



STUDY SUMMARY

Title	A Phase II, open label, single center study of pre-surgical and adjuvant treatment of recurrent glioblastoma with Tremelimumab and MEDI4736 alone and in combination to determine immunologic changes from treatment.
Version	11.29.18
Study Design	Phase II trial
Study Center(s)	Robert H. Lurie Cancer Center of Northwestern University.
Objectives	Primary: 1) To determine the T-cell changes that occur in recurrent GBM treated with tremelimumab and durvalumab as single agents and in combination. Secondary: 1) To evaluate the safety of either tremelimumab or MEDI4736 alone and in combination in patients with recurrent GBM. 2) To determine post-surgery, the time to progression (per Modified RANO criteria and iRANO criteria, see below) for patients treated with either Tremelimumab or MEDI4736 alone and in combination of both. 3) To determine post-surgery, the overall survival for patients treated with Tremelimumab or MEDI4736 alone and in combination of both. 4) To assess post-surgery, the MRI changes in patients treated with either Tremelimumab or MEDI4736 alone and in combination of both. Exploratory: To correlate T-cell changes and PDL1 expression with patient outcomes.
Sample Size	There will be three groups of patients, one group on each agent alone and one group treated with the combination agents. A total of 10 evaluable patients per group will be necessary for study endpoints. To attain 10 patients in each arm who are evaluable for the primary endpoint, a total of 45 patients will be accrued to the study. Sample sizes of 10 per group allow for the estimation of the proportion of responders in evaluable patients to be within 31% of its true value with 95% confidence. Mean change will be compared between arms. Using standard deviations of change, a sample size of 10 per group will allow the detection of differences of 1.25 standard deviations between groups with 80% power assuming a two-tailed test and a Type I error rate of 5%.

Key Eligibility Criteria	1) Patients must have a grade IV glioma that has failed standard RT and TMZ. 2) Patients must have had radiographic evidence of tumor progression by brain MRI or CT scan with contrast. 3) Patients must be > 12 weeks from completion of radiation therapy unless there is tissue confirmation of tumor recurrence or there is progression outside the radiation treatment field. 4) Prior therapy with gamma knife or other focal high-dose radiotherapy is allowed, but the patient must have subsequent histologic documentation of recurrence, unless the recurrence occurs remote from the treated site. 5) Patients must be surgical resection candidates. 6) Have resolved toxicity (>CTCAE grade < 2) from previous anti-cancer therapy. 7) Life expectancy of ≥ 12 weeks 8) Patients can only be on non-enzyme inducing anti-convulsants. If they are on an enzyme inducing anti-convulsant, they may be converted to a non-enzyme inducing anti-convulsants but they will need a 2 week wash out period from time of drug discontinuation.
Treatment Plan	Patients will be randomly assigned to each arm using block randomization. Treatment Arms: Arm 1) Tremelimumab- 75 mg every 4 weeks. The 1st dose will be given 14 days pre-surgery. The drug will be restarted 14 days after surgery once the surgical wound has healed and then every 4 weeks after surgery. If there is no progression of disease, they will continue on treatment for up to 24 months. Arm 2) MEDI4736- 750 mg every 2 weeks. The 1st dose will be given 14 days pre-surgery. The drug will be restarted 14 days after surgery once the surgical wound has healed and then every 2 weeks after surgery. If there is no progression of disease, they will continue on treatment for up to 24 months Arm 3) Tremelimumab 75 mg + MEDI4736 750mg. The 1st dose will be given 14 days pre-surgery. The drug will be restarted 14 days after surgery once the surgical wound has healed. Tremelimumab will be administered IV every 4 weeks (Day 1 of each cycle) and MEDI4736 750mg every 2 weeks (Day 1 and Day 15 of each cycle) until the patients have received 7 doses of Tremelimumab and 14 doses of MEDI4736. Thereafter, from Cycle 7 (Week 25), Tremelimumab will be given every 12 weeks (+/-7 days) and MEDI4736 will be given every 2 weeks (+/- 2 days) until permanent discontinuation criteria (e.g. disease progression) is met. If there is no progression of disease, they will continue on treatment for up to 24 months.

Statistical Methodology	Immunologic measures will be summarized over the three or more time points (pre-treatment, following first treatment/pre-surgery, and post-surgery) and changes in these measures will be assessed using repeated measures analysis of variance or Cochran's Q, followed by the paired t-test or the signed rank test for pairwise comparisons using Bonferroni corrections. Safety of the agents alone or in combination will be assessed by summarizing the frequency of adverse events by type, timing, grade and attribution. Immunologic changes will be correlated with MRIs in a descriptive fashion. The secondary endpoint of progression-free survival as well as overall survival will be analyzed using Kaplan-Meier curves. Immunologic changes of T-cells and PDL1 levels will be correlated to survival outcomes using Cox regression analysis. MRI changes will be summarized using means or proportions and statistically analyzed using the signed rank test.

1.0 INTRODUCTION – BACKGROUND & RATIONALE

1.1 Disease Background

Malignant gliomas are unfortunately a uniformly fatal tumor in most cases. Despite aggressive surgery, radiation treatment (RT) and chemotherapy at initial diagnosis these tumors almost always recur. Patients seen in academic centers are often recruited to clinical trials that utilize novel agents in combination with standard therapy in newly diagnosed patients or those with recurrent disease. We know that gliomas are highly vascular tumors and there is data from the "Brain Trial" and "NIH trial" showing high response rates and reasonably good progression free survival at 6 months for patients treated with bevacizumab. [1,2] Unfortunately, data using bevacizumab in newly diagnosed patients with GBM did not provide any survival benefit but it did improve PFS at 6 months in the AVAGLIO trial but not RTOG trial. [3]

1.1.2 Glioblastoma

For clinical trials in glioblastoma (GBM), many have looked at target specific agents added to standard therapy; however none of them has been of benefit to date. There've also been a few trials looking at patients with an unmethylated MGMT promoter but none have shown a significant impact in this patient population, but it remains a group where more work is needed.

More novel approaches in oncology and in neuro-oncology are to use immunologic therapies. In GBM, there are vaccine therapies that are either derived from the patient's known tumor (HSPPC-96) or are designed to target specific epitopes on the tumor cells such as EGFRvIII (CDX-110) or a number of other epitopes (ICT-107) targeted by other vaccines. Phase II data using CDX-110, ICT 107, HSPPC-96 and others have shown some promise. While preliminary data looks promising with these agents, the most advanced has not proven effective in a randomized phase 3 study (ICT-107) (Press Release) but data will be emerging on CDX-110 as the trial is completing enrollment.

Currently there are several agents under investigation that target the local tumor immune-protection in solid tumors-particularly melanoma, such CTLA-4 blockade, PD1 and PDL1 blockade. While the majority of trials have occurred in melanoma, there is recent data in other cancers such as renal cell and small cell lung cancer [4,5,6]. While expected in melanoma and renal cell due to immunologic aspects of these diseases, the efficacy in other tumors was less clear but benefit has been shown in lung cancer. Recently MK-3475 was approved in US for advanced melanoma.

A recent review highlighted the many immunologic approaches to GBM. [7] More relevant to gliomas is the research that shows gliomas can upregulate B7-H1 expression in circulating monocytes and tumor-infiltrative macrophages through modulation of autocrine/paracrine IL-10 signaling, resulting in an immunosuppressive phenotype. [8] Glioma-associated cancer-initiating cells have been shown to express the co-stimulatory inhibitory molecule B7-H1 [9] which has previously been shown to be a key factor mediating immune resistance in gliomas [10] and can induce T-cell apoptosis [11]. Direct cell-to-cell contact experiments have shown that the glioma-associated cancer-initiating cells induced T-cell apoptosis in the setting of B7-H1 expression. [9] Wei et al. [9] found that cancer-initiating cells markedly inhibited T-cell proliferation and activation, induced regulatory T cells, and triggered T-cell apoptosis that was mediated by B7-H1 and soluble Galectin-3. Loss of tumor suppressor PTEN function increases B7-H1 expression and immunoresistance in glioma. [10] It also been shown that glioma associated cancer initiating cells induce immunosuppression thereby allowing tumor cells to evade immunosurveillance. Yao et al. [12] found that B7-H1 was correlated with the malignancy

grade of human astrocytic tumors, but preferentially in the non-dividing tumor cells. It was also upregulated at the growing edge of the tumors and had a negative correlation with tumor-infiltrating CD8T-cells.

Importantly, tumor infiltrating lymphocytes and PD-L1 expression are seen in the majority of GBM samples [13] and rationale for these using checkpoint inhibitors is reviewed by Kim and Lim [14].

1.2 PD-1 and PD-1

Immune responses directed against tumors are one of the body's natural defenses against the growth and proliferation of cancer cells. However, over time and under pressure from immune attack, cancers develop strategies to evade immune-mediated killing allowing them to develop unchecked. One such mechanism involves upregulation of surface proteins that deliver inhibitory signals to cytotoxic T cells. Programmed cell death ligand 1 (PD-L1) is one such protein, and is upregulated in a broad range of cancers with a high frequency, with up to 88% expression in some tumor types. In a number of these cancers, including lung [15], renal [16-18], pancreatic [19, 20], ovarian cancer [21], and hematologic malignancies [22, 23] tumor cell expression of PD-L1 is associated with reduced survival and an unfavorable prognosis.

Programmed cell death ligand 1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 acts at multiple sites in the body to help regulate normal immune responses and is utilized by tumors to help evade detection and elimination by the host immune system tumor response. In the lymph nodes, PD-L1 on antigen-presenting cells binds to PD-1 or CD80 on activated T cells and delivers an inhibitory signal to the T cell (Keir, 2008}. This results in reduced T-cell activation and fewer activated T cells in circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 and CD80 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T cells, preventing them from killing target cancer cells and protecting the tumor from immune elimination (Zou and Chen, 2008).

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades[24]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies.[11, 25-28] In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). [29, 30] The structure of murine PD-1 has been resolved [9]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. [29, 31-33] The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [13; 14]. PD-1 was shown to be expressed on

activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells.[34, 35] Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. [36] The ligands for

PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. [36-39] Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. [40] Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). [41] This suggests that the PD-1/PD-L1

pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

MEDI4736 is being developed as a potential anticancer therapy for patients with advanced solid tumors. MEDI4736 is a human monoclonal antibody (MAb) of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of programmed cell death ligand 1 (PD-L1) (B7 homolog 1 [B7-H1], cluster of differentiation [CD]274) to programmed cell death 1 (PD-1; CD279) and CD80 (B7-1). MEDI4736 is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. MEDI4736 contains a triple mutation in the constant domain of the immunoglobulin (Ig) G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma (Fcγ) receptors involved in triggering effector function.

1.3 Durvalumab (MEDI4736) Background

MEDI4736 is being developed as a potential anticancer therapy for patients with advanced solid tumors. MEDI4736 is a human monoclonal antibody (MAb) of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of programmed cell death ligand 1 (PD-L1) (B7 homolog 1 [B7-H1], cluster of differentiation [CD] 274) to programmed cell death 1 (PD-1; CD279) and CD80 (B7-1). MEDI4736 is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. MEDI4736 contains a triple mutation in the constant domain of the immunoglobulin (Ig) G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma (Fcγ) receptors involved in triggering effector function.

1.3.1 Summary of non-clinical experience

MEDI4736 binds with high affinity and specificity to human PD-L1 and blocks its interaction with PD-1 and CD80. *In vitro* studies demonstrate that MEDI4736 antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFN-γ). Additionally, MEDI4736 demonstrated a lack of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) in cell-based functional assays. In vivo studies show that MEDI4736 inhibits tumor growth in a xenograft model via a T lymphocyte (T-cell) dependent mechanism. Moreover, an anti-mouse PD-L1 antibody demonstrated improved survival in a syngeneic tumor model when given as monotherapy and resulted in complete tumor regression in > 50% of treated mice when given in combination with chemotherapy. Combination therapy (dual targeting of PD-L1 and cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4]) resulted in tumor regression in a mouse model of colorectal cancer.

Cynomolgus monkeys were selected as the only relevant species for evaluation of the pharmacokinetics (PK)/pharmacodynamics and potential toxicity of MEDI4736. Following intravenous (IV) administration, the PK of MEDI4736 in cynomolgus monkeys was nonlinear. Systemic clearance (CL) decreased and concentration half-life (t1/2) increased with increasing doses, suggesting saturable target binding-mediated clearance of MEDI4736. No apparent gender differences in PK profiles were observed for MEDI4736.

In general, treatment of cynomolgus monkeys with MEDI4736 was not associated with any MEDI4736-related adverse effects that were considered to be of relevance to humans. Adverse findings in the non-Good Laboratory Practice (GLP) PK/pharmacodynamics and dose range-finding study, and a GLP 4-week repeat-dose toxicity study were consistent with antidrug antibody (ADA)-associated morbidity and mortality in individual animals. The death of a single animal in the non-GLP, PK/pharmacodynamics, and dose range-

finding study was consistent with an ADA- associated acute anaphylactic reaction. 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:MEDI4736 immune complexes were identified in a subsequent non-GLP, investigative immunohistochemistry study. Similar observations were reported in cynomolgus monkeys administered human mAbs unrelated to MEDI4736. Given that immunogenicity of human mAbs in nonclinical species is generally not predictive of responses in humans, the ADA-associated morbidity and mortality were not considered for the determination of the no-observed-adverse-effect level (NOAEL) of MEDI4736.

Finally, data from the pivotal 3-month GLP toxicity study with MEDI4736 in cynomolgus monkeys showed that subchronic dosing of MEDI4736 was not associated with any adverse effects. Therefore, the NOAEL of MEDI4736 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 MEDI4736 to human or cynomolgus monkey tissues was observed in GLP tissue cross-reactivity studies using normal human and cynomolgus monkey tissues.

As of the data cutoff date of 14Jul2014, a total of 509 subjects have been enrolled and treated with MEDI4736 in 10 ongoing clinical studies: 5 employing MEDI4736 as monotherapy and 5 as combination therapy. No studies have yet been completed. Clinical experience with MEDI4736 is fully described in the current version of the MEDI4736 Investigator's Brochure.

1.3.2 Pharmacokinetics and Product Metabolism

MEDI4736 monotherapy exhibited nonlinear (dose-dependent) PK. The area under the concentration-time curve from 0 to 14 days (AUC0-14) increased in a greater than dose-proportional manner over the dose range of 0.1 to 15 mg/kg and approached linearity at ≥ 3 mg/kg, suggesting that the nonlinear PK of MEDI4736 is likely due to saturable target-mediated clearance. Exposures following multiple doses (currently up to a maximum of 26 doses) demonstrated accumulation consistent with PK parameters estimated from the first dose.

Suppression of free soluble PD-L1 (sPD-L1) was correlated with MEDI4736 PK concentrations. Following administration of MEDI4736 monotherapy, free sPD-L1 levels were below the lower limit of quantitation (LLOQ) in the majority of subjects with available data (n = 38) at all timepoints following IV doses ≥ 1 mg/kg every 2 weeks (Q2W).

Overall, a low incidence of ADA was observed. Of the 220 subjects who received MEDI4736 monotherapy and for whom PK/ADA data were available, 5 were detected ADA positive, with an impact on PK/pharmacodynamics reported in 1 subject.

1.3.3 Safety

As of 14Jul2014, no identified risks are clearly associated with the use of MEDI4736. Important potential risks based on the mechanism of action of MEDI4736 and its related molecules include immune-mediated reactions such as enterocolitis, dermatitis, hepatitis/hepatotoxicity, endocrinopathy, pneumonitis, and neuropathy. Additional important potential risks include infusion-related reactions, hypersensitivity, serious allergic reactions, serious infections, and immune complex disease.

The majority of the safety data are from the monotherapy study, CD-ON-MEDI4736-1108, specifically the 10 mg/kg Q2W cohort (N = 393). In this cohort, the most frequently reported (≥ 10% of subjects) adverse events (AEs; all grades, regardless of causality) were fatigue (29.8%), nausea (20.1%), dyspnea (19.6%), decreased appetite (19.1%), constipation (14.0%), diarrhea and vomiting (12.5% each), cough (11.5%), pyrexia and back pain (10.4% each), and rash (10.2%). In approximately half of the subjects, the highest AE severity was Grade 1 (25.2% of subjects) or Grade 2 (22.9% of subjects). Most of these events were managed clinically without the need for dose modifications or

delays. Grade 3 or higher AEs that occurred in > 1% of subjects were dyspnea (5.1%), increased gamma-glutamyltransferase (3.3%), fatigue, general physical health deterioration, increased aspartate aminotransferase, and back pain (2.3% each), anemia and dehydration (1.8% each), and abdominal pain, vomiting, sepsis, syncope, and hypotension (1.3% each). Treatment-related Grade 3 AEs in 2 or more subjects were fatigue (4 subjects), increased gamma-glutamyltransferase (3 subjects), and vomiting, increased alanine aminotransferase, increased aspartate aminotransferase, and arthralgia (2 subjects each). There were 2 subjects with treatment-related Grade 4 events (hypercalcemia, fatigue) and 1 subject with a treatment-related Grade 5 event (angiopathy). In general, Grade 3 or higher AEs were manageable and reversible with standard toxicity management guidelines.

Serious adverse events (SAEs) and other significant AEs occurred in fewer than one-third of subjects treated with MEDI4736 10 mg/kg Q2W in Study CD-ON-MEDI4736-1108. The most frequently reported SAEs (regardless of causality; > 5 subjects) were dyspnea (15 subjects), general physical health deterioration (9 subjects), pyrexia (8 subjects), back pain and abdominal pain (7 subjects each), and dehydration and pleural effusion (6 subjects each). One subject (with Stage IV lung cancer and a history of cardiac disease) died due to angiopathy considered by the investigator as related to MEDI4736. Adverse events that resulted in permanent discontinuation of MEDI4736 in ≥ 2 subjects were dyspnea (7 subjects), general physical health deterioration (5 subjects), and death, increased transaminases, pulmonary embolism, and respiratory failure (2 subjects each).

No dose-limiting toxicities (DLTs) have been reported in any of the dose-escalation cohorts of the monotherapy studies. Overall, the AE profile of MEDI4736 was consistent with the pharmacology of the target. No tumor types appeared to be associated with unique AEs.

This section summarizes the safety profile of MEDI4736 and data from studies in the context of relevant or similar therapies, AESIs that may impact the risk-benefit balance of MEDI4736. The probability of these events occurring with MEDI4736 use continue to be characterized based on the overall strength of evidence, from greatest to least, clinical data, nonclinical data, and pharmacologic class effects/mechanism of action. Clinically significant risks of interest include immune-mediated reactions such as enterocolitis, hepatitis/hepatotoxicity, dermatitis, neuropathy, endocrinopathy, pneumonitisand their associated signs and symptoms, risks due to immunogenicity and other events suchpotential risks.

All tabulations of treatment-emergent AEs are based on available clinical safety data from sponsored MEDI4736 clinical studies as serious infections, infusion-related of the DCO for this IB.

1.3.3.1 Immune-mediated Reactions

Immune-mediated reactions, anaphylaxis or /irAEs, also considered to be AESIs, are important risks of immune checkpoint inhibitors, and are being closely monitored in clinical studies with MEDI4736 monotherapy and combination therapy. irAEs observed with MEDI4736 include colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis, and nephritis. In addition, pancreatitis is an important potential risk particularly with MEDI4736 and tremelimumab combination therapy.

Other inflammatory responses with potential immune-mediated etiology reported with MEDI4736 and similar molecules include, but are not limited to, myocarditis, pericarditis, and uveitis.

Colitis

Immune-mediated colitis is an inflammation of the small intestine and/or colon caused by dysregulation of gastrointestinal mucosal immunity, and can involve any part of the bowel but most commonly the descending colon [42-44]. Endoscopic findings have revealed mucosal inflammation with ulceration and biopsies demonstrating neutrophilic, lymphocytic, or mixed neutrophilic- lymphocytic infiltrates [42, 45]. Mild to severe diarrhea is the most frequently observed sign/symptom potentially associated with immune-mediated colitis, and may be accompanied by other signs and symptoms including changes in bowel habits from baseline, abdominal pain, nausea/vomiting, or hematochezia. In severe cases, patients may experience significant dehydration, fever, peritoneal signs, bowel perforation, or ileus [46].

Across the Phase 1 to Phase 3 clinical studies with MEDI4736 monotherapy, as of the DCO dates for this IB, treatment-emergent colitis-type events, regardless of causality, were reported in 9 of 1,149 subjects (0.8%) receiving 10 mg/kg MEDI4736 IV Q2W. The time to onset ranged from 43 to 138 days post first dose. The severity of colitis was Grade 1 (1 case), Grade 2 (4 cases), Grade 3 (3 cases), and Grade 4 (1 case). Investigators are instructed to begin diarrhea management early to minimize the risk of colitis. Early initiation of diarrhea treatment guidelines has been shown to reduce bowel perforation and colectomy rates, drug- related diarrhea, and serious gastrointestinal irAEs by up to 50% in patients treated with ipilimumab [43].

Pneumonitis

Immune-mediated pneumonitis is characterized by inflammation focally or diffusely affecting the lung parenchyma that may be result of effects of checkpoint inhibitors against the normal lung parenchyma [47]. Presentations of

pneumonitis range from asymptomatic lung infiltrates to those that mimic severe bacterial pneumonia. For symptomatic patients, complaints and findings may include dyspnea, cough, tachypnea, pleuritic chest pain, and hypoxia.

In clinical studies with MEDI4736 monotherapy, as of the DCO dates for this IB, 23 of 1,149 subjects (2.0%) reported 24 serious allergic reaction, and immune complex and non- serious events (10 serious; 14 non-serious) of pneumonitis/interstitial lung disease across all doses and indications in 4 of the 5 open-label monotherapy studies (MEDI4736-1108, D4190C00002, D4190C00007, D4191C00003). There were no events from study D4193C00001. In the largest study population (Study CD-ON-MEDI4736-1108), the reporting rate of pneumonitis was highest at 1.8% (n/N = 13/736). Most AEs were non- serious and Grade 1 or 2 in severity. Across the MEDI4736 clinical studies, moderate to severe immune-mediated pneumonitis, as assessed by the investigator, was reported in 0.4% of subjects (n/N = 5/1,149). Time to onset for pneumonitis post first dose ranged from 4 to 10 weeks (4/5 subjects) to occurring 2 months after discontinuing MEDI4736 (1/5 subjects). With steroid treatment 80 mg/day, 2 subjects recovered within 3 days and 2 subjects within 1 to 2 weeks. One subject died from the event of pneumonitis and did not receive steroids as treatment for the event.

Hepatitis/Hepatotoxicity
Immune-mediated hepatitis/ hepatic toxicity is the inflammation of the liver due to the dysregulation of host immunity caused by immune checkpoint inhibitors and often manifests as asymptomatic elevated levels of hepatic transaminases (ALT, AST, bilirubin. In anti-CTLA-4-treated patients, clinical manifestations of hepatitis included nonspecific symptoms of mild fever, general weakness, fatigue, nausea and/or abdominal pain.

Across approximate 1,200 subjects who have received MEDI4736 monotherapy 10 mg/kg Q2W, 0.3% of subjects experienced an event of 'hepatitis'. One of the 4 subjects received steroids to treat the event. In Study CD-ON-MEDI4736-1108, 3 subjects (0.4%) reported an event of autoimmune hepatitis. Two of the 3 subjects were ≥ Grade 3, the other was Grade 2 in severity. In Study D4191C00003 Cohort 2, one event of hepatitis toxic was reported. The subject had elevated ALT and AST. MEDI4736 dosing was delayed and the subject received treatment with ursodeoxycholic acid and glutathione sodium. The events resolved and the subject continues on treatment with no further increases in liver enzymes.

Neuropathy/Neuromuscular Toxicity
Acquired peripheral neuropathies may be caused by infections or autoimmune disorders affecting nerve tissue. Some neuropathies are caused by inflammation resulting from immune system activities. Inflammatory neuropathies can develop quickly or slowly, and chronic forms can exhibit a pattern of alternating remission and relapse. Symptoms of peripheral neuropathy include numbness, tingling, paresthesia (pins and needles sensations), sensitivity to touch, or muscle weakness. In subjects with extreme symptoms, they may present with burning pain, muscle wasting, paralysis, or organ dysfunction. Acute inflammatory demyelinating neuropathy, better known as Guillain-Barre syndrome, can damage motor, sensory, and autonomic nerve fibers. Most people recover from this syndrome although severe cases can be life-threatening. Neuropathy can be difficult to assess due to the transient and non-specific nature of events. Subjects should be monitored for signs and symptoms that may include peripheral sensory neuropathy, muscle weakness, peripheral neuropathy including numbness, tingling, and sensitivity to touch.

Endocrinopathy
Immune-mediated endocrinopathy is the inflammation of any organ in the hypothalamic- pituitary-adrenal axis, but is most typically reported to affect the

pituitary, thyroid and/or adrenal glands in patients treated with checkpoint inhibitors, leading to hypophysitis, thyroid dysfunction, and/or adrenal insufficiency [48]. The clinical presentation of immune-mediated endocrinopathies most often include hypothyroidism, hyperthyroidism, and nonspecific symptoms of headache and fatigue, but may also include myalgias, visual field defects, behavioral changes, electrolyte disturbances, loss of appetite and hypotension [43]. Subjects will generally have abnormal endocrine laboratory test results that include thyroid-stimulating hormone, free T4, total and free T3, cortisol, adrenocorticotrophic hormone, luteinizing hormone, follicle-stimulating hormone, and testosterone.

Dermatitis

Immune-mediated dermatitis is generally mild and presents as mild local or diffuse maculopapular, erythematous rash on the trunk or extremities, which may be accompanied by pruritus, alopecia, and vitiligo, suggestive of inflammatory response to melanocytes [49]. In rare cases, severe dermatitis has been reported to manifest as Stevens-Johnson syndrome, toxic epidermal necrolysis, or rashes complicated by dermal ulceration or necrotic, bullous, or hemorrhagic manifestations [43, 46].

Nephritis

The major clinical syndromes produced by immune-mediated renal injury include nephrotic syndrome, rapidly progressive glomerulonephritis, and acute renal failure[50]. In association to immune-checkpoint inhibitors, two different forms of ipilimumab-induced renal damage are reported, acute kidney injury due to predominant acute granulomatous tubulointerstitial nephritis and nephrotic syndrome in lupus nephritis [51]. Signs and symptoms include increase in serum creatinine, decrease in urine output, peripheral edema, hematuria, loss of appetite. Subjects should be monitored for elevated serum creatinine prior to and periodically during treatment.

Pancreatitis

Immune-mediated pancreatitis, an important potential risk, is an inflammatory condition of the pancreas that typically manifests initially as asymptomatic elevations of amylase and lipase in patients treated with immune checkpoint inhibitors. Clinical presentation frequently includes low-grade abdominal pain with accompanying fever and malaise [52, 53] Biopsies showed diffuse T-cell infiltrate consistent with immune- mediated pancreatitis {Weber, 2012}. Across the clinical development program for ipilimumab, immune-mediated pancreatitis has been reported in ≤ 1% [i]to 3% of patients (Yervoy, 2015)[52, 53]. In monotherapy clinical studies of anti-PD-1 agents in melanoma, clinically significant immune-mediated pancreatitis was reported in < 1% of treated patients (Keytruda, 2015; Opdivo, 2015). Grade 3 or 4 treatment-related increased lipase was reported in 2% to 5% and increased amylase in < 10% of patients (Opdivo, 2015). In nivolumab and ipilimumab combination therapy studies, Grade 3 or 4 elevations in lipase and amylase were reported, respectively, in 16% and 5% of renal cell carcinoma patients, and 8% and 4% of NSCLC patients [44, 54]. Subjects should be monitored for signs and symptoms of pancreatitis including Grade 3 or 4 elevations in lipase and/or amylase. For Grade 3 and above asymptomatic amylase or lipase levels hold study drug/regimen and if complete work up shows no evidence of pancreatitis, may continue or resume study drug/regimen. In ongoing sponsored studies with MEDI4736 and

tremelimumab combination therapy, cumulatively, 4 serious events that occurred in 3 subjects (pancreatitis in 1 subject, pancreatitis acute in 1 subject, and amylase increased [redacted] and lipase increased in 1 subject) have been assessed by the investigator as related to MEDI4736 and tremelimumab combination therapy.

1.3.3.2 Hypersensitivity Reactions

Drugs that activate the immune system by delivering agonistic signals through activating receptors, such as CD28 [55]. Such agents, have an increased potential to

trigger systemic, nonspecific activation of T cells since they can exert their effects in the absence of any antigen-specific T-cell receptor signals. In contrast,

agents[55]. Agents that act via antagonism of an inhibitory pathway modulate an existing antigen-specific T--cell receptor signal and have a limited potential to drive systemic, nonspecific activation of T cells. This is exemplified clinically by molecules targeting CTLA--4 and PD--1, which are not associated with acute, severe adverse effects, such as cytokine storm [56, 57, 45]. Like these molecules, MEDI4736 antagonizes an inhibitory receptor (PD-L1).[45, 56, 57]. With the

administration of polyclonal immunoglobulin preparations and mAbs, major safety concerns associated with immunogenicity include serious allergic reactions and anaphylaxis, cytokine-release syndrome, infusion-related reactions, and delayed hypersensitivity associated to immune complex disease, which can potentially be severe or life-threatening leading to death.

Infusion-related Reactions

Adverse reactions that occur during or shortly after infusion may include fever, chills, hypotension, dyspnea, tachycardia, cyanosis, respiratory failure, urticarial and pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension rash, headache, flushing, sweating, myalgia, nausea, vomiting, unresponsiveness, and hemodynamic instability. The typical onset can be within 30 minutes to 2 hours after the initiation of drug infusion, although symptoms may be delayed for up to 24 hours. The majority of reactions occur after the first or second exposure to the agent, but between 10% and 30% occur during subsequent treatments {Lenz, 2007}. Cytokine-release syndrome is described as an exaggerated systemic immune response involving the potential release of more than 150 inflammatory mediators and occurs during or immediately after an infusion. Certain mAb therapeutics have been shown to induce a range of acute infusion reactions including cytokine-release syndrome that can lead to AEs in subjects.

In clinical studies with MEDI4736 as a monotherapy, the incidence of reported potential infusion-related reaction was low. In particular for the serious case reports of investigator assessed infusion-related reaction, 10 of 1,265 subjects treated with MEDI4736 in 5 sponsored monotherapy studies (CD-ON-MEDI4736-1108, D4190C00002, D4190C00007, D4191C00003, and D4193C00001) reported 14 cases of infusion-related reactions, giving an overall frequency of 0.8% (10/1,265). These events/reactions respond to antihistamine, drug interruption/withdrawal, decrease in infusion rate and supportive treatment. Comorbidities include concurrent systemic illnesses, history of allergies/asthma, multiple concomitant medications and recent history of infusion-related reactions.

Anaphylaxis and Serious Allergic Reactions

Anaphylaxis is a systemic, immediate hypersensitivity reaction that is mediated by interactions between factors released from IgE and mast cells; these interactions result in an antigen-antibody reaction. Clinical manifestations of acute allergic reactions may range from localized skin reactions at the injection site to AEs, which can include, but are not limited to, those events similar to infusion-related reactions. Severe reactions including anaphylaxis, drug hypersensitivity syndromes, Stevens-Johnson syndrome and toxic epidermal necrolysis are also associated with significant morbidity and mortality. These reactions are more common with higher doses, higher rates of infusion, and in subjects with a history of allergies. MEDI4736 antagonizes an inhibitory receptor (PD-L1). As such, in the absence of an antigen-specific T-cell receptor signal, inhibition of function of PD-L1 is not anticipated to elicit any response. This expectation is supported by published data showing no effect for anti-PD- L1 antibodies in the absence of a T-cell receptor stimulus [58]

Immune-complex Disease

Treatment of humans with mAbs carries the theoretical risk of induction of ADA responses and adverse effect as the consequence of the formation of ADA: drug immune complexes. Manifestations of so-called immune complex disease include arthralgia, serum-sickness, nephritis, and vasculitis. Additionally, ADA may mediate enhanced clearance or neutralization of mAbs and biologics in general. The potential risk of immune complex disease for MEDI4736 is

theoretical based on the known risk associated with mAbs and other proteins. The incidence of MEDI4736 ADA-positive subjects in clinical studies is low, and hence the risk of immune complex disease is likely to be low. Subjects in clinical studies will be closely monitored for induction of ADA, and signs and symptoms of immune complex disease.

1.3.3.3 Other Potential Risks Serious Infections

The potential risk of serious infections is based on safety findings from nonclinical studies with MEDI4736 that demonstrated that MEDI4736 partially suppressed the primary antibody response to a T-cell dependent antigen (KLH). Secondary antibody responses to this antigen were normal. The relevance of this finding with respect to a human immune response is that it could be a potential risk; a reduction in humoral immunity may result in a reduced primary antibody response to vaccination and an increased risk of infection. Serious and/or ≥ Grade 3 infections requiring hospitalization including, but not limited to, sepsis, pneumonia, lung infections, have been reported in clinical trials with MEDI4736, but are often confounded by underlying disease and use of concomitant medications (i.e., steroids and other immunosuppressives) that may cause opportunistic infections. Subjects should be monitored for serious infections while receiving MEDI4736.

For complete details on MEDI4736 safety experience, please refer to current IB. A population PK model was developed for MEDI4736 using monotherapy data from a Phase 1 study (*study 1108; N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors*). Population PK analysis indicated only minor impact of body weight (WT) on PK of MEDI4736 (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of MEDI4736 was evaluated by comparing predicted steady state PK concentrations (5^{th}, median and 95^{th} percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen.

Similarly, a population PK model was developed for tremelimumab using data from Phase 1 through Phase 3 (*N=654; doses= 0.01 to 15 mg/kg Q4W or Q90D; metastatic melanoma*).[61] Population PK model indicated minor impact of body WT on PK of tremelimumab (coefficient of ≤ 0.5). The WT-based (1 mg/kg Q4W) and fixed dosing (75 mg/kg Q4W; based on median body WT of ~75 kg) regimens were compared using predicted PK concentrations (5^{th}, median and 95^{th} percentiles) using population PK model in a simulated population of 1000 patients with body weight distribution of 40 to 120 kg. Similar to MEDI4736, simulations indicated that both body WT-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-subject variability with fixed dosing regimen.

Similar findings have been reported by others.[62-65] Wang and colleagues

investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies.[63] In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in pharmacokinetic/pharmacodynamics parameters.[64]

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 750 mg Q2W MEDI4736 (equivalent to 10 mg/kg Q2W), 1500 mg Q4W MEDI4736 (equivalent to 20 mg/kg Q4W) and 75 mg Q4W tremelimumab (equivalent to 1 mg/kg Q4W) is included in the current study.

1.3.4 Efficacy

As of 14Jul2014, partial efficacy data are available for 2 monotherapy studies (CD-ON-MEDI4736-1108 and D4190C00002) and 1 combination therapy study of MEDI4736 plus tremelimumab (D4190C00006). Tumor assessments were based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines (Eisenhauer et al, 2009).

Clinical activity has been observed across the 3 studies. In Study CD-ON-MEDI4736-1108, 169 of 414 subjects treated with MEDI4736 (all dose levels) were evaluable for response analysis, which included subjects who had at least 24 weeks of follow-up as of the data cutoff date and had either at least 1 post-baseline tumor assessment or experienced clinical progressive disease (PD) or death. Nineteen subjects (11.2%) had a best overall response of complete response (CR)/partial response (PR; confirmed and unconfirmed). The disease control rate (DCR; CR + PR + stable disease [SD] ≥ 12 weeks) was 32% (54 of 169 subjects). Tumoral programmed cell death ligand 1 status was known for 143 of the 169 evaluable subjects, of whom 30 had tumors that were PD- L1 positive. A best overall response of CR/PR (confirmed and unconfirmed) was observed in 7 of 30 (23.3%) PD-L1-positive subjects and in 6 of 113 (5.3%) PD-L1- negative subjects. By tumor type, responses were observed in subjects with non-small- cell lung cancer (NSCLC), squamous cell carcinoma of the head and neck (SCCHN), hepatocellular carcinoma (HCC), cutaneous melanoma, gastroesophageal cancer, and pancreatic adenocarcinoma. In Study D4190C00002, 12 of 18 subjects had at least 1 post-baseline tumor assessment. One subject had a best overall response of PR (unconfirmed) and 6 subjects had SD (irrespective of tumoral PD-L1 expression). In Study D4190C00006, 13 of 18 subjects had at least 1 tumor assessment. Five subjects had best overall responses of PR (1 confirmed and 4 unconfirmed) and 3 subjects had SD (again irrespective of tumoral PD-L1 expression).

1.4 Tremelimumab Background

Tremelimumab (formerly CP-675,206) is a human immunoglobulin (Ig) G2 monoclonal antibody (mAb) being investigated as a cancer immunotherapeutic agent. Tremelimumab is specific for human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4; cluster of differentiation [CD]152), a cell surface receptor that is expressed primarily on activated T cells and acts to inhibit their activation.

Summary of non-clinical experience: Tremelimumab has no cross-reactivity to related human proteins, or to mouse, hamster, rat, or rabbit CTLA-4, but it does demonstrate cross reactivity to cynomolgus monkey CTLA-4. Cytotoxic T lymphocyte-associated antigen 4 delivers a negative regulatory signal to T cells upon binding of B7.1 (CD80) or B7.2 (CD86) ligands on antigen-presenting cells. Tremelimumab completely blocks the interaction of human CTLA-4 with B7.1

and B7.2, resulting in increased release of cytokines (interleukin [IL]-2 and interferon [IFN]-γ) from human T cells, peripheral blood mononuclear cells (PBMCs) and whole blood, and cynomolgus monkey whole blood cultured in the presence of activating stimuli. In contrast, addition of tremelimumab to human whole blood in the absence of additional stimuli does not induce levels of cytokines in vitro that would be predictive of cytokine-release syndrome in vivo. In addition, tremelimumab shows minimal specific binding to constant fragment of antibodies (Fc) receptors, does not induce natural killer (NK) cell-mediated antibody-dependent cell-mediated cytotoxicity (ADCC) activity, and does not deliver inhibitory signals following plate-bound aggregation. As tremelimumab does not cross-react with mouse CTLA-4, an anti-mouse CTLA-4 surrogate mAb (9H10) was used to assess the antitumor activity of anti-CTLA-4 in the SA1N mouse model of fibrosarcoma. Antibody 9H10 demonstrated dose-dependent antitumor activity and, at the maximum dose tested, resulted in tumor regression in 4 of 5 treated animals. These animals were shown to be resistant to tumor rechallenge, demonstrating a durable antitumor immunity. Antitumor activity was observed in the model when antibody was present at a plasma concentration of 30 μg/mL. **Thus, a concentration of 30 μg/mL 9H10 was identified as the target plasma concentration for tremelimumab.**

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.

1.4.1 Pharmacokinetics and Product Metabolism

The pharmacokinetics (PK) of tremelimumab was linear (dose-proportional) within the dose range examined following single and multiple administrations. Overall, tremelimumab toxicities in monkeys 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 hematological parameters. Clinical dose-limiting toxicities (DLTs; gastrointestinal effects) and non-DLTs (e.g., 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 Day 20 to Day 50 of gestation at doses of 0, 5, 15, or 30 mg/kg did not elicit maternal toxicity, developmental toxicity, or teratogenicity.

As of the data cutoff date of 12Nov2014 (for all studies except D4190C00006 that has a cutoff date of 04Dec2014), 22 sponsored clinical studies have been conducted as part of the tremelimumab clinical development program. Of these studies, 13 have been completed and 9 are ongoing. Tremelimumab has been administered as monotherapy to 973 subjects participating in 10 of the 22 clinical studies, 2 of which are ongoing. An additional 497 subjects have received tremelimumab or placebo in the ongoing double-blinded, Phase 2b mesothelioma study, D4880C00003 (DETERMINE; data remain blinded). Tremelimumab in combination with other anticancer agents has been administered to 208 subjects with a variety of tumor types in 12 of the 22 clinical studies, 7 of which are ongoing.

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

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 mechanism of action. Response rates to anti-

CTLA-4 antibodies are generally low, approximately 10%. However, in subjects who respond, the responses are generally durable, lasting several months even in subjects with aggressive tumors such as refractory metastatic melanoma. Some subjects may have what is perceived to be progression of their disease in advance of developing disease stabilization or a tumor response. Overall, the impact on conventionally-defined progression-free survival (PFS) can be small; however, the durable response or stable disease seen in a proportion of subjects can lead to significant prolongation of overall survival (OS). Recently, ipilimumab was shown to significantly improve OS in both first- and second-line treatment of subjects with metastatic melanoma. The melanoma data with ipilimumab clearly demonstrate that a small proportion of subjects with an objective response and a small impact on PFS rates can lead to significant prolongation of OS, and support development of this class of agent in other tumors. In a large, single-arm Phase 2 tremelimumab study in subjects with advanced refractory and/or relapsed melanoma, objective responses (primary endpoint) following tremelimumab 15 mg/kg administered once every 90 days (Q90D) were observed in 7% of subjects. In each case, the response was durable (present at ≥ 6 months from enrollment). A Phase 3, open-label, randomized study comparing tremelimumab 15 mg/kg Q90D (Arm A) to either dacarbazine or temozolomide (Arm B) in subjects with advanced melanoma was terminated following a pre-specified interim futility analysis. Based on the final analysis, the median OS (primary endpoint) was 12.6 months in Arm A and 10.7 months in Arm B (hazard ratio [HR] = 1.1416, p = 0.1272).

1.4.2 Safety

The profile of adverse events (AEs) and the spectrum of event severity have remained stable across the tremelimumab clinical program and are consistent with the pharmacology of the target. To date, no tumor type or stage appears to be associated with unique AEs (except for vitiligo that appears to be confined to subjects with melanoma). As of the data cutoff date of 12Nov2014 (for all studies except D4190C00006 that has a cutoff date of 04Dec2014), AEs (all grades, regardless of causality) reported in > 10% of subjects in the completed and rollover tremelimumab monotherapy studies (N = 973, integrated data) were diarrhea (45.3%), fatigue (37.5%), nausea (32.5%), rash (28.9%), pruritus (27.3%), decreased appetite (22.8%), vomiting (22.5%), pyrexia (15.3%), cough (15.0%), constipation (14.4%), abdominal pain (13.9%), headache (13.8%), dyspnea (12.4%), and decreased weight (10.2%). Based on integrated data from completed studies of tremelimumab in combination with other agents (N = 116), AEs (all grades, regardless of causality) reported in > 15% of subjects were diarrhea (54.3%); nausea (40.5%); fatigue (38.8%); rash (35.3%); pruritus, decreased appetite (30.2% each); vomiting (27.6%); pyrexia (26.7%); influenza like illness (20.7%); arthralgia (19.8%); constipation (19.0%); thrombocytopenia, injection site reaction (18.1% each); and increased aspartate aminotransferase (15.5%). Most of these events occurred at a higher rate with tremelimumab plus sunitinib than with other combinations. The events of diarrhea, rash, and pruritus are considered identified risks of tremelimumab. Acute renal failure was reported in subjects who received the combination of tremelimumab and sunitinib; 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 following current guidelines for the management of immune-related toxicities.

MEDI4736 and tremelimumab

The safety profile of MEDI4736 and tremelimumab combination therapy in the 102 subjects with advanced NSCLC in Study D4190C00006 is generally consistent with that observed across 177 subjects treated with MEDI4736 and tremelimumab combination therapy (not including subjects treated with blinded investigational product). As of 15Apr2015, 95 of 102 subjects (93.1%) reported at least 1 AE. All subjects in the tremelimumab 3 and 10 mg/kg dose cohorts experienced AEs; subjects in the

MEDI4736 20 mg/kg and tremelimumab 1 mg/kg Q4W cohort experienced the lowest AE rate (77.8%). Treatment-related AEs were reported in 74 of 102 subjects (72.6%), with events occurring in > 10% of subjects being diarrhea (27.5%), fatigue (22.5%), increased amylase and pruritus (14.7% each), rash (12.7%), colitis (11.8%), and increased lipase (10.8%). Treatment-related ≥ Grade 3 AEs reported in ≥ 5% of subjects were colitis (8.8%), diarrhea (7.8%), and increased lipase (5.9%). Five subjects reported treatment-related Grade 4 events (sepsis, increased ALT, and increased AST in 1 subject; increased amylase in 2 subjects; myasthenia gravis in 1 subject; and pericardial effusion in 1 subject) and 2 subjects had treatment-related Grade 5 events (polymyositis and an uncoded event of neuromuscular disorder [VT]); the Grade 4 event of myasthenia gravis and Grade 5 polymyositis occurred in 1 subject. There were 2 subjects (both in the MEDI4736 20 mg/kg + tremelimumab 3 mg/kg Q4W cohort) with dose-limiting toxicities (DLTs): 1 subject with Grade 3 increased AST, and 1 subject with Grade 3 increased amylase and Grade 4 increased lipase. Fifty-six subjects (54.9%) reported SAEs, with events occurring in > 5% of subjects being colitis (9.8%) and diarrhea (7.8%). Thirty-six subjects (35.3%) experienced treatment-related SAEs. Twenty-seven subjects (26.5%) permanently discontinued treatment due to AEs. Treatment-related AEs resulting in discontinuation in ≥ 2 subjects were colitis (7 subjects), pneumonitis (5 subjects), diarrhea (3 subjects), and increased AST (2 subjects).

MEDI4736 and Tremelimumab Fixed Dosing Regimens

A population PK model was developed for MEDI4736 using monotherapy data from the Phase 1 study, CD-ON-MEDI4736-1108 (N = 292; doses of 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight on PK of MEDI4736 (coefficient of ≤ 0.5). The impact of body weight-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of MEDI4736 was evaluated by comparing predicted steady-state PK concentrations (5th, median and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body weight of ~75 kg). A total of 1000 subjects were simulated using body weight distribution of 40 to 120 kg. Simulation results demonstrate that body weight- based and fixed dosing regimens yield similar median steady-state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen.

Similarly, a population PK model was developed for tremelimumab using data from Phase 1 through Phase 3 (N = 654; doses of 0.01 to 15 mg/kg Q4W or every 90 days; metastatic melanoma; Wang et al, 2014). The population PK model indicated minor impact of body weight on PK of tremelimumab (coefficient of ≤ 0.5). The weight-based (1 mg/kg Q4W) and fixed dosing (75 mg/kg Q4W; based on median body weight of ~75 kg) regimens were compared using predicted PK concentrations (5th, median and 95th percentiles) using population PK model in a simulated population of 1,000 subjects with body weight distribution of 40 to 120 kg. Similar to MEDI4736, simulations indicated that both body weight-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-subject variability with fixed dosing regimen.

Similar findings have been reported by others (Ng et al, 2006; Wang et al, 2009; Zhang et al, 2012; Narwal et al, 2013). Wang and colleagues investigated 12 mAbs and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al, 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in PK/pharmacodynamics parameters (Zhang et al, 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and

reduced dosing errors. Given expectation of similar PK exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on an average body weight of 75 kg, a fixed dose of 750 mg Q2W MEDI4736 is equivalent to 10 mg/kg Q2W, 1500 mg Q4W MEDI4736 is equivalent to 20 mg/kg Q4W, and 75 mg Q4W tremelimumab is equivalent to 1 mg/kg Q4W.

Dosing schedule for Tremelimumab and Durvalumab

The two drugs will be administered in 3 different arms as per current IB specifications:

Treatment Arms:

On all arms, patients will be given the 1st dose(s) of study treatment 14 days pre-surgery. Patients will then undergo standard surgical resection. Dosing will then resume approximately 14 days after surgery (once the surgical wound has healed) and will follow the schedule outlined below (depending on the arm to which they were assigned):

Arm 1) Tremelimumab- 75 mg every 4 weeks. The drug will be restarted 14 days after surgery once the surgical wound has healed and then every 4 weeks after surgery. If there is no progression of disease, they will continue on treatment for up to 24 months

Arm 2) MEDI4736- 750 mg every 2 weeks. The drug will be restarted 14 days after surgery once the surgical wound has healed and then every 2 weeks after surgery. If there is no progression of disease, they will continue on treatment for up to 24 months

Arm 3) In the combination arm,14 days after surgery, the drugs will be administered as follows: Tremelimumab will be administered IV every 4 weeks (Day 1 of each cycle) and MEDI4736 750mg every 2 weeks (Day 1 and Day 15 of each cycle) until the patients have received 7 doses of Tremelimumab and 14 doses of MEDI4736. Thereafter, from Cycle 7 (Week 25), Tremelimumab will be given every 12 weeks (+/-7 days) and MEDI4736 will be given every 2 weeks (+/- 2 days) until permanent discontinuation criteria (e.g. disease progression) is met. If there is no progression of disease, they will continue on treatment for up to 24 months.

(Note: This change to a 12 week regimen for tremelimubab after the first 6 doses is based on the current IB specifications and recent trial data).

Please refer to current Tremelimumab and Durvalumab IBs for more details

1.5 Rationale for the Current Study

The preclinical activity in glioma and the data in other solid tumors suggest that checkpoint inhibitors may be beneficial in GBM and should be evaluated especially since there is a high degree of PD-L1 seen in GBM. However, to further understand the effects of a cancer immunology approach in tumors, a pre-treatment trial to assess the immunologic changes in tumors prior to surgery would be important in understanding the effect of treatment.

This trial will assess the effect of each agent alone and then in combination.

1.5.1 Exploratory Studies

For patients who progress on trial and remain surgical candidates, tissue post treatment with Tremelimumab or MEDI4736 or the combination will be analyzed and compared to the prior specimen.

Additional exploratory studies will include assessment of:

1) Profile peripheral blood lymphocytes (PBL)
2) Tumor-infiltrating lymphocytes (TIL) throughout treatment.

3) Serum for tryptophan and downstream catabolites, as well as for cytokines.

2.0 OBJECTIVES & ENDPOINTS

2.1 Primary Objective & Endpoints

To determine the T-cell changes that occur in recurrent GBM treated with Tremelimumab and MEDI4736 as single agents and in combination. The changes from baseline will be assessed in blood samples and tissue samples before treatment and post-surgery for all patients in the 3 arms. A comparison between the changes observed in the 3 arms will be made.

2.2 Secondary Objectives & Endpoints

2.2.1 To evaluate the safety of either Tremelimumab or MEDI4736 alone and in combination in patients with recurrent GBM. The endpoints will be the number, frequency, and severity of adverse events (as defined by the NCI Common Terminology Criteria for Adverse Events or CTCAE version 4.03).

2.2.2 To determine post-surgery, the time to progression(per Modified RANO criteria and iRANO criteria see below) for patients treated with either Tremelimumab or MEDI4736 alone and in combination of both, This will be defined as the number of months from the time of first dose of study treatment until progression of disease or death by any cause.

2.2.3 To determine post-surgery the overall survival for patients treated with Tremelimumab or MEDI4736 alone and in combination of both. This will be defined as the number of months surviving from the time of first dose of study treatment until death by any cause.

2.2.4 To assess post-surgery, MRI changes in patients treated with either Tremelimumab or MEDI4736 alone and in combination of both.

2.3 Exploratory Objectives & Endpoints

2.3.1 To correlate T-cell changes and PDL1 expression with patient outcomes.

3.0 PATIENT ELIGIBILITY

The target population for this study is patients with recurrent glioblastoma. This will be a single-center trial conducted at neuro-oncology clinic of Northwestern University.

A total of 30 evaluable subjects will be needed for this trial. The accrual cap is 45 patients, in order to cover those patients that do not make it to the first evaluable time point. Hence, the total accrual per arm will be up to 15. Approximately 4 potentially eligible patients are seen per month, and it is anticipated that at least 2 per month will be accrued. Potential patients may be referred to the Principal Investigator (PI) at Northwestern University, Dr. Karan Dixit , at (312) 503-4724.

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and none of the exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

3.1.1 Patients must have a prior diagnosis of Grade IV glioma (Glioblastoma) per 2016 WHO criteria that has progressed after standard radiotherapy (RT) and Temozolomide (TMZ).

(*Note: Pathology will need to be reviewed locally but registration can occur based on pathology report*).

3.1.2 Patients must have had radiographic evidence of tumor progression by brain MRI or CT scan with contrast.

3.1.3 Prior therapy with gamma knife or other focal high-dose radiotherapy is allowed, but the patient must have subsequent histologic documentation of recurrence, unless the recurrence occurs remote from the treated site.

3.1.4 Patients must be surgical resection candidates.

3.1.5 Patients must have had no more than 3 prior lines of chemotherapy. This includes the initial treatment and two relapses. Concurrent and adjuvant TMZ-based chemotherapy, including the combination of TMZ with another agent, is considered one line of chemotherapy. For clarification, please contact the PI, Dr. Karan Dixit at (312) 503-4724

3.1.6 Patients must be age ≥ 18 years. Both male and female are eligible.

3.1.7 Patients must exhibit a KPS ≥ 70 (Appendix C).

3.1.8 Life expectancy of ≥ 12 weeks (per treating investigator's discretion).

3.1.9 Patients must be on a stable or decreasing dose of corticosteroids within 5 days prior to CT scan or MRI (which is done to determine eligibility). Patients must be on no more than 8 mg a day but an attempt should be made to keep the dose at 4 mg or less. Please contact the PI if doses of > 4 mg are needed.

3.1.10 Patients must have adequate organ and bone marrow function within 14 days prior to registration, as defined below.

(Note: The CBC and chemistries will be repeated within 72 hours of 1st dose of study treatment if baseline tests were more than 7 days prior to dosing).

- leukocytes ≥ 3,000/mcL
- absolute neutrophil count ≥ 1,500/mcL
- platelets ≥ 100,000/mcl
- hemoglobin (Hb) >10.0 g/dL (can be transfused to this level)
- INR, PT, or APTT as follows:
  - In the absence of therapeutic intent to anticoagulate the patient:
    - INR < 1.5, **or**
    - PT < 1.5×ULN, **or**
    - aPTT < 1.5×ULN
  - In the presence of therapeutic intent to anticoagulate the patient:
    - INR or PT and aPTT within therapeutic limits (according to the medical standard in the institution) and the patient has been on a stable dose of anticoagulants for at least 2 weeks before registration.
- total bilirubin ≤ 1.5 x ULN (except in patients with Gilbert's disease)
- AST (SGOT)/ALT (SPGT) ≤ 2.5 x institutional upper limit of normal (ULN)
- Serum creatinine < 1.5 x ULN
- Serum creatinine CL >40 mL/min by the Cockcroft-Gault formula

(Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

Males: Creatinine CL (mL/min)	Weight (kg) x (140 – Age) x 1.0 72 x serum creatinine (mg/dL)
Females: Creatinine CL (mL/min)	Weight (kg) x (140 – Age) x 0.85 72 x serum creatinine (mg/dL)

3.1.11 Females of child-bearing potential (FOCBP) and males must agree to use adequate contraception (e.g. hormonal or barrier method of birth control – see appendices acceptable birth control methods) prior to registration, for the duration of study participation, and for 180 days after the last dose of MEDI4736 + tremelimumab combination therapy or 90 days after the last dose of MEDI4736 or tremelimumab monotherapy. Should a female patient become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

NOTE: A FOCBP is *any woman* (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets both of the following criteria:

- *Has not* undergone a hysterectomy or bilateral oophorectomy.
- *Has had* menses at any time in the preceding 12 consecutive months (and therefore has not been naturally postmenopausal for > 12 months).

3.1.12 FOCBP must have a negative pregnancy test (serum or urine) within 7 days prior to registration on study.

3.1.13 Patients must have the ability to understand and the willingness to sign a written informed consent prior to registration on study.

3.1.14 Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

3.1.15 Patients must have given written, signed and dated informed consent prior to registration on the study. NOTE: no study-specific screening procedures may be performed until consent has been given.

3.2 Exclusion Criteria

3.2.1 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site); Previous enrolment or randomization in the present study.

3.2.2 Has received prior therapy with an anti-PD-1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

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

3.2.4 Known active human immunodeficiency virus (HIV1/2 antibodies).

3.2.5 Treatment with radiation therapy within 12 weeks prior to the first dose of study treatment, unless there is tissue confirmation of tumor recurrence or there is progression outside the treatment field.

3.2.6 Administration of any of the following within the specified timeframe prior to the first dose of study drug:

- 4 weeks for TMZ,
- 6 weeks for nitrosoureas,
- 3 weeks for a biologic or targeted agent (i.e. small molecule)
- 4 weeks for a VEGF inhibitor (i.e. bevacizumab)

3.2.7 Patient has history of primary immunodeficiency OR has received any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment, excluding intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses. Attempts should be made to have patient on lowest possible dose of steroids (acceptable range4-8 mg. please contact PI if dose is >4 mg), and weaned to off as is feasible.

3.2.8 Patients receiving any other investigational chemotherapeutic agents within 28 days prior to the first dose of trial treatment.

3.2.9 Patients on an enzyme-inducing anti-convulsant who cannot be switched to a non-enzyme-inducing anti-convulsant with a 2 week wash-out period from time of drug discontinuation until Day 1 of study treatment.

3.2.10 Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from an electrocardiograms (ECGs) using Bazett's Correction. If first ECG is abnormal, then the mean will be calculated from 3 consecutive ECGs (taken 2-5 minutes apart). Please contact the PI for further clarification.

3.2.11 Active or prior documented history of immunologic disorder including autoimmune disease within the past 2 years NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.

3.2.12 Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis).

3.2.13 History of allogeneic organ transplant.

3.2.14 Uncontrolled intercurrent illness including, but not limited to:

- ongoing or active infection,
- symptomatic congestive heart failure,
- uncontrolled hypertension
- unstable angina pectoris,
- cardiac arrhythmia,
- active peptic ulcer disease or gastritis,
- active bleeding diatheses, or
- psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent.

3.2.15 Known history of previous clinical diagnosis of tuberculosis.

3.2.16 History of leptomeningeal carcinomatosis.

3.2.17 Patients with a history of active malignancy within 3 years prior to registration. Note: exceptions to this requirement include adequately treated non-melanoma skin cancer or lentigo maligna or carcinoma in situ without evidence of disease or prostate cancers with a Gleason score < 8 and with prostatectomy and no lymph node involvement.

3.2.18 Receipt of live attenuated vaccination within 30 days prior to study entry (or due to receive one within 30 days of receiving either MEDI4736 or tremelimumab).

3.2.19 Female subjects who are pregnant, breast-feeding or male or female patients of

reproductive potential who are not employing an effective method of birth control.

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

3.2.21 Subjects with uncontrolled seizures.

3.2.22 Patients who have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to MEDI3475 are not eligible.

4.0 TREATMENT PLAN

4.1 Overview

Patients will be treated with either Tremelimumab 75 mg alone, MEDI4736 750 mg alone, or both in combination. Patients will be randomly allocated using block randomization to ensure equal sample sizes per arm. Up to 45 patients (15 per arm) will be randomized to ensure that 30 patients are evaluable for immunologic response (10 per arm).

Patients will then undergo a surgical resection of their tumor that is part of their medical care 2 weeks later to remove the tumor. Two weeks is expected to be enough time for immunologic changes to occur in the tumor. Standard pre-surgical testing will be done prior to surgery. At the time of surgery, tissue will be removed for local pathology review and send to Dr. Bloch's Laboratory for evaluation (see Section 9.0 for details).

Post-operative care will be standard for patients who undergo a craniotomy and tumor resection at NMH. Patients will have a standard post-operative MRI or CT scan of the brain within 72 hours of surgery. Following surgery, patients will resume treatment on the same regimen they were assigned to receive before surgery. Treatment may continue until disease progression or unacceptable toxicity.

4.2 Treatment Administration

Treatment Administration Summary

Arm	Treatment	Dose	Route	Schedule	Supportive Therapies**
1	Tremelimumab monotherapy	75 mg	IV at 250ml/hr	Once within 14 d (+/-3) pre-surgery. Adjuvant: Every 4 weeks	Acetaminophen and/or antihistamine or equivalent[3]
2	MEDI4736 monotherapy	750 mg	IV over 60min+/-5 mins[2]	Once within 14 d (+/-3) pre-surgery. Adjuvant: Every 2 weeks	Acetaminophen and/or antihistamine or equivalent[3]

3	Tremelimumab + MEDI4736 combination therapy	75 mg + 750mg	IV[1] 1 hour for each drug	Once within 14 d (+/-3) pre-surgery. Then, treme every 4 weeks (for 7 doses post-surgery) + MEDI every 2 weeks (for 14 doses post-surgery); then Treme every 12 weeks and MEDI every 2 weeks from C7 (wk 25).	Acetaminophen and/or antihistamine or equivalent[3]

1 Tremelimubab administered first, then MED14736 infused after a gap of 1 hour for the first cycle. If tolerated, then can be given one after the other for subsequent infusions (at discretion of PI)

2 Use a 0.2 micron in-line filter

3 As per institutional policy, at the discretion of the investigator. May also be used as pre-medications for infusions

**Antiemetic therapy may be used as needed; 5HT antagonists are recommended. Hematopoietic growth factors (G-CSF) may be used per ASCO guidelines after cycle one. Corticosteroids should be used in the smallest dose to control symptoms of cerebral edema and mass effect, and should be discontinued if possible. Febrile neutropenia may be managed according to the institution's infectious disease/ASCO guidelines.

Patients will be allocated randomly using block randomization to ensure equal sample sizes per arm, with up to 12 patients being enrolled into each arm (in order to achieve 10 evaluable per arm). On all arms, patients will be given the 1st dose(s) of study treatment 14 days pre-surgery. Patients will then undergo standard surgical resection. Dosing will then resume approximately 14 days after surgery (once the surgical wound has healed) and will follow the schedule outlined above (depending on the arm to which they were assigned). For the combination Arm 3. Tremelimumab will be administered IV every 4 weeks (Day 1 of each cycle) and MEDI4736 750mg every 2 weeks (Day 1 and Day 15 of each cycle) until the patients have received 7 doses of Tremelimumab and 14 doses of MEDI4736, post-surgery. Thereafter, from Cycle 7 (Week 25), Tremelimumab will be given every 12 weeks (+/-7 days) and MEDI4736 will be given every 2 weeks (+/- 2 days) until permanent discontinuation criteria (e.g. disease progression) is met. On all arms, if there is no progression of disease, patients may continue on treatment for up to 24 months. If at the time of progression, the patient is a candidate for surgery, tissue will again be sent to Dr. Bloch's laboratory for evaluation.

Any patient who has disease progression as defined in section 6.0 or clinical decline and undergoes further surgery will have the option to use their tumor tissue for research to understand the immunologic changes occurring at the time of presumed drug failure. If on pathologic review, there is no evidence of significant tumor and the changes on MRI were likely treatment related, the patient will be allowed re-start treatment. The patient will be advised of the pathology results and that they may not derive any further benefit from therapy and they will need to re-sign the informed consent prior to starting therapy.

4.3 Supportive Care Guidelines & Concomitant Medications/Restrictions on Study

4.3.1 Supportive Care

All medications used by patients during the study, with the reasons for use, will be recorded in the medical record and documented in the appropriate eCRF. For all subsequent visits, all concomitant therapy that is continuing or has been added, discontinued, or had a dosage change since the previous visit must be recorded in the medical record/eCRF as well.

- Antiemetic therapy may be used as needed and will be recorded in the medical record; 5HT antagonists are recommended.

- Hematopoietic growth factors (G-CSF) may be used per American Society of Clinical Oncology (ASCO) guidelines after cycle one.
- Corticosteroids should be used in the smallest dose to control symptoms of cerebral edema and mass effect, and should be discontinued if possible. Please confirm appropriate use with the PI.
- Febrile neutropenia may be managed according to the institution's infectious disease/ASCO guidelines. Measures may include appropriate laboratory testing, including blood and urine cultures and the initiation of broad-spectrum antibiotics. If a source for the fever is not identified or the fever resolves when the neutrophil count recovers, antibiotics may be discontinued and the patient observed. In this case growth factors may be used.
- If neurosurgical intervention is required for indications not related to tumor progression, these procedures must be documented, including the indications for surgery, surgical operative note, and pathology report.

4.3.2 Restrictions While on Treatment

Contraception

Females of childbearing potential who are sexually active with a nonsterilised male partner must use 2 methods of effective contraception (refer to appendices) from screening, and must agree to continue using such precautions for 90 days after the final dose of investigational product, or for at least 90 days following the last infusion of MEDI4736 or until after 4-5X the half-life of Tremelimumab, whichever occurs longest; cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

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

Non-sterilised males who are sexually active with a female partner of childbearing potential must use 2 acceptable methods of effective contraception (see appendices) from Day 1 and for 90 days after receipt of the final dose of investigational product.

Blood donation

Subjects should not donate blood while participating in this study, or for at least 90 days following the last infusion of MEDI4736 or until after 4-5X the half-life of Tremelimumab, whichever occurs longest.

4.3.3 Permitted concomitant medications

- Investigators may prescribe concomitant medications or treatments (e.g., acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care
- 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 for palliative intent is acceptable (e.g., by local surgery or radiotherapy)
- Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed for different indications, at the discretion of the principal investigator (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.). Dexamethasone may be used but attempts should be made to keep

it less than 4 mg/day.

- Inactivated vaccines, are permitted.

4.3.4 Prohibited concomitant medications

The following medications are considered exclusionary during the study.

- Any investigational anticancer therapy other than the protocol specified therapies
- Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic or hormonal therapy for cancer treatment, other than any stated comparator or combination regimens.)
- Immunosuppressive medications including methotrexate, azathioprine, and Tumor Necrosis Factor alpha-blockers (TNF-α blockers).
- Enzyme inducing anti-convulsants (e.g.: Carbamazepine, Phenytoin, Primidone, Topiramate). Please check with PI if have further questions.
- Live attenuated vaccines within 30 days of MEDI4736 and/or Tremelimumab dosing (i.e., 30 days prior to the first dose, during treatment with MEDI4736 and/or Tremelimumab and for 30 days post discontinuation of MEDI4736 and/or Tremelimumab).

4.4 Toxicity Management & Dose Delays/Modifications

Any patient who receives at least one dose of study therapy will be evaluable for toxicity endpoints. Each patient will be assessed for the development of toxicity according to the timeframe referenced in the Schedule of Events table. Toxicity will be assessed according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Following the first dose of MEDI4736 and/or tremelimumab, subsequent administration of MEDI4736 and/or tremelimumab can be modified based on toxicities observed (see Table 1, 2, and 3 below). Dose reductions are not permitted.

Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy With Tremelimumab or Tremelimumab Monotherapy)

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 v4.03. 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. **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	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

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. 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	e.g infliximab(also refer to 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 – 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.

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)	

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; imAE immune-mediated adverse event; IV intravenous; NCI National Cancer Institute; PO By mouth.

Pediatric Considerations	
Dose Modifications	**Toxicity Management**
The criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity is the same for pediatric patients as it is for adult patients, as well as to permanently discontinue study drug/study regimen if unable to reduce corticosteroid ≤ a dose equivalent to that required for corticosteroid replacement therapy **within 12 weeks** after last dose of study drug/study regimen	All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended. – The recommendations for dosing of steroids (i.e., mg/kg/day) and for IV IG and plasmapheresis that are provided for adult patients should also be used for pediatric patients. – The infliximab 5 mg/kg IV dose recommended for adults is the same as recommended for pediatric patients ≥ 6 years old. For dosing in children younger than 6 years old, consult with a pediatric specialist. – For pediatric dosing of mycophenolate mofetil, consult with a pediatric specialist.

	– With long-term steroid and other immunosuppressive use, consider need for PJP prophylaxis, gastrointestinal protection, and glucose monitoring

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade**	**General Guidance**	**For Any Grade:** -Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. -Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up , and high-resolution CT scan
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose 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 instruemental 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 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 recommnedation][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) (Grade4: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, 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		**For Grade 1:**
	(Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only)	No dose modifications.	-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 (Diarrrhea: stool frequency of 4 to 6 over baseline per day)(Colitis:abdominal pain;mucus or blood in stool)	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** -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. - 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; Grade 4 diarrhea: life threatening consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs; Grade 4 colitis: life- threatening consequences, urgent intervention indicated)	**Grade3** 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]
Hepatitis **(elevated LFTs)** Infliximab should not be used for management of immune-related hepatitis	**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).

PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in HCC patients	**Grade 1**		**For Grade 1:**
	(Based on ULN regardless of baseline LFT) (AST or ALT >ULN and ≤3.0×ULN and/or TB > ULN and ≤1.5xULN)	• No dose-modifications. • If it worsens, then treat as Grade 2 event.	Continue LFT monitoring per protocol.
	Grade 2 **(Based on ULN regardless of baseline LFT)** (AST or ALT >3.0×ULN and ≤5.0×ULN and/or TB >1.5×ULN and ≤3.0×ULN)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – 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 guidelines for treatment of cancer-related infections[Category 2B recommendation])[a]

	Grade 3 or 4	For Grade 3:	For Grade 3 or 4:
	(Based on ULN regardless of baseline LFT) (Grade 3: AST or ALT >5.0×ULN and ≤20.0×ULN and/or TB >3.0×ULN and ≤10.0×ULN) (Grade 4: AST or ALT >20×ULN and/or TB >10×ULN)	For elevations in transaminases ≤ 8 × ULN, or elevations in bilirubin ≤5 × ULN: • Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade ≤1or 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	- 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]

		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 study drug/study regimen.	

THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients

immune-related hepatitis. See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing**	– Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load >2000 IU/ml – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥2-fold – For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above

bilirubin or signs of DILI/liver decompensation	**Grade 1** (Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline)	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as Grade 2 event. For all grades, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	
	Grade 2 (Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline) (Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline)	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or Grade 4. If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to

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

	>20×ULN, whether normal or elevated at baseline)		**(except would recommend obtaining liver biopsy early)**
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR): - **Manage dosing for Grade 1 transaminase rise as instructed for Grade 2 transaminase rise** - **Manage dosing for Grade 2 transaminase rise as instructed for Grade 3 transaminase rise** - **Grade 3-4: Permanently discontinue study drug/study regimen**			
Nephritis or renal dysfunction (elevated serum creatinine)	**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 after completion of steroid taper.	**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 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 formations)	**Any Grade** (refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED.**
	Grade 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, then permanently discontinue study drug/study regimen. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – 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] – 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 v4.03 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.
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	**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

	may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of 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	**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

		per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	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]
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 v4.03 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 improves to	**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).

		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)	**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 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 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 4:** Permanently discontinue study drug/study regimen.	**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. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. o 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: 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.
Cardiac toxicities (including arrhythmia, Conduction disorder heart Failure,IV dysfunction, Myocarditis	**Any Grade General Guidance** Discontinue drug permanently **upon diagnosis of** myocarditis, **regardless of grade**.	**For Any Grade:** − The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. − Consider, as necessary, discussing with the study physician. − Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. − Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)
Grade 1 (asymptomatic with	-No dose modifications required unless clinical suspicion for myocarditis is high, in	**For Grade 1 (no definitive findings):** - Monitor and closely follow up in 2 to 4 days for clinical

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

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

		Consider Barium swallow for evaluation of dysphagia or dysphonia. Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
Grade 1 (mild pain)	- No dose modifications.	**For Grade 1:** − Monitor and closely follow up in 2 to 4 days for clinical

		symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
Grade 2 (moderate pain 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 refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Grade 3 or 4 (pain associated with severe weakness; limiting self-care ADLs)	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study	**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

	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.	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]

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

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

AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; imAE immune-mediated adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Infusion-Related Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	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 (e.g., 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 (e.g., 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 (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

CTCAE Common Terminology Criteria for Adverse Events; IM intramuscular; IV intravenous; NCI National Cancer Institute.

Non–Immune-Mediated Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
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 Sponsor.).	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.

4.5 Duration of Therapy

Patients on all arms will remain on study as long as there is no disease progression for up to 24 months or until any of the following occur:

- Disease progression
- Development of an inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
  - See section on dose modifications: Treatment delay of > 4 weeks due to treatment related toxicities.
  - Protracted (>2 weeks) medically concerning grade 2 cardiac, pulmonary, renal, gastrointestinal, skin, or CNS toxicities.
- The treating investigator determines that the patient should be taken off treatment for any reason (i.e. changes in condition, inability to comply with study treatment or procedures).

4.6 Duration of Follow Up

All subjects will be followed for survival for up to 2 years/ 24 months from stopping study treatment. Subjects who decline to return to the site for evaluations will be offered follow-up by phone every 8-16 weeks as an alternative.

Note that patients who discontinue treatment permanently for any reason other than progression will be followed for evidence of tumor response and disease status.

Any patient who withdraws their consent, will be considered as an early discontinuation, and may be replaced if this occurs before they have received the first dose of treatment. Patients who withdraw consent but receive at least one dose of treatment will be evaluable for toxicity even if they are not fully evaluable for response. The accrual goal has been set to allow up to 45 patients to be enrolled in order to allow for early discontinuations.

If a patient withdraws consent, no further treatment or study-specific testing will be completed. The primary reason for a patient's withdrawal from the study is to be recorded in the source documents. All patients will be followed until death or 2 years/24 months from stopping treatment.

Subjects who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment.

Subjects who are permanently discontinued from receiving investigational product will be followed for safety for 30 days post last-dose visit including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study. If a subject is enrolled in another clinical study, they will be followed until all AEs are resolved or stable. If enrolled onto another clinical study, it is not necessary to follow the subject for survival or progression.

4.7 Removal of Subjects from Study Treatment and/or Study as a Whole

Patients can be taken off the study treatment and/or study as a whole at any time at their own request, or they may be withdrawn from study treatment at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation from study treatment must be clearly documented on the appropriate eCRF and may include:

- Patient voluntarily withdraws from treatment (follow-up permitted)
- Patient withdraws consent (no follow-up permitted)
- Patient is unable to comply with protocol requirements
- Patient demonstrates disease progression

- Patient experiences unacceptable toxicity
  - See section on dose modifications: Treatment delay of > 4 weeks due to treatment related toxicities.
  - Protracted (>2 weeks) medically concerning grade 2 cardiac, pulmonary, renal, gastrointestinal, skin, or CNS toxicities.
- Grade ≥ 3 infusion reaction
- Treating physician determines that continuation on the study would not be in the patient's best interest
- Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk
- Patient becomes pregnant or wants to become pregnant
- Patient develops a second malignancy that requires treatment which would interfere with this study
- Patient becomes lost to follow-up (LTF)
- Initiation of alternative anticancer therapy including another investigational agent
- Confirmation of PD and investigator determination that the subject is no longer benefiting from treatment with MEDI4736

4.8 Patient Replacement/ Addition

- Any patient who is consented but does not receive at least one dose of investigational drug will be replaced.
- Any patient who withdraws their consent or otherwise discontinues study for any reason prior to undergoing surgery, will be considered as an early discontinuation, and another patient may be added as necessary.

5.0 STUDY PROCEDURES

5.1 Pre-Surgery & Surgery

Assessment/Activity	Screening & Baseline[2]	14 days (+/- 3 d) prior to surgery	Within 7 days prior to Surgery	Day of surgery	Within 72 hours Post-surgery
Informed Consent[3]	X				
Review of eligibility criteria	X				
Medical History	X				
Concomitant Medications	X		X	X	X
Neurologic and Physical Exam[1]	X		X		X
KPS	X		X		
Serum or Urine Pregnancy Test	X				
Brain MRI or CT with contrast[4]	X				X[4]
CBC with diff & clinical chemistry[9]	X	X	X		
Magnesium and Phosphorus	X	X	X		
Thyroid testing[10]	X				
PTT/PT/INR[11]	X				
12-lead ECG[5]	X				
Urinalysis with micro	X				
Creatinine Clearance	X				
Hepatitis serologies[12]	X				
Toxicity assessment	X			X	X
1st Dose Study Treatment[6]		X[1]			
Archival Tissue for research[7]	X				
Fresh Tissue for research				X[13]	
Blood for research[8]		X		X	

[1] Includes vital signs (pulse, temperature, blood pressure, & weight). Height required at baseline only.
On the first day of treatment , vital signs will be measured within an hour prior to start of initial study drug administration, at 30 minutes during the infusion (± 5 minutes), at the end of infusion (+ 5 minutes), and at 30 and 60 minutes (± 5 minutes each) post-infusion. If the infusion takes longer than 60 minutes, blood pressure and pulse measurements should follow the principles described here or more frequently if clinically indicated.

[2] Baseline procedures (with the exception of informed consent and archival tissue) must be obtained within 14 days of registration. The CBC and chemistries will be repeated within 72 hours of 1 st dose of study treatment if baseline tests were more than 7 days prior to dosing.

[3] Informed consent should be obtained within 28 days prior to registration.

[4]

The baseline MRI can be up to 21 days prior to registration. The post-surgical MRI of brain should be done within 72 hours after surgery.

[5] Twelve-lead ECGs will be obtained after the subject has been resting in a supine position for at least 5 minutes. ECG will be in triplicate (taken 2-5 minutes apart).

[6] Patients will receive one dose of tremelimumab 75 mg (if on Arm 1), MEDI4736 750 mg (if on Arm 2) or the combination of both (if on Arm 3) approximately 2 weeks (14 days +/- 7 days) before surgery.

[7] Tumor from prior surgeries will be requested on all patients. Tissue will be analyzed in the Bloch Laboratory. Please refer to Section 9.3 and laboratory manual for details.

[8] Blood samples will be collected for various research tests at 1 st pre-operative treatment, day of surgery, C1D1 and at each adjuvant treatment imaging visits (i.e. every 2 cycles or 8 weeks):

a) 10ml blood in one 10ml Sodium heparin tube: To be collected and processed by the Bloch lab for peripheral blood lymphocytes (PBLs).
b) 8m (2x4ml) blood in two 5ml EDTA (purple top) tubes: To be collected and processed by the Wainwright lab for gene expression profile using mononuclear cells.
c) 10ml blood in one 10ml red top tube: To be collected and processed by the Wainwright lab for analysis of tryptophan catabolites and cytokines.

Please refer to section 9.0 and laboratory manual for more details

[9] Chemistries should include electrolytes, calcium, , albumin, alkaline phosphatase, bilirubin (total), SGPT(ALT), SGOT(AST), serum creatinine, and BUN.

[10] TSH, T4, T3

[11] Required at baseline only but may be repeated as clinically indicated thereafter.

[12] Includes hepatitis A antibody, hepatitis B (HBsAg reactive), and Hepatitis C (HCV RNA [qualitative] detection).

[13] Please refer to Section 9.1 and the laboratory manual for details.

5.2 Post-Surgery/Adjuvant Therapy

Time Period	Adjuvant Treatment[8]			Off Treatment		
Assessment/Activity	**Cycle 1 Day 1[2] (+/- 2d)**	**Cycle 2 Day 1 (+/- 2d)**	**Cycle 3+ Day 1 (+/- 2d)**	**Treatment Discontinuation**	**90 Days Post Last Dose (+/- 7d)**	**Follow-up[11]**
Concomitant medications	X	X	X			
Toxicity assessment	X	X	X	X	X	
Neurological exam and KPS[4]	X	X	X	X	X	
Vital signs & weight[1]	X	X	X			
CBC with diff[3]	X		X	X	X	
Comprehensive Chemistry Panel	X	X	X	X	X	
Thyroid Function Tests[6]	X		X	X	X	
ECG[7]	X			X		
Tumor Imaging (MRI/CT)	X[5]		X[5]	X[5]		
Tremelimumab monotherapy[12]	X	X	X			
MEDI4736 monotherapy[13]	X	X	X			
Combination therapy[14]	X	X	X[14]			
Research tissue	X[10]					
Research blood[9]	X		X[9]			
Survival status						X

[1] Includes weight, BSA, and vital signs (temperature, blood pressure, pulse rate, and). Following the initial pre-surgery dose, for subsequent doses, the post dose vitals and 1-hour observation period will not be required unless a subject experiences an infusion-related reaction. Vital signs will be measured within an hour prior to start of study drug administration, at 30 minutes during the infusion (± 5 minutes), at the end of infusion (+ 5 minutes). If needed, vital signs will be done at 30 and 60 minutes (± 5 minutes each) post-infusion. If the infusion takes longer than 60 minutes, blood pressure and pulse measurements should follow the principles described here or more frequently if clinically indicated.

[2] Adjuvant treatment (cycle 1 day 1) will resume approximately 14 days (+/- 7 days) after surgery, once the surgical wound has healed.

[3] Will be done every other week while on adjuvant treatment.

[4] Will be done prior to each cycle (monthly) while on adjuvant treatment.

[5] **If patients are unable to start treatment within 21 days of the post-surgical imaging, then repeat imaging with**

enhanced MRI or CT scan should be performed prior to initiation of adjuvant therapy. During adjuvant treatment, contrast-enhanced MRI or CT scan will be done approximately every 2 cycles or 8 weeks (prior to each odd cycle). If there is no progression of disease, patients will continue on treatment for up to 24 months. If a patient has disease progression (as defined in section 6.4) or clinical decline and undergoes further surgery but is found to have no pathologic evidence of significant tumor, the patient may then re-start treatment.

[6] Thyroid function tests will be done every 2 cycles (approximately every 2 months) during treatment. TSH will be done each time; free T3 and free T4 only if TSH is abnormal.

[7] ECGs are required within 1 hour prior to starting study treatment and at least once after the infusion is completed (anywhere from 0-3 hours) on Cycle 1 Day 1, again after approximately 16 weeks on treatment, and at the end of treatment. ECGs may be repeated at any other time point if clinically indicated. ECGs recorded during the treatment phase will be single tracing. Twelve-lead ECGs will be obtained after the subject has been resting in a supine position for at least 5 minutes in each case.

[8] During adjuvant treatment, one cycle is defined as 4 weeks for patients on Arms 1 and 2. For patients on Arm 3, please refer to the schedule outlined in footnote #14.

[9] Blood samples will be collected for various research tests at 1 st pre-operative treatment, day of surgery, C1D1 and at each adjuvant treatment imaging visits (i.e. every 2 cycles or 8 weeks):

a) 10ml blood in one 10ml Sodium heparin tube: To be collected and processed by the Bloch lab for peripheral blood lymphocytes (PBLs).
b) 8m (2x4ml) blood in two 5ml EDTA (purple top) tubes: To be collected and processed by the Wainwright lab for gene expression profile using mononuclear cells.
c) 10ml blood in one 10ml red top tube: To be collected and processed by the Wainwright lab for analysis of tryptophan catabolites and cytokines.

Please refer to section 9.0 and laboratory manual for more details

[10] Any patient who undergoes further surgery will have the option to use their tumor tissue for research to understand the immunologic changes occurring at the time of presumed drug failure. Please refer to Section 9 and laboratory manual for details.

[11] Follow up for disease progression (if not already documented) and survival will occur every 8-16 weeks once off treatment. All patients will be followed until death or 2 years/24 months from stopping treatment.

[12] Patients enrolled on Arm 1 will receive tremelimumab monotherapy: one 75 mg dose IV on day 1 (+/- 2 days) per cycle (every 4 weeks) up to 24 months.

[13] Patients enrolled on Arm 2 will receive MEDI4736 monotherapy: one 750 mg dose IV on days 1 and 15 (+/- 2 days allowed for each) per cycle (every 2 weeks) up to 24 months.

[14] Patients enrolled on Arm 3 will receive combination therapy (tremelimumab 75 mg + MEDI4736 750 mg) according to the following schedule: Tremelimumab will be administered IV every 4 weeks (Day 1 of each cycle) and MEDI4736 750mg every 2 weeks (Day 1 and Day 15 of each cycle) until the patients have received 7 doses of Tremelimumab and 14 doses of MEDI4736. Thereafter, from Cycle 7 (Week 25), Tremelimumab will be given every 12 weeks (+/-7 days) and MEDI4736 will be given every 2 weeks (+/- 2 days) until permanent discontinuation criteria (e.g. disease progression) is met. If there is no progression of disease, they will continue on treatment for up to 24 months.

6.0 ENDPOINT ASSESSMENT

6.1 Primary Endpoint

To determine the T-cell changes (immunologic changes) that occur in recurrent GBM treated with Tremelimumab and MEDI4736 as single agents and in combination. The changes from baseline will be assessed in blood samples and tissue samples before treatment and post-surgery for all patients in the 3 arms. A comparison between the changes observed in the 3 arms will be made.

Only patients who have had pre-treatment blood sampling, have undergone surgery with pre-surgical blood sampling, and are able to continue to post-operative drug treatment with blood sampling prior to the first post-surgical dose will be evaluable for this endpoint.

6.2 Secondary Endpoints

1. To evaluate the safety of either Tremelimumab or MEDI4736 alone and in combination for patients with recurrent GBM. The endpoints will be the number, frequency, and severity of adverse events (as defined by the NCI Common Terminology Criteria for Adverse Events or CTCAE version 4.03). Only patients who have been administered at least one dose of investigational drug will be evaluable for this endpoint.

2. To determine post-surgery, the time to progression (per Modified RANO criteria and iRANO criteria see below) for patients treated with either Tremelimumab or MEDI4736 alone and in combination of both. This will be defined as the number of months from the time of first dose of study treatment until progression of disease or death by any cause. Only patients who have been administered at least one dose of investigational drug and undergone surgery will be evaluable for this endpoint.

3. To determine post-surgery the overall survival for patients treated with Tremelimumab or MEDI4736 alone and in combination of both. This will be defined as the number of months surviving from the time of first dose of study treatment until death by any cause. Only patients who have been administered at least one dose of investigational drug and undergone surgery will be evaluable for this endpoint.

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4. To assess post-surgery, the MRI changes in patients treated with either Tremelimumab or MEDI4736 alone and in combination of both. Only patients who have been administered at least one dose of investigational drug, undergone surgery, and have undergone at least one post-surgery disease assessment will be evaluable for this endpoint.

6.3 Exploratory Endpoints

1. To correlate T-cell changes and PDL1 expression with patients outcome. Only patients who have been administered at least one dose of investigational drug and undergone surgery will be evaluable for this endpoint.

6.4 Response Assessment (Modified RANO criteria)

RANO Criteria for Response [66]				
	CR	PR	SD	PD
T1 gadolinium enhancing disease	None	≥ 50% decrease	< 50% decrease but < 25% increase	≥ 25% increase
T2/FLAIR	Stable or decrease	Stable or decrease	Stable or decrease	increase
New lesion	None	None	None	Present[1]
Corticosteroids	None	Stable or decrease	Stable or decrease	n/a
Clinical status	Stable or increase	Stable or increase	Stable or increase	decrease
Requirement for response	All	All	All	Any

The response to immunotherapy may differ from the typical responses observed with cytotoxic chemotherapy including the following (Wolchok et al 2009, Nishino et al 2013):

- Response to immunotherapy may be delayed
- Response to immunotherapy may occur after PD by conventional criteria
- The appearance of new lesions may not represent PD with immunotherapy
- SD while on immunotherapy may be durable and represent clinical benefit

Based on the above-described unique response to immunotherapy and based on guidelines from regulatory agencies, e.g., European Medicines Agency's "Guideline on the evaluation of anti-cancer medicinal products in man" (EMA/CHMP/205/95/Rev.4) for immune modulating anti-cancer compounds, the study use a modified RANO criteria to define PD:

Progressive disease post-baseline is defined as one or more of the following:

- New contrast-enhancing lesion outside of radiation field on decreasing, stable, or increasing doses of corticosteroids.
- Increase by > 50% (modified from >25% according to published RANO criteria) enhancement from the first post-surgical scan, or a subsequent scan with smaller tumor size, and the scan 8 weeks or later on stable or increasing doses of corticosteroids.
- Clinical deterioration not attributable to concurrent medication or comorbid conditions is sufficient to declare progression on current treatment.

Treatment with MEDI4736, Tremelimumab or both would continue between the initial assessment of progression and confirmation for progression. In addition, subjects may continue to receive MEDI4736, Tremelimumab or both beyond confirmed PD in the absence of clinically significant deterioration and if investigators consider that subjects continue to receive benefit from treatment.

As a secondary measure, for all response assessments, iRANO will be used for assessment.

RANO and iRANO criteria (iRANO= immunotherapy Response Assessment in Neuro-Oncology)				
	Response	**Malignant glioma**	**Low-grade glioma**	**Brain metastasis**
1.	Complete Response	Disappearance of all enhancing disease for ≥4 weeks; no new lesions; stable or improved T2/FLAIR; no more than physiological steroids; clinically stable or improved	Disappearance of all enhancing and T2/FLAIR disease for ≥4 weeks; no new lesions; no more than physiological steroids; clinically stable or improved	Disappearance of all enhancing target and non-target lesions for ≥ 4 weeks; no new lesions; no steroids; clinically stable or improved
2.	Partial response	≥50% decrease in the sum of biperpendicular diameters of enhancing disease for ≥4 weeks; no new lesions; stable or improved T2/FLAIR; stable or decreased steroid dose; clinically stable or improved	≥50% decrease in the sum of biperpendicular diameter of T2/FLAIR disease for ≥4 weeks; no new lesions; stable or decreased steroid dose; clinically stable or improved	≥30% decrease in sum of longest diameters of target lesions for ≥4 weeks; no new lesions; stable or decreased steroid dose; clinically stable or improved
3.	Stable Disease	NA	25–49% decrease in the sum of biperpendicular diameters of T2/FLAIR disease for ≥4 weeks; no new lesions; clinically stable or improved	NA
4.	Progressive Disease	≥25% decrease in the sum of biperpendicular diameters of enhancing disease; or new lesions; or substantial worsened T2/FLAIR; or substantial clinical decline	≥25% decrease in the sum of biperpendicular diameters of T2/FLAIR disease; or new lesions; or substantial clinical decline	≥20% decrease in the sum of longest diameters of target lesions; or unequivocal progression of enhancing non-target lesions; or new lesions; or substantial clinical decline
The iRANO criteria integrate into the existing RANO criteria for malignant glioma, low-grade glioma, and brain metastases by providing recommendations for the interpretation of progressive imaging changes. Specifically, iRANO recommends confirmation of disease progression on follow-up imaging 3 months after initial radiographic progression if there is no new or substantially worsened neurological deficits that are not due to comorbid events or concurrent medication, and it is 6 months or less from starting immunotherapy. If follow-up imaging confirms disease progression, the date of actual progression should be back-dated to the date of initial radiographic progression. The appearance of new lesions 6 months or less from the initiation of immunotherapy alone does not define progressive disease. FLAIR=fluid attenuated inversion recovery; N/A=not applicable				

7.0 ADVERSE EVENTS

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. The level of risk attributed to this study

requires high intensity monitoring, as outlined in the DSMP. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations.

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (see Section 5 for timepoints). In addition, certain adverse events must be reported in an expedited manner to allow for optimal monitoring and patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be followed until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

7.2 Definitions & Descriptions

7.2.1 Adverse Event

The International Conference on Harmonization (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 pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

Adverse events may be treatment emergent (i.e., 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 term AE is used to include both serious and non-serious AEs.

7.2.2 Severity of AEs

All adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE v4.03 is available at http://ctep.cancer.gov/reporting/ctc.html

If no CTCAE grading is available, the severity of an AE is graded as follows:

- Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
- Moderate (grade 2): the event causes discomfort that affects normal daily activities.
- Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- Life-threatening (grade 4): the patient was at risk of death at the time of the event.
- Fatal (grade 5): the event caused death.

All deaths that occur during the study, or within the protocol-defined 90-day post-last dose of study drug safety follow-up period must be reported 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 as a SAE within **24 hours** (see Section 7.3.3 for further details). 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. Deaths that occur following the protocol-defined 90-day post-last-dose of study drug safety follow-up period will be documented as events for survival analysis, but will not be reported as an SAE.

7.2.3 Serious Adverse Events (SAEs)

All SAEs, regardless of attribution, occurring from time of signed informed consent, through 90 days after the last administration of study drug, must be reported upon discovery or occurrence.

An SAE is defined in regulatory terminology as any untoward medical occurrence that:

- **Results in *death*.**
  - If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- **Is life-threatening.**
  - The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- **Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.**
- **Results in persistent or significant disability or incapacity.**
- **Is a congenital anomaly/birth defect in the offspring of the subject.**
- **Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.**

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event". For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

The causality of SAEs (their relationship to all study treatment/procedures) will be

assessed by the investigator(s) and communicated to AstraZeneca.

7.2.4 Adverse events of special interest (AESI)

Adverse events of special interest (AESIs) are events of scientific and medical interest specific to the further understanding of the MEDI4736 and/or Tremelimumab safety profile and require close monitoring and rapid communication by the investigator to the sponsor. MEDI4736 and/or Tremelimumab AESIs may be serious or non-serious. The rapid reporting of these AESIs allows ongoing analysis of these events in order to characterize and understand them in association with the use of this investigational product.

MEDI4736, an anti-PD-L1 antibody, and Tremelimumab, an anti-CTLA-4 antibody belong to a class of anticancer therapies, called "checkpoint-inhibitors" that amplify antitumor immune responses by blocking inhibitory signaling pathway modulated by the co-inhibitory or co-stimulatory receptors, CTLA-4 and PD-1, expressed on T cells (Callahan and Wolchok, 2013). This class of drugs can have a wide spectrum of immune-mediated reactions that have been considered inflammatory in nature and can affect any organs of the body. Based on this mechanism of action of MEDI4736 and related molecules Adverse events of special interest include immune-mediated reactions such as enterocolitis, dermatitis, hepatotoxicity or hepatitis, pancreatitis endocrinopathy, neuropathy and pneumonitis.

7.2.4.1 Pneumonitis

Adverse events of pneumonitis are of interest for AstraZeneca/Medimmune, as pneumonitis has been reported with anti-PD-1 MAbs (Topalian et al, NEJM 2012). Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended. Guidelines for the management of subjects with immune-mediated events including pneumonitis are outlined in Table 1.

Immune-mediated pneumonitis is characterized by inflammation focally or diffusely affecting the lung parenchyma that may be result of off-target effects of checkpoint inhibitors against the normal lung parenchyma. (Chow, 2013) Presentations of pneumonitis range from asymptomatic lung infiltrates to a mimic of severe bacterial pneumonia. For symptomatic patients, complaints and findings may include dyspnea, cough, tachypnea, pleuritic chest pain, and hypoxia. The frequency of immune-mediated pneumonitis in clinical trials with immune checkpoint-inhibitors ranged from ≤1% to 4%. (Topalian et al, 2012; Brahmer et al, 2012).

Because pneumonitis can quickly escalate and become fatal, early recognition is essential. Initial workup includes chest imaging; however, pneumonitis can have highly variable appearances on chest CT scans. In patients with pulmonary metastases or cardiopulmonary comorbidities, evaluation can be particularly challenging as it can be difficult to differentiate between infection, early pulmonary edema, alveolar hemorrhage, immune-mediated pneumonitis, immune-related tumor inflammation, and tumor progression (Topalian et al, 2012). Pneumonitis has also been reported as a complication of cancer treatment associated with lung and breast cancer.

Guidelines for the management of subjects with immune-mediated events including pneumonitis are outlined in Table 1.

7.2.4.2 Anaphylaxis and Serious Allergic Reactions

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 (IgE-mediated) and anaphylactoid reactions against the MAb, and serum sickness. Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy (Brahmer et al 2012).

Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnoea, cyanosis, respiratory failure, urticaria, pruritis, 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 Table 1.

7.2.4.3 Infusion-Related Reactions

The frequency of Infusion-related reactions (IRR) in clinical trials with immune checkpoint-inhibitors ranged from ≤1% to 10%. A high frequency of mild infusion reactions, was observed with anti-PD-L1 and anti-PD-1 therapy (Brahmer et al 2012).

Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritis, angioedema, hypotonia, urticaria, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness. The typical onset can be within 30 minutes to two hours after the initiation of drug infusion, although symptoms may be delayed for up to 24 hours. The majority of reactions occur after the first or second exposure to the agent, but between 10 and 30 percent occur during subsequent treatments (Lenz, 2007).

7.2.4.4 Hepatic function abnormalities (hepatotoxicity)

Immune-mediated hepatitis/ hepatic toxicity is the inflammation of the liver due to the dysregulation of host immunity related to immune checkpoint inhibitors and often manifests as asymptomatic elevated levels of hepatic transaminases (ALT, AST,) and bilirubin) (Kim et al, 2013). In clinical trials, the frequency of immune-mediated hepatitis was typically around ≤1%. (Brahmer et al, 2012; Topalian et al, 2012; Hamid et al, 2013; Tarhini, 2013). In published studies with anti-CTLA-4 mAbs, immune-mediated hepatitis, manifesting as elevations in AST and ALT, has been reported to occur in 3-9% of treated patients (Weber et al, 2012).

In Ipilimumab-treated patients, clinical manifestations of hepatitis included nonspecific symptoms of mild fever, general weakness, fatigue, nausea and/or abdominal pain. In the absence of clinical symptoms, treatment-emergent hepatitis presented asymptomatically as elevated hepatic transaminases. Ultrasonograms of the liver can appear normal or may demonstrate homogenous hepatomegaly, edema, or enlarged perihepatic lymph nodes. Biopsy of the liver most commonly shows a diffuse T-cell infiltrate. Other reported pathology patterns include inflammation focused around either hepatocytes or bile ducts.

If subject presents with liver dysfunction, a high suspicion for irAE(Infusion Related Adverse Event) hepatitis is warranted, however, it is important to distinguish treatment-related toxicity and rule out other causes of hepatic injury, such as infection, preexisting medical conditions, immunosuppression, metabolic or cardiovascular derangements, other medications, or tumor progression.

Hepatic function abnormality is defined as any increase in ALT or AST greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product. Guidelines for management of subjects with hepatic function abnormality are outlined in Table 1.

Cases where a subject shows an AST **or** ALT ≥ 3x ULN **or** total bilirubin ≥ 2x ULN may need to be reported as SAEs. These cases should be reported as SAEs if, after evaluation they meet the criteria for a Hy's Law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

Criteria for Hy's Law (FDA Guidance 2009)

- The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo
- Among trial subjects showing such aminotransferase elevations, often with aminotransferases much greater than 3 x ULN, one or more also show elevation of serum total bilirubin to >2 x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
- No other reason can be found to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B, or C; pre- existing or acute liver disease; or another drug capable of causing the observed injury.

7.2.4.5 Dermatitis

Grade 1 and 2 dermatologic toxicities are among the most commonly seen irAEs in patients treated with immune checkpoint inhibitors. Mild dermatitis manifests as a local or diffuse maculopapular rash or erythroderma. Pruritus can accompany the rash or, less commonly, can present as an isolated complaint in the absence of skin findings. Blisters are rarely seen, and their presence signals significant toxicity. Grade 3 to 4 dermatologic irAEs that constitute severe and fatal dermatologic inflammation include Stevens-Johnson syndrome, toxic epidermal necrolysis, or rashes complicated by dermal ulceration or necrotic, bullous, or hemorrhagic manifestations (Tarhini, 2013; Kaehler, et al 2010).

The frequency of immune-mediated dermatitis (including eczema, eythema, rash maculopapular, rash and pruritus) in clinical trials with immune checkpoint-inhibitors ranged from 1.5% to 33%. (Brahmer et al, 2012; Topalian et al, 2012; Hamid et al, 2013; Tarhini, 2013). Other Life-threatening dermatologic complications such as Steven's Johnson Syndrome or toxic epidermal necrolysis have been seen in fewer than1% of patients. It is important to accurately qualify and quantify cutaneous toxicities.

Pathologic evaluations of biopsy specimens of affected skin often demonstrate eosinophilic infiltration or leukocytoclastic vasculitis; or, they may reveal a lymphocytic predominance characterized by CD8+ T cells, sometimes with tropism for melanin-containing cells. Specifically, in metastatic melanoma patients, the rash associated with immune-checkpoint inhibitors may be indicative of immune response to melanocytes and may progress to vitiligo in some cases. Biopsies showed severe dermatitis with papillary dermal edema,

sometimes accompanied by perivascular lymphocytic infiltrate.

Guidelines for the management of subjects with immune-mediated events including dermatitis are outlined in Table 1.

7.2.4.6 Enterocolitis

Immune-mediated enterocolitis/colitis generally manifests as mild to severe watery diarrhea accompanied by any changes in normal bowel habits or changes from baseline, abdominal pain, nausea/vomiting, or hematochezia. Any grade diarrhea has been the most frequently observed sign/symptom potentially associated with immune-mediated colitis. In severe cases, patients may experience significant dehydration, fever, ileus or peritoneal signs consistent with bowel perforation. Deaths secondary to bowel perforation have occurred.

The frequency of immune-mediated enterocolitis/colitis in clinical trials with immune checkpoint-inhibitors typically ranges from ≤1-8% (Brahmer et al, 2012; Topalian et al, 2012; Hamid et al, 2013; Tarhini, 2013).

Patients with mild symptoms (e.g., grade 1 abdominal pain or diarrhea) should be evaluated for infection, including Clostridium difficile infection. Endoscopy performed in these cases may identify an inflamed mucosa with ulceration, which can involve any part of the bowel but most commonly the descending colon (Weber et al, 2012; Wolchock et al, 2010). Tissue biopsies of the colon typically reveal significant inflammatory cell infiltrate.

Guidelines for the management of subjects with immune-mediated events including enterocolitis are outlined in Table 1.

7.2.4.7 Endocrinopathy (hypothyroidism, hyperthyroidism, hypopituitarism)

Immune-mediated endocrinopathies frequently reported in patients treated with checkpoint inhibitors include thyroiditis (hypo- or hyper-), hypopituitarism, hypophysitis, and/or adrenal insufficiency. The frequency of immune-mediated endocrinopathies in clinical trials with immune checkpoint-inhibitors ranged from ≤ 1% to 17%. (Tarhini, 2013; Topalian et al, 2012; Hamid et al, 2013). The most common endocrinopathy seen with ipilimumab is hypophysitis. In clinical trials with other PD-1/PD-L1 inhibitors, endocrine irAEs reported were similar to those reported for ipilimumab, but in contrast, generally milder with fewer events of severe to life-threatening (grades 3–4) irAEs (Sznol and Chen, 2013; Topalian et al, 2012; Wolchok et al, 2013; Hamid et al; 2013).

Clinical presentations of these endocrinopathies include a range of nonspecific symptoms resembling other causes, such as brain metastases or progression of underlying disease. The most common clinical presentation of endocrine irAEs includes nonspecific headache and fatigue, but may also include myalgias, visual field defects, behavioral changes, electrolyte disturbances, loss of appetite and hypotension. (Tarhini, 2013). Patients will generally have abnormal endocrine laboratory test results, that include TSH, free T4, total and free triiodothyronine (T3), cortisol, ACTH, luteinizing hormone, follicle-stimulating hormone, and testosterone (in men).

It is important to note that despite vague symptomatic presentation, there is a risk for serious morbidity or death if the endocrinopathy is not promptly identified and treated. Guidelines for the management of subjects with immune- mediated events including endocrinopathy are outlined in Table 1.

7.2.4.8 Neuropathy/Neuromuscular Events (to include MG and GB)

The frequency of immune-mediated neuropathy (including peripheral sensory neuropathy, neuropathy peripheral and peripheral motor neuropathy) in clinical trials with immune checkpoint-inhibitors ranged from ≤1% to 4.5%. (Sznol and Chen, 2013; Topalian et al, 2012; Wolchok et al, 2013; Hamid et al; 2013) Although they are rare, severe neuropathies and myopathies have been observed in patients treated with immune checkpoint inhibitors and include Guillain-Barré syndrome, transverse myelitis, or myasthenia gravis, among other diagnoses. Neuropathies associated with ipilimumab have been difficult to assess because these irAEs are transient and present with vague symptoms. Presentations of neurotoxicity may include a mild peripheral sensory neuropathy or muscle weakness. Symptoms of peripheral neuropathy include numbness, tingling, paresthesia (pins and needles sensations), sensitivity to touch, or muscle weakness. In patients with extreme symptoms, they may present with burning pain, muscle wasting, paralysis, or organ dysfunction. Symptoms are typically detected with physical examination findings ranging from sensory changes to loss of deep-tendon reflexes.

Depending on presentation, patients may require neuroimaging, nerve conduction studies, and, potentially, nerve or muscle biopsy to arrive at the diagnosis. Guidelines for the management of subjects with immune-mediated events including neuropathy or neuromuscular events are outlined in Table 1.

7.2.4 Unanticipated Problems Involving Risks to Subject or Others

A UPIRSO is a type of SAE that includes events that meet ALL of the following criteria:

- Is *unanticipated* in terms of nature, severity, or frequency
- Places the research subject or others at a different or *greater risk of harm*
- Is deemed to be *at least possibly related* to participation in the study.

Any AE deemed to be a UPIRSO will be reported to the local IRB as well as the NU QAM/DSMC.

7.2.5 Overdose

An overdose is defined as a subject receiving a dose of MEDI4736 or Tremelimumab in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study subject with MEDI4736 Tremelimumab, with or without associated AEs/SAEs, is required to be reported along the same timeframe as an SAE (see 7.3.3). If the overdose results in an AE, the event must also be recorded as an AE. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE. There is currently no specific treatment in the event of an overdose of MEDI4736 Tremelimumab. The treating investigator will use clinical judgment to treat any overdose.

7.2.6 Hepatic function abnormality

Hepatic function abnormality (as defined previously) in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to the QAM and AstraZeneca/MedImmune Patient Safety using the designated Safety e-mailbox (see 7.3.3.4), unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed. If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study subject

will be based on the clinical judgment of the investigator.

If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay. Each reported event of hepatic function abnormality will be followed by the treating investigator and evaluated by the PI and AstraZeneca/MedImmune.

7.2.7 Pregnancy

Pregnancy itself, or pregnancy of a subject's partner, is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/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 any conception occurring from the date of the first dose until 90 days after the last dose (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was withdrawn from the study.

Pregnancy in a female subject who has received investigational product is required to be reported ***within 24 hours of knowledge of the event*** to the QAM and AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox (7.3.3.4).
Subjects who become pregnant during the study period must not receive additional doses of investigational product but will not be withdrawn from the study. The pregnancy will be followed for outcome of the mother and child (including any premature terminations) and should be reported to AstraZeneca/MedImmune Patient Safety or designee after outcome. Male subjects should refrain from fathering a child or donating sperm during the study and for through 180 days after the last dose of MEDI4736 + tremelimumab combination therapy or 90 days after the last dose of MEDI4736 or tremelimumab monotherapy.

Should the investigator become aware of a pregnancy in the partner of a male study subject who has received investigational product this should be reported ***within 24 hours of knowledge of the event*** to the QAM and AstraZeneca/MedImmune Patient Safety or designee using the Safety Fax Notification Form. The funding sponsor will endeavor to collect follow-up information on such pregnancies provided the partner of the study subject provides consent.

7.3 Adverse Event Reporting

7.3.1 Routine Reporting

Adverse events will be recorded 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 the QAM and AstraZeneca/MedImmune Patient Safety.

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Changes in NCI CTCAE grade and the maximum CTC grade attained
- Whether the AE is serious or not

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

- Date AE met criteria for serious AE

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

All routine adverse events, such as those that are expected, or are unlikely or definitely not related to study participation, are to be reported on the appropriate eCRF. Routine AEs will be reviewed by the Data and Safety Monitoring Committee (DSMC) according to the study's phase and risk level, as outlined in the DSMP.

Adverse events and serious adverse events will be recorded from time of signature of informed consent, throughout the treatment period and including the follow-up period (90 days after the last dose of MEDI4736 or tremelimumab or the combination of both). During the course of the study all AEs and SAEs should be proactively followed up for each subject. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

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

The investigator is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation. AstraZeneca/MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

7.3.2 Determining if Expedited Reporting is Required

This includes all events that occur within 90 days of the last dose of protocol treatment.

1) Identify the type of adverse event using the NCI CTCAE v 4.03.
2) Grade the adverse event using the NCI CTCAE v 4.03.
3) Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:
    - Definite: AE is clearly related to the study treatment.
    - Probable: AE is likely related to the study treatment.
    - Possible: AE may be related to the study treatment.
    - Unlikely: AE not likely to be related to the study treatment.
    - Unrelated: AE is clearly NOT related to the study treatment.
4) Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:
    - the current protocol
    - the drug package insert
    - the current Investigator's Brochure

7.3.3 Expedited Reporting of SAEs/Other Events

7.3.3.1 Reporting to the Northwestern University QAM/DMC

All SAEs must be reported to the assigned QAM within 24 hours of becoming

aware of the event. Completion of the NU CTO SAE Form is required.

The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:

- Protocol description and number(s)
- The patient's identification number
- A description of the event, severity, treatment, and outcome (if known)
- Supportive laboratory results and diagnostics
- The hospital discharge summary (if available/applicable)

All SAEs will be reported to, and reviewed by, the DSMC at their next meeting.

7.3.3.2 Reporting to the Northwestern University IRB

The following information pertains to the responsibilities of the lead site (Northwestern University). Additional participating sites should follow their local IRB guidelines for reporting to their local IRBs.

- Any death of an NU subject that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB within 24 hours of notification.
- Any death of an NU subject that is actively on study treatment (regardless of whether or not the event is possibly related to study treatment)
- Any death of a non-NU subject that is unanticipated and at least possibly related and any other UPIRSOs will be reported to the NU IRB within 5 working days of notification.
- All other deaths of NU subjects not previously reported, other non-NU subject deaths that were unanticipated and unrelated, and any other SAEs that were not previously reported as UPIRSOs will be reported to the NU IRB at the time of annual continuing review.

7.3.3.3 Reporting to the FDA

The FDA will be notified within 7 calendar days of any SAE that is associated with study treatment, is unexpected, and is fatal or life-threatening.

The FDA will be notified within 15 calendar days of any SAE that is associated with the study treatment, unexpected, and serious but *not fatal or life-threatening*. This includes any previous SAEs that were not initially deemed reportable, but are later determined to meet the criteria for reporting (i.e. by the DSMC).

All other SAEs will be reported on an annual basis as part of the annual FDA report.

7.3.3.4 Reporting to AstraZeneca/MedImmune

All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 90 days after the last dose of MEDI4736 or until the initiation of alternative anticancer therapy. The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

NOTE TO AUTHOR: For trials conducted in the United States, the following must be included (similar language must be included, referencing the appropriate health authority and reporting mechanism, for studies conducted outside of the

United States). Note that all serious or unexpected adverse events must be reported to AstraZeneca regardless of the country where the study is conducted.

The investigator and/or sponsor must inform the FDA as outlined in 7.3.3.3 above, and will concurrently forward all such reports to AstraZeneca. A copy of the MedWatch report must be faxed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the sponsor to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

The NU CTO SAE report should accompany the MedWatch 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-14-10508)

The NU CTO SAE report will indicate 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 the SAE report and accompanying cover page by way of e-mail 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 (as applicable). Serious adverse events that do not require expedited reporting to the FDA still need to be reported to AstraZeneca using the NU CTO SAE form. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

8.0 DRUG INFORMATION

8.1 MEDI4736

8.1.1 Other names

Durvalumab

8.1.2 Classification - type of agent

MEDI4736, a human IgG1κ mAb directed against PD-L1, contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to C1q and the Fcγ receptors

8.1.3 Mode of action

MEDI4736 is being developed as a potential anticancer therapy for patients with advanced solid tumors. MEDI4736 is a human monoclonal antibody (MAb) of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of programmed cell death ligand 1 (PD-L1) (B7 homolog 1 [B7-H1], cluster of differentiation [CD]274) to programmed cell death 1 (PD-1; CD279) and CD80 (B7-1). MEDI4736 is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. MEDI4736 contains a triple mutation in the constant domain of the immunoglobulin (Ig) G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma (Fcγ) receptors involved in triggering effector function.

8.1.4 Storage and stability

MEDI4736 is formulated at 50 mg/mL in 26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, pH 6.0.

Lyophilized formulation: MEDI4736 is formulated at 50 mg/mL. The investigational product is supplied as a white to off-white lyophilized powder in clear 10R glass vials closed with an elastomeric stopper and a flip-off cap overseal. Each vial contains 200 mg (nominal) of active investigational product. MEDI4736 should be reconstituted with 4.0 mL sterile WFIwater for infusion to give a final concentration of 50 mg/mL.
Liquid formulation: MEDI4736 is formulated at 50 mg/mL. The investigational product is supplied as a vialed liquid solution in clear 10R glass vials closed with an elastomeric stopper and a flip-off cap overseal. Each vial contains 500 mg (nominal) of active investigational product at a concentration of 50 mg/mL.

Total in-use storage time from needle puncture of MEDI4736 vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2-8°C (36-46°F). If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration. MEDI4736 does not contain preservatives and any unused portion must be discarded.

8.1.5 Protocol dose specifics

MEDI4736 will be dosed at 750 mg intravenously (IV) every 2 weeks. Patients on Arm 2 will receive MEDI4736 monotherapy and patients on Arm 3 will receive MEDI4736 in combination with tremelimumab.

8.1.6 Preparation

MEDI4736 will be supplied in liquid form. Each vial is formulated at 50 mg/mL in 26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02% (weight/volume [w/v]) polysorbate 80, pH 6.0. Calculate the dose volume of MEDI4736 and number of vials needed for the subject to achieve the accurate dose.

The preparation of infusion bags should be done under aseptic conditions by trained personnel; it should **not to** be prepared on the floor. The reconstituted solution (for lyophilized product) or liquid product is to be diluted with 0.9% (w/v) saline or 5% (w/v) dextrose for IV infusion.

An additional volume of 0.9% (w/v) saline equal to the calculated volume of MEDI4736 to be added to the IV bag must be removed from the bag prior to addition of MEDI4736. The calculated volume of MEDI4736 is then added to the 250 ml 0.9% (w/v) saline IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

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. Vials should be used for specific subjects and should not be shared between subjects.

Total in-use storage time from reconstitution of MEDI4736 to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). If storage time exceeds these limits, a new dose must be prepared from new vials.

8.1.7 Route of administration for this study

MEDI4736 will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral vein. A central line can be used if needed. Following preparation of MEDI4736, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2-μm in-line filter.

The IV line will be flushed with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered. Document if the line was not flushed.

8.1.8 Incompatibilities

No formal drug-drug interaction studies have been conducted with MEDI4736. There are no known clinically significant interactions of MEDI4736 with other medicinal products. No incomtabilities between MED14736 and polyethylene, polypropylene, polyvinylchloride, or polyolefin copolymers have been observed.

Since the compatibility of MEDI4736 with other IV medications and solutions, other than normal saline (0.9% [w/v][sodium chloride for injection), is not known, the MEDI4736 solution should not be infused through an IV line in which other solutions or medications are being administered.

8.1.9 Availability & Supply

The Investigational Products Supply section of AstraZeneca/MedImmune will supply MEDI4736 to the investigator at Northwestern University as a concentrate for solution for infusion.

Investigational products will be supplied by Medimmune in containers with identical appearances in coded kits for each product respectively. Each investigational product kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each container within the carton). Each carton and vial is labeled with the same unique sequence number range. The investigational product is supplied as a vialed liquid solution in clear 10R glass vials closed with an elastomeric stopper and a flip-off cap overseal. Each vial contains 500 mg (nominal) of active investigational product at a concentration of 50 mg/mL (500 mg/vial).

8.1.10 Side effects

Frequent - Expected to occur in 10% to 25% of people (10 to 25 out of 100 people):

- Fatigue (13.5%)

Not Frequent – Expected to occur in 2% to less than 10% of people (2 to less than 10 out of 100 people):

- Nausea (8.4%)
- Diarrhea (5.3%)
- Decreased appetite (5.3%)
- Rash (5.3%)
- Vomiting (4.8%)
- Itchiness (4.1%)
- Difficulty breathing (3.8%)
- Fever (3.1%)
- Low thyroid (2.8%)
- Increased liver enzymes (2.5%)
- Cough (2.5%)
- Muscle pain (2.3%)
- Stomach pain (2.0%)
- Dizziness (2.0%)

Related and serious side effects reported in subjects receiving MEDI4736 alone were:

- Blockage in the urinary tract

- Fluid in the space surrounding the lung and inflammation of the lung
- Increase in calcium in the blood
- Joint pain
- Worsening of cancer
  Increase in liver enzymes and blockage of the tract between the liver and small intestine
- Spinal cord swelling
- Irregular heart beat or rhythm
- Chest pain and fluid in the abdomen
- Dehydration
- Disorder in the blood vessels of the organs
- Swelling of the tumor
- Lack of muscle control during walking or picking up objects

Uncommon side effects (≤1% - Expected to occur in less than 1 out of 100 people):

- Myocarditis
- Neutropenia
- Increased risk of infection e.g. pneumonia
- Myositis,
- Cerebral vasculitis,
- Sarcoidosis
- Arthritis, including arthritis of the jaw,
- Papilledema
- Cytokine release syndrome (CRS)

There was one death felt to be related to MEDI4736 when administered alone. The subject who had a prior history of cardiac illness including a prior heart attack died due to a disorder of the blood vessels. The Study Doctor also indicated possible other causes of the fatal event.

Please refer to current IB for more details and a complete list of side-effects.

8.1.11 Nursing implications

Subjects will be monitored during and after the infusion with assessment of vital signs (temperature, pulse, blood pressure and respiratory rate) at the times specified in the Schedule of Assessment (see Section 5.0). On treatment days, vital signs will be measured within an hour prior to start of drug administration, at 30 minutes during the infusion (± 5 minutes), at the end of infusion (+5 minutes), and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post-infusion. If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should follow the principles described here or more frequently if clinically indicated. For subsequent doses, the 1-hour observation period will not be required unless a subject experiences an infusion-related reaction.

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug 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.

For subjects with a ≤Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is ≥ Grade 3 or higher in severity, study drug will be discontinued.

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately

available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

8.1.12 Return and Retention of Study Drug
Any unused study drug will be destroyed per Northwestern policy.

8.1.13 Accountability and dispensation
Drug supply will be kept in the research pharmacy at Northwestern Memorial Hospital.

8.2 Agent Tremelimumab

8.2.1 Other names

8.2.2 Classification - type of agent
Tremelimumab is a human IgG2 anti-CTLA-4 mAb.

8.2.3 Mode of action
Tremelimumab is a human IgG2 mAb directed against CTLA-4. Tremelimumab has an overall molecular weight of approximately 149 kDa including oligosaccharides. Cytotoxic T lymphocyte-associated antigen 4 is a critical regulatory signal for T-cell expansion and activation following an immune response, and it serves as a natural braking mechanism that maintains T-cell homeostasis. During T-cell activation, T cells upregulate CTLA-4, which binds to B7 ligands on antigen-presenting cells, sending an inhibitory signal that limits T-cell activation. Tremelimumab blocks the inhibitory signal resulting from CTLA-4 binding to B7, leading to prolongation and enhancement of T-cell activation and expansion.

8.2.4 Storage and stability
Tremelimumab is supplied as a sterile IV solution, 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 mL accounting to 400 mg/vial) of Tremelimumab, in an isotonic solution at pH 5.5.

Tremelimumab should be stored at refrigerated temperatures (2°C to 8°C), and should not be frozen. The 20 mg/mL solution will be diluted into a saline bag for IV infusion. Vials containing Tremelimumab may be gently inverted for mixing, but should not be shaken. 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 2°C to 8°C (36°F to 46°F). If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Tremelimumab does not contain preservatives and any unused portion must be discarded.

8.2.5 Protocol dose specifics
Tremelimumab will be given at a dose of 75 mg IV every 4 weeks. Patients on Arm 1 will receive tremelimumab monotherapy and patients on Arm 3 will receive tremelimumab in combination with MEDI4736.

8.2.6 Preparation
Tremelimumab Drug Product is formulated at a nominal concentration of 20 mg/mL in 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.02% (weight/volume [w/v]) polysorbate 80, 0.27 mM disodium edetate dihydrate (EDTA), pH 5.5.

The Drug Product is supplied as a sterile IV solution in 20 mL clear glass vials with a rubber stopper and aluminum seal. Each vial contains 20 mg/mL of tremelimumab with a nominal fill of 20 mL (accounting to 400 mg/vial). Vials containing tremelimumab must be stored at 2^{o} C to 8°C (36°F to 46°F) and must not be frozen. Vials containing

tremelimumab may be gently inverted for mixing, but should not be shaken.

The product should be protected from light when not in use. 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 investigational product vial to 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). It is recommended that the prepared final IV bag be stored in the dark at 2°C to 8°C until needed. If storage time exceeds these limits, a new dose must be prepared from new vials. The refrigerated infusion solutions in the prepared final IV bag should be equilibrated at room temperature for about 2 hours prior to administration.

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

- IV infusion bags of 0.9% (w/v) sodium chloride injection (250 mL size).
- Saline bags must be latex-free and can be made of polyvinyl chloride (PVC)
- or polyolefins (eg, polyethylene), manufactured with DEHP or DEHP-free. IV infusion lines made of PVC/DEHP or PVC/tri octyl trimellitate or polyethylene or polyurethane. All DEHP-containing or DEHP-free lines are acceptable. Lines should contain a 0.22 or 0.2 μm in-line filter. The in-line filter can be made of polyethersulfone or polyvinylidene fluoride. Lines containing cellulose-based filters should not be used with tremelimumab.
- Catheters/infusion sets made of polyurethane or fluoropolymer with silicone and stainless steel and/or PVC components.
- Syringes made of polypropylene and latex-free. Polycarbonate syringes should not be used with tremelimumab.
- Needles made of stainless steel.

8.2.7 Route of administration for this study

Tremelimumab is to be administered as an IV solution at a rate of 250 mL/hr., followed by observation for 60 minutes.

For the combination arm, tremelimumab will be administered first. MEDI4736 infusion will start approximately 1 hour after the end of the tremelimumab infusion for the first infusion only. If there are no clinically significant concerns after the first cycle, the MEDI4736 infusion may be administered immediately after the tremelimumab infusion has finished in all other cycles, at the discretion of the investigator. The duration of each infusion will be approximately 1 hour.

8.2.8 Incompatibilities

No formal drug-drug interaction studies have been conducted with tremelimumab. However, in RCC studies, acute renal failure has been reported with the combination of tremelimumab and sunitinib. It is unknown whether a similar reaction will be observed when tremelimumab is combined with other tyrosine kinase inhibitors.

8.2.9 Availability & Supply

Investigational products will be supplied by Medimmune in containers with identical appearances in coded kits for each product respectively. Each investigational product kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each container within the carton). Each carton and vial is labeled with the same unique sequence number range.

Tremelimumab is formulated at 20 mg/mL in 20 mM histidine/histidine-HCl, 222 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, and 0.27 mM disodium edetate dihydrate, pH 5.5. The investigational product is supplied as a clear to opalescent,

colorless to yellowish liquid in a 20-mL clear, glass vial with a rubber stopper aluminum seal. Each vial contains 400 mg (nominal) of active investigational agent. The standard supply of tremelimumab is delivered in a white carton with 16 vials of tremelimumab within foam inserts.

Tremelimumab will be provided to Northwestern University by MedImmune. Northwestern University will request tremelimumab submitted via email. Please allow approximately 10 days for drug delivery.

8.2.10 Side effects

Below are safety data from 973 subjects with various types of cancer who received tremelimumab alone. Related side effects reported in subjects receiving tremelimumab alone were:

Very Frequent – Expected to occur in more than 25% of people (more than 25 out of 100 people):

- Diarrhea (41.2%)
- Itching (25.1%)

Frequent - Expected to occur in 10% to 25% of people (10 to 25 out of 100 people):

- Fatigue (23.8%)
- Nausea (21.9%)
- Vomiting (13.5%)
- Decreased appetite (11.3%)

Not Frequent – Expected to occur in more than 5% to less than 10% of people (more than 5 to less than 10 out of 100 people):

- Headache (7.2%)
- Fever (7.0%)
- Stomach pain (6.7%)
- Inflammation of the large intestine (5.5%)

Related and serious side effects reported in more than 1% of people (more than 1 out of 100 people) receiving tremelimumab alone were:

- Diarrhea (9.2%)
- Inflammation of the large intestine (3.6%)
- Vomiting (2.3%)
- Nausea (1.8%)
- Dehydration (1.8%)

Deaths thought to be related to tremelimumab when given alone were reported in approximately 0.5% of subjects treated (approximately 1 out 200 people). There were five deaths reported that were thought to be related to side effects caused by tremelimumab. The deaths per subject are summarized with the causes noted (where known):

Sudden death in a subject with advanced skin cancer who had a history of smoking. The subject had a family history of sudden cardiac death and had recently changed antidepressant medications. While on tremelimumab treatment, the subject had symptoms that might be consistent with decreased blood flow to the heart. However, the exact cause of death was not confirmed.

Lack of oxygen to the brain due to sudden and unexpected loss of heart function in a subject whose skin cancer had spread to the lungs. The subject had a history of medical conditions that could increase the risk for heart problems including diabetes, increased blood pressure, elevated levels of fat in the blood and diarrhea. One week before loss of

heart function, the subject experienced kidney failure, dehydration, fever and increased creatinine (a compound in the blood removed by the kidney that when high can indicate poor kidney function). The study doctor thought there was a possibility that the side effects and loss of heart function could be related to tremelimumab.

Imbalance of essential minerals necessary for body function due to long lasting diarrhea in a subject with advanced skin cancer. Blood clot in the lungs in a subject with advanced skin cancer that had worsened. In a subject with advanced skin cancer, respiratory failure in relation to an infection that occurred after complications from surgery performed to treat inflammation and bleeding of the large intestine was the immediate cause of death. The study doctor thought the large intestine inflammation and complications that followed after surgery were related to tremelimumab.

Subjects will be monitored during and after the infusion with assessment of vital signs at the times specified in the Schedule of Assessment (see Section 6.2)
On treatment days, vital signs will be measured within an hour prior to start of drug administration, at 30 minutes during the infusion (± 5 minutes), at the end of infusion (+ 5 minutes), and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post-infusion. If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should follow the principles described here or more frequently if clinically indicated. For subsequent doses, the 1-hour observation period will not be required unless a subject experiences an infusion-related reaction

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug 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.

For subjects with a ≤Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is ≥Grade 3 or higher in severity, study drug will be discontinued.

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

8.2.12 Return and Retention of Study Drug

Any unused study drug will be destroyed per Northwestern policy.

8.2.13 Accountability and dispensation

Drug will be kept in the research pharmacy at Northwestern Memorial Hospital.

9.0 CORRELATIVES/SPECIAL STUDIES

9.1 Tumor and peripheral lymphocyte changes

Samples will be collected and sent to the laboratory of:
Dr. Orin Bloch
300 E Superior Street-Tarry Bldg 2-725
Chicago, IL 60611
Lab Phone: (312) 503-4345
Office Phone: (312) 695-3799
PAGER NUMBER 19329

Tissue and blood samples from the operating room and from clinic will be collected by laboratory personnel and sent to the laboratory of Dr. Orin Bloch in Tarry 2-725 for processing.

Fresh Tumor tissue: removed at surgery will be used to extract tumor-infiltrating lymphocytes (TIL) for analysis. In addition, fresh frozen and formalin fixed paraffin embedded tissue will be banked for analysis. Extracted TILs will be used to evaluate the tumor infiltrative lymphocyte population by flow cytometry and paraffin embedded tissue will be used to evaluate TILs in situ by immunohistochemistry. If a patient has progression of disease and undergoes further surgery, they will have the option of allowing tissue to be analyzed for the above.

Blood sample: 10ml blood in one 10ml Sodium heparin tube. This will be collected at 1st pre-operative treatment, day of surgery, C1D1, and at each adjuvant treatment imaging visits (i.e. every 2 cycles or 8 weeks).

Blood collected prior to treatment on 1st pre-operative treatment day will be used for baseline evaluation of activated peripheral lymphocytes. Patients will then have blood drawn on day of surgery, and on the day of each MRI scan (i.e. every 2 cycles or 8 weeks) with extraction and banking of peripheral blood leukocytes (PBL).

PBLs obtained prior to drug administration will be studied by flow cytometry to identify relative populations of CD8 T cells (CD3+, CD8+, PD1+/-), CD4 T cells (CD3+, CD8+, PD1+/-), regulatory T cells (CD4+, CD25+, FoxP3+), and suppressive monocytes (CD45+, CD11b+, PD-L1+). Repeat assessment of PBL markers will be determined by flow cytometry of subsequent samples taken on the day of surgery, post operatively (C1D1) and then on MRI days. Additionally, TILs extracted from patient tissue will be evaluated for relative populations of activated CD8 T cells (CD3+, CD8+, IFN-g+, PD1+/-), activated CD4 T cells (CD3+, CD8+, IFN-g+, PD1+/-), regulatory T cells (CD4+, CD25+, FoxP3+), and suppressive monocytes (CD45+, CD11b+, CD163+, PD-L1+). CTLA-4 expression on effector and regulatory T cells can also be measured by flow cytometry. Double-labeled tissue immunofluorescence can also be performed on FFPE sections to obtain immune effector cell counts, reported as # cells / 10 hpf. Optimized labeling schemes include: CD8/IFN-g, CD4/IFN-g, CD8/PD-1, CD4/PD-1, CD68/PD-L1, GFAP/PD-L1 (to identify PD-L1+ tumor cells).

We will use our stimulation protocol for IFN-g from PBL to look for increased peripheral T cell reactivity before and after drug treatment

Banked PBLs, TILs and FFPE tissue from prior patients treated without the study drug will serve as comparative controls.

NOTE: Any leftover tissue from the study patients will be banked for future use. This should be clearly stated in the consent form.

Please refer to laboratory manual for further details on collection, labeling, shipping, processing and storage.

9.2 Peripheral blood analysis for gene expression, tryptophan metabolism and cytokine abundance

Additional blood samples will be collected at 1st pre-operative treatment, day of surgery, C1D1, and at each adjuvant treatment imaging visits (i.e. every 2 cycles or 8 weeks):

a) 8m (2x4ml) blood in two 5ml EDTA (purple top) tubes: PBMCs will be isolated, separated and analyzed to generate a gene expression profile.
b) 10ml blood in one 10ml red top tube: Serum will be analyzed 1) via HPLC for tryptophan and downstream catabolites, as well as for 2) cytokines via an array-based platform.

Responders and non-responders (if separable) will be identified based on progression free- and/or

overall-survival and cross-referenced with gene expression/tryptophan catabolite/cytokine analysis.

Samples will be picked up by laboratory personnel and sent to:
Dr. Derek Wainwright's laboratory.
300 E Superior Street-Tarry Bldg 2-703 (Office); 2-725 (Lab)
Chicago, IL 60611
Lab Phone: (312) 503-5168;
Office Phone: (312) 503-3161

Please refer to laboratory manual for further details on collection, shipping, processing and storage.

9.3 Archival Tissue for PD- L1 analysis

Four unstained slides cut at 5µ from a representative tumor block will be delivered to the Bloch lab for PD-L1 analysis (see section 9.1 for contact information).

An additional 3 unstained slides cut at 5 microns will be hand delivered to PCF IHC **within 7 days of sectioning** for commercial analysis of PD-L1. We will use the commercially available assay [e.g. Ventana Medical Systems, Inc. (Ventana)].

Please refer to laboratory manual for further details on collection, shipping, processing and storage.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

To determine the T-cell changes that occur in recurrent GBM treated with Tremelimumab and MEDI4736 as single agents and in combination.

- To evaluate the safety of either Tremelimumab or MEDI4736 alone and in combination in patients with recurrent GBM.
- To determine the time to progression for patients treated with either Tremelimumab or MEDI4736 alone and in combination of both post-surgery.
- To determine the overall survival for patients treated with Tremelimumab or MEDI4736 alone and in combination of both post-surgery.
- To correlate T-cell changes and PDL1 expression with patients outcome.
- To assess MRI changes in patients treated with either Tremelimumab, or MEDI4736 alone, and in combination of both post-surgery.

10.3 Sample Size, Accrual and Data Analyses Plans

There will be three groups of patients, one group on each agent alone and one group treated with the combination agent. There will be 10 patients per group for a total of 30 patients. These 30 patients must be evaluable for the primary endpoint, meaning that they must have undergone surgery and their blood and tissue samples are available at both the pre- and post-surgery times. In order to attain 10 evaluable patients in each arm, a total of 45 patients will be accrued to the study. Sample sizes of 10 per group allow for the estimation of the proportion of responders in evaluable patients to be within 31% of its true value with 95% confidence. Mean change will be compared between arms. Using standard deviations of change, a sample size of 10 per group will allow the detection of differences of 1.25 standard deviations between groups with 80% power assuming a two-tailed test and a Type I error rate of 5%.

Immunologic measures will be summarized over the three or more time points (pre-treatment, following first treatment/pre-surgery, post-surgery) and changes in these measures will be assessed using repeated measures analysis of variance or Cochran's Q, followed by the paired t-test or the signed rank test for pairwise comparisons using Bonferroni corrections. Safety of the agents alone or in combination will be assessed by summarizing the frequency of adverse events by type, timing, grade and attribution. Response criteria will be based on RANO (including upcoming Immunologic RANO criteria) but since all patients will be post-surgery, the degree, if any, of

residual disease will vary. A patient is evaluable for efficacy if they have undergone at least one follow-up MRI after adjuvant therapy. Immunologic changes will be correlated with MRIs in a descriptive fashion. The secondary endpoint of progression-free survival as well as overall survival will be analyzed using Kaplan-Meier curves. Immunologic changes of T-cells and PDL1 levels will be correlated to survival outcomes using Cox regression analysis. MRI changes will be summarized using means or proportions and statistically analyzed using the signed rank test.

Performance Status: Patients will be graded according to Karnofsky Performance Status (KPS)(see appendix C).

Evaluation of toxicity. All patients will be evaluable for toxicity from the time of their first treatment as per NCI CTCAE version 4.03

Time to Progression: From date of first treatment to the date of first observation of definitive progressive disease, non-reversible neurologic progression or increasing steroid requirements (applies to stable disease only), death due to any cause, or early discontinuation of treatment. Patients not reaching the progression endpoint at last follow-up will be censored at that time.

Time to Death: From date of first treatment to date of death due to any cause. Patients alive at last follow-up will be censored at that time.

11.0 STUDY MANAGEMENT

11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to ICH/Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.2 Amendments

The Principal Investigator will formally initiate all amendments to the protocol and/or informed consent. All amendments will be subject to the review and approval of the appropriate local, institutional, and governmental regulatory bodies, as well as by Astra Zeneca/MedImmune Amendments will be distributed by the lead institution (Northwestern) to all affiliate sites upon approval by the Northwestern University IRB.

11.3 Registration Procedures

BEFORE a patient can be treated on study, please complete and submit the following items to confirm eligibility and receive a subject identification number:

- Eligibility eCRF (complete in NOTIS)
- Eligibility checklist (signed and dated by the treating physician – upload in NOTIS)
- Signed and dated informed consent document (upload in NOTIS)
- Pathology Report (upload in NOTIS)

The QAM will review the registration, register the patient, assign an identification number, and send a confirmation of registration to involved personnel. Registration will then be complete and the patient may begin study treatment.

11.4 Data Submission

Once a subject is confirmed and registered to the study, eCRFs should be submitted according to the study procedures table (see Section 5.0). Generally, for all phase II patients, data are due at the end of every cycle.

11.5 Data Management and Monitoring/Auditing

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern. The level of risk attributed to this study requires high intensity monitoring, as outlined in the DSMP. The assigned QAM, with oversight from the Data and Safety Monitoring Committee, will monitor this study in accordance with the study phase and risk level.

11.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.6.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within 5 business days of making the change, and the QAM must be notified within 24 hours of such change.

11.6.2 Other Protocol Deviations

All other deviations from the protocol must be reported to the assigned QAM using the appropriate form.

A protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs.
- Has no substantive effect on the risks to research participants.
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected.
- Did not result from willful or knowing misconduct on the part of the investigator(s).

A protocol deviation may be considered an instance of Reportable New Information (RNI) if it:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.
- Any deviation that would constitute an instance of Reportable New Information must be reported to the Northwestern IRB within 5 business days of knowledge or notification.

11.7 Investigator Obligations

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The PI is responsible for personally overseeing the treatment of all study patients. The PI must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected, entered onto the appropriate eCRFs, and submitted within the study-specific timeframes. Periodically, monitoring visits may be conducted and the Principal

entry. The study may also be subject to routine audits by the Audit Committee, as outlined in the DSMP.

11.8 Publication Policy

All potential publications and/or data for potential publications (e.g. manuscripts, abstracts, posters, clinicaltrials.gov releases) must be approved in accordance with the policies and processes set forth in the Lurie Cancer Center DSMP. For trials that require high intensity monitoring the assigned QAM will prepare a preliminary data summary (to be approved by the DSMC) no later than 3 months after the study reaches its primary completion date (the date that the final subject is examined or receives an intervention for the purposes of final data collection for the primary endpoint). If the investigator's wish to obtain DSMC-approved data prior to this point (or prior to the point dictated by study design), the PI must send a written request for data to the QAM which includes justification. If the request is approved, data will be provided no later than 4 weeks after this request approval. The data will be presented to the DSMC at their next available meeting, and a final, DSMC-approved dataset will be released along with any DSMC decisions regarding publication. The investigators are expected to use only DSMC-approved data in future publications. The investigators should submit a copy of the manuscript to the biostatistician to confirm that the DSMC-approved data are used appropriately. Once the biostatistician gives final approval, the manuscript may be submitted to external publishers.

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APPENDIX A – COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V4.03 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

APPENDIX B – ACCEPTABLE METHODS OF CONTRACEPTION

Table 5 - Effective methods of contraception (two methods must be used)

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

[a] This is also considered a hormonal method.

NOTE: Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

APPENDIX C – KARNOFSKY PERFORMANCE SCALE (KPS)

Points	Description
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity
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
60	Requires occasional assistance but is able to care for most of his/her needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization indicated. Death not imminent
20	Very sick; hospitalization necessary; active support treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

APPENDIX D – PROTOCOL SUMMARY OF CHANGES

Amendment 1 –January 15th, 2016 (before initial IRB submission)			
Sections(s) Affected	***Prior Version***	***Amendment 1 Changes***	***Rationale***
Section 1.3.3 Durvalumab safety	Previous safety information	***Added:*** additional safety information based on updated IB version 9	***Per new Investigator's Brochure(IB) (v9)***
Section 1.4.2 Tremelimumab safety	Previous safety information	***Added***: Additional safety information about Durvalumab and Tremelimumab combination therapy	***Per new Investigator's Brochure(IB) (v9)***
Section 4.5 Toxicity management tables	Previous tables	Deleted previous tables Inserted Updated tables according to new IB	***Per new Investigator's Brochure(IB) (v9)***

Table 2 Infusion-Related Reactions	Grade 2 The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event (upto 4 hours).	***Updated:*** Grade 2 The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event	***Per new Investigator's Brochure(IB) (v9)***
Section 8.1.4 Durvalumab Storage and Stability	The investigational product is supplied as a vialed liquid solution in clear 10R glass vials closed with an elastomeric stopper and a flip-off cap overseal. Each vial contains 500 mg (nominal) of active investigational product at a concentration of 50 mg/mL (500 mg/vial). The solution will be diluted with 0.9% (weight/volume [w/v]) saline for IV infusion. Unopened vials of liquid MEDI4736 must be stored at 2°C to 8°C (36°F to 46°F). MEDI4736 must be used within the individually assigned expiry date on the label.	**Lyophilized formulation:** MEDI4736 is formulated at 50 mg/mL. The investigational product is supplied as a white to off-white lyophilized powder in clear 10R glass vials closed with an elastomeric stopper and a flip-off cap overseal. Each vial contains 200 mg (nominal) of active investigational product. MEDI4736 should be reconstituted with 4.0 mL sterile WFIwater for infusion to give a final concentration of 50 mg/mL.	***Per new Investigator's Brochure(IB) (v9)***

Section 8.1.6 Durvalumab preparation	Previous information	***Added*** . The reconstituted solution (for lyophilized product) or liquid product is to be diluted with 0.9% (w/v) saline or 5% (w/v) dextrose for IV infusion.	***Per new Investigator's Brochure(IB) (v9)***
Amendment 2 –July 05, 2016			
Sections(s) Affected	***Prior Version***	***Changes made***	***Rationale***
Throughput Study Schema Study summary Section 4.2 Section 4.6 Section 5.2	The FDA reviewer noted that protocol was inconsistent throughout with respect to the duration of treatment of patients on the combination arm (Arm 3).	Language added to clarify that 'In all arms, if there is no progression of disease, patients will continue on treatment for up to 24 months.'	***In response FDA request for clarification.***
Title;	A Phase II, open label, clinical trial of pre-surgical and adjuvant treatment of recurrent malignant glioma with Tremelimumab and Durvalumab (MEDI4736) alone and in combination to determine immunologic changes from treatment.	A Phase II, open label, clinical trial of pre-surgical and adjuvant treatment of recurrent Glioblastoma with Tremelimumab and Durvalumab (MEDI4736) alone and in combination to determine immunologic changes from treatment.	***In response to FDA request for clarification.*** The clinical protocol was inconsistent with respect to the study population to be enrolled. Language has been added/modified to clarify this.

Section 3.1	Study population to be enrolled: Grade III or IV glioma patients	Study population to be enrolled: Patients with prior diagnosis of Grade IV glioma (glioblastoma), according to WHO 2016 criteria	***In response to FDA request for clarification.*** The clinical protocol was inconsistent with respect to the study population to be enrolled. Language has been added/modified to clarify this.

Study summary; Section 2.1, 2.2; 3.0; 6.1; 6.2;10.1	patient population was stated as glioblastoma	Added the word recurrent to state 'recurrent glioblastoma'	***In response to FDA request for clarification.*** The clinical protocol was inconsistent with respect to the study population to be enrolled. Language has been added/modified to clarify this.
Section 4.2	"Any patient who has disease progression as defined in section 6.0 or clinical decline and undergoes further surgery will have the option to use their tumor tissue for research to understand the immunologic changes occurring at the time of presumed drug failure. If on pathologic review, there is no evidence of significant tumor and the changes on MRI were likely treatment related, the patient can re-start treatment."	**Modified sentence**: "If on pathologic review, there is no evidence of significant tumor and the changes on MRI were likely treatment related, the patient will be allowed to re-start treatment." **Added language:** "The patient will be advised of the pathology results and that they may not derive any further benefit from therapy and they will need to re-sign the informed consent prior to starting therapy."	***In response to FDA request for clarification***. FDA requested that in Section 4.2 the said patients should be re-consented prior to re-treatment to inform them of the uncertain nature of a "negative" pathology finding and the possibility that they may derive no benefit from re-treatment."
Study summary; Section 4.1 and 4.2	Patients will be randomly allocated using variable size block randomization to ensure equal sample sizes per arm	Patients will be randomly allocated using **block randomization** to ensure equal sample sizes per arm.	***Per statistician***

Section 3.1.13	"Males: Creatinine CL (mL/min)= Weight (kg) x (140 – Age) 72 x serum creatinine (mg/dL)" "Females: Creatinine CL (mL/min)=Weight (kg) x (140 – Age) 72 x serum creatinine (mg/dL)"	**Modified Language:** "Males: Creatinine CL (mL/min)=Weight (kg) x (140 – Age) x 1.0 72 x serum creatinine (mg/dL)" "Females: Creatinine CL (mL/min)=Weight (kg) x (140 – Age) x 0.85 72 x serum creatinine (mg/dL)"	**Correction in formula.**
Schema		**Added Text Box:** "CT or MRI w contrast every 2 cycles"	**Clarification**
Section 3.1 & 3.2	" 3.1.18 Malignancy treated with curative intent and with no known active disease ≥3 years before the first dose of study drug and of low potential risk for recurrence. NOTE: the exceptions to this requirement include adequately treated non-melanoma skin cancer or lentigo maligna or carcinoma in situ without evidence of disease." **"**3.1.19 Patients can only be on non-enzyme inducing anti-convulsants. If they are on an enzyme inducing anti-convulsant, they may be converted to a non-enzyme inducing anti-convulsants but they will need a 2 week wash out period from time of drug discontinuation until day 1 of study treatment."	**Reworded and moved from Inclusion to Exclusion Criteria** "3.2.7 Patients on an enzyme-inducing anti-convulsant who cannot be switched to a non-enzyme-inducing anti-convulsant with a 2 week wash-out period from time of drug discontinuation until Day 1 of study treatment." "3.2.15 Patients with a history of active malignancy within 3 years prior to registration. Note: exceptions to this requirement include adequately treated non-melanoma skin cancer or lentigo maligna or carcinoma in situ without evidence of disease."	**Administrative**

Section 4.3.4	"Enzyme inducing anti-convulsants"	**Added:** "Enzyme inducing anti-convulsants (eg: Carbamazepine, Phenytoin, Primidone, Topiramate). Please check with PI if have further questions."	**To Add Clarity**
Table 1 & List of Abbreviations		**Removed Abbreviations from the End of Table 1 in Section 4.5 and incorporated them into the List of Abbreviations**	**Administrative**
Section 4.7	"Subjects who are permanently discontinued from receiving investigational product will be followed for safety including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study."	**Added Language:** "Subjects who are permanently discontinued from receiving investigational product will be followed for safety for 30 days post last-dose visit including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study. If a subject is enrolled in another clinical study, they will be followed until all AEs are resolved or stable. If enrolled onto another clinical study, it is not necessary to follow the subject for survival or progression."	**To Add Clarity**

Section 4.7	"Subjects who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative."	**Changed to:** "Subjects who decline to return to the site for evaluations will be offered follow-up by phone every 8-16 weeks as an alternative."	**Correction**

Amendment 3 – November 22, 2016			
Sections(s) Affected	***Prior Version***	***Changes made***	***Rationale***
Study summary	First key eligibility criteria read" grade or IV glioma"	Corrected to read" grade IV glioma"	***Correction of typographical error***.
Study summary; Section 4.2 treatment administration; Section 5.2 Study procedures table (Post-Surgery/Adjuvant Therapy)	Day 1 tremelimumab + MEDI4736, Day 15 MEDI4736. This will be followed until patients have received 14 and 7 doses of tremelimumab and MEDI4736 respectively. Thereafter, both drugs will be given together once every 12 weeks up to 24months	Language modified to : Tremelimumab will be administered IV every 4 weeks (Day 1 of each cycle) and MEDI4736 750mg every 2 weeks (Day 1 and Day 15 of each cycle) until the patients have received 7 doses of Tremelimumab and 14 doses of MEDI4736. Thereafter, from Cycle 7 (Week 25), Tremelimumab will be given every 12 weeks (+/-7 days) and MEDI4736 will be given every 2 weeks (+/- 2 days) until permanent discontinuation criteria (e.g. disease progression) is met. If there is no progression of disease, they will continue on treatment for up to 24 months.	***To increase clarity regarding dosing schedule***
Section 1.4.2 background and rationale	language regarding fixed dosing of MEDI4736 and tremelimumab	Inserted language regarding dosing schedule for both Tremelimiumab and durvalumab in the 3 Arms. Arm 3 language updated as in rest of protocol.	***To increase clarity***
Study summary Section 3.1.5 Inclusion criteria	"patients must be surgical candidates"	Modified to state "Patients must be surgical resection candidates"	***To increase clarity and specificity***

Section 3.1.11 Inclusion criteria	The goal should be dexamethasone 4 mg or less at the time of starting treatment. If patient requires > 4mg of steroid, please check with the PI. Requirement for greater than 10mg of steroid will make the patient ineligible.	Modified to : "Patient's must be on no more than 8 mg a day but an attempt should be made to keep the dose at 4 mg or less. Please contact the PI if doses of > 4 mg are needed."	***For clarity and flexibility***
Section 3.2.6 Exclusion criteria	Patients receiving any other investigational chemotherapeutic agents within 30 days prior to the first dose of trial treatment.	The window has been changed from 30 days to '28 days'.	***For convenience and to be in alignment with other windows in the study.***
Study summary Section 4.2 and Section 5.2	Arm 3 MED14736 dose was stated as 10mg/kg	Modified to state fixed dosing of MED14736, which is 750mg (per sponsor specifications).	***To be consistent with rest of the protocol. A memo was sent out earlier regarding this***
Section 4.2 Table Treatment administration	Arm 3: Treme every 4 weeks (for 7 doses) + MEDI every 2 weeks (for 14 doses); then T every 12 weeks together Arm1 and 2: Only adjuvant therapy dose listed	Updated to : Treme every 4 weeks (for 7cycles) + MEDI every 2 weeks (for 14 doses); then Treme every 12 weeks and MEDI every 2 weeks from C7(wk. 25). Updated to include pre-surgery and adjuvant doses	***For consistency, in keeping with modifications made to treatment administration***
Section 4.4 Events Requiring Dose Modification	A couple of sentences referring to DLT was inserted in error	All DLT language removed	***Correction of error. DLT language not required in this protocol since it is a Phase II trial.***
Section 4.5 Toxicity Management & Dose Delays/Modifications Table 2	Table 2 describing Infusion-Related Reactions	A row added in the table stating Grade 3 –first occurrence specifications. Next row renamed as "Grade 3 repeat occurrence or if /Grade 4"	***To maintain consistency with Merck template specifications that are stated in section 4.4***

Study table(Pre-surgery and surgery) Section 5.1	Screening MRI window was 14 days. .	Added language to footnote 4 stating that screening MRI window can be up to 21 days prior to registration.	***The window has been increased by the PI so that previously done MRIs can be used.***
Section 5.1 and 5.2 Pre-surgery and Post-Surgery/Adjuvant Therapy tables. Footnote 1: instruction regarding vital sign monitoring	"On treatment days, vital signs will be measured within an hour prior to start of study drug administration." "For subsequent doses, 1-hour observation period will not be required unless a subject experiences an infusion-related reaction." Respiratory rate included as part of vitals in both tables.	Footnote 1 in 5.1. Modified to indicate that pre and post vitals will be done for the first dose. Footnote 1 in 5.2 modified to indicate that for subsequent doses, the post dose 30 and 60 minute vitals and 1-hour observation period will be done only if there is an infusion related reaction. Removed respiratory rate from vitals in both tables	***For clarity and convenience.***
Section 7.3 Adverse Event Reporting	Inconsistency regarding AE reporting period wherein 30 days and 60 days are stated in two different sub-sections	AE reporting period stated to be 60 days	***Correction to improve clarity and consistency***
Section 8.1.10	List of side effects of MED14736	Added language: *Please refer to current IB for more details and a complete list of side-effects.*	***To accommodate any future IB updates.***

Section 5.1 and 5.2(study procedures table) & Section 9.0 Correlative/Special studies	Research blood: 5 ml in EDTA tube and 5 ml in red top tube.	Updated to a) 10ml blood in one 10ml Sodium heparin tube: To be collected and processed by the Bloch lab for peripheral blood lymphocytes (PBLs). b) 8m (2x4ml) blood in two 5ml EDTA (purple top) tubes: To be collected and processed by the Wainwright lab for gene expression profile using mononuclear cells. c) 10ml blood in one 10ml red top tube: To be collected and processed by the	***Per updates from Dr.Bloch and Dr.Wainwright***

		Wainwright lab for analysis of tryptophan catabolites and cytokines. Samples to be collected: At 1st pre-operative treatment, day of surgery, C1D1 and at each adjuvant treatment imaging visits (i.e. every 2 cycles or 8 weeks). Also added: Details about archival tissue use for PD-L1 analysis(consistent with laboratory manual language). Language added to make 'fresh' and 'archival' tissue sections distinct. *Section 9.0 updated with similar language .* *All information made consistent with the current laboratory manual .* *Sentence inserted in protocol "Please refer and laboratory manual for more details".* *The 'X's in the tables have been updated accordingly.* Pager number for Dr.Bloch's lab added in section 9.0	
Section 7.2.4.6 Adverse Event of special Interest	Spelling error 'Entercolitis'	Corrected to 'Enterocolitis'	***Correction of typographical error***
Section 7.3.3.4 Reporting to AstraZeneca	AstraZeneca's designated mailbox: AEMailboxLPTCSnaP@astrazeneca.com	Updated to : AEMailboxClinicalTrialTCS@astrazeneca.com	***Per information received from AstraZeneca***
Section 8.1.10 side effects of MED14736	Listing of main side-effects	Added language "Please refer to current IB for more details and a complete list of side-effects."	***To accommodate for any updates to the IB and list of side effects.***

Amendment 4 5.19.17 (10.20.17 with additional changes after initial SRC approval)			
Section(s) Affected	**Prior Version**	**Amendment 4 changes**	**Rationale**
Protocol page	Dr.Jeffrey Raizer as PI and IND holder	Removed Dr.Raizer as PI and added Dr.Orin Bloch as PI and IND holder Dr.Raizer is included as one of the sub-investigators Added Karan Dixit, MD as Sub-Investigator	***Dr.Raizer has handed over the study to Dr.Bloch due to COI issues***
Study summary	Primary and secondary objectives stated	Objectives reworded to be consistent with the rest of the protocol	***For consistency***
Section 2.1 and Section 6.1	Blood samples will be used for assessment	Both blood and tissue samples will be used for assessment. Language in both sections updated for consistency	***Per PI, for flexibility***
Section 2.2.1, 2.2.2, 2.2.3, 2.2.4	Secondary objectives stated	Secondary objectives reworded to be consistent with section 6	***For consistency***
Section 3.1.3 Inclusion criteria	"Patients must be > 12 weeks from completion of radiation therapy unless there is tissue confirmation of tumor recurrence or there is progression outside the radiation treatment field."	It has been converted into an exclusion criteria 3.2.5 and the timepoint of former treatment exposure is to the start of study drug and not to registration.	***For clarity and convenience***
Section 3.1. 6(now 3.1.5) Inclusion criteria	Had contact information of PI, Dr.Raizer	Replaced with Dr.Orin Bloch with his contact information	***Orin Bloch, MD is the new PI, as stated above***
Section 3.1.7	Specifications for patients on some drugs to be included in the___14 study.	Has been converted to exclusion criteria 3.2 .6 All other footnotes re-numbered to match the changes.	***For clarity***

Section 3.1.12 (now 3.1.10) inclusion criteria	The baseline blood tests for organ and bone marrow function were required to be done within 7 days of registration	The window has been extended to 14 days. A note has been added: "The CBC and chemistries will be repeated within 72 hours of 1st dose of study treatment if baseline tests were more than 7 days prior to dosing."	***For convenience***
Section 3.2.15 Exclusion criteria	Patients with a history of active malignancy within 3 years prior to registration. Note: exceptions to this requirement include adequately treated non-melanoma skin cancer or lentigo maligna or carcinoma in situ without evidence of disease	Added prostate cancer to this list of exceptions: "prostate cancers with a Gleason score < 8 and with prostatectomy and no lymph node involvement."	***For ease of enrollment***
Section 4.4 Events requiring dose modifications	List of events requiring dose modifications anytime during the study.	Removed this section	***Conflicts with information provided in section 4.5, which also lists dose delays/modifications.***
Section 5.1 Study procedures table for pre-surgery and surgery	Footnote 9 has list of serum chemistries which included magnesium and phosphorus	Removed magnesium and phosphorus from this list and inserted them in a separate row in the table.	***For clarity and convenience, since magnesium and phosphorus are not part of the routine serum chemistry.***
	Informed consent was to be obtained within 14 days of registration	Informed consent to be obtained within 28 days of registration. Footnote 2 and 3 updated to reflect this.(Footnote 3 was earlier related to MRI but is now redundant. So this was deleted and updated with information regarding ICF).	***For convenience.***
Section 6.2 Secondary endpoints	Secondary endpoints stated	Language added to state evaluable subjects for each endpoint. Also, language updated to be consistent with section 2	***For clarity and consistency***

Section 7.3.1 and 7.3.2	AEs and SAEs will be recorded from time of signature of ICF, throughout the treatment period and including the follow-up period (60 days after the last dose of Durvalumab or Tremelimumab or combination of both).	Changed the window from 60 to 90 days. Expedited reporting would include all events that occur within 90 days of the last dose of protocol treatment	***Correction of error. To maintain consistency with the rest of the protocol.***
Section 8.1.10 Side effects of Durvalumab	List of side effects	List updated based on updates made to ICF based on UPIRSOs	***In compliance with recommendations made by NU IRB***
Amendment 5 3.20.18			
Section(s) Affected	**Prior Version**	**Amendment 4 changes**	**Rationale**
Title page and section 7.3.3.4	Coordinating center was stated as Clinical Research Office of RHLCCC	Updated to "Clinical Trials Office" and the link to the website has been added.	***Administrative.***
List of abbreviations and section 7.3	DSMB was listed as one of the abbreviations	Replaced by DSMC-Data and Safety Monitoring Committee	***Administrative.***
Throughout	A total of 30 subjects will be needed for this trial. The accrual cap was 36 patients and total accrual per arm will was 12	The accrual cap has been increased to 45 patients with each arm enrolling 15 patients in order to obtain 30 evaluable patients (10 in each arm) for immunologic response.	***Per DSMC approval, in order to help the study obtain its primary objective.***
Study summary and Section 6.	Stated as one of the secondary objectives: "To correlate T-cell changes and PDL1 expression with patient outcomes."	This objective has been moved to Exploratory Objective	***For consistency with Section 2. Correction of error.***

Section 3.0 Patient eligibility	PI was listed as Dr.Jeffrey Raizer.	PI name updated to Dr.Orin Bloch with contact information.	***The new PI information was not updated earlier in this section, in error.***

	A total of 30 subjects will be needed for this trial. The accrual cap is 36 patients, in order to cover those patients that do not make it to surgery.	Language modified to "A total of 30 evaluable subjects will be needed for this trial. The accrual cap is 45 patients, in order to cover those patients that do not make it to the first evaluable time point."	***To be in alignment with changes made to the rest of the protocol.***
Section 3.2.7 Exclusion criteria	Acceptable range of steroid was stated as 4-10mg.	Modified the range to 4-8mg. (*For safety, the steroid dose should remain at no more than 8mg daily at enrollment with a goal of 4mg or less).*	***For safety and to be in alignment with inclusion criteria 3.1.9.***
Section 3.2.14 Exclusion criteria	Uncontrolled hypertension defined as 150/90mmHg	Removed the specific defining level of hypertension (150/90mmHg). The treating physician will decide if the patient has uncontrolled hypertension.	***For flexibility***
Section 4.2 Treatment administration summary table	Arm 3 Tremelimumab +MEDI4736 combination therapy. Only post-surgery doses were stated. The footnote with "**" was not assigned to anything specific in the table.	Added the first combination dose within 14d (+/-3 days) pre-surgery. The rest specified as post-surgery doses. The footnote with "**"has been assigned to the Supportive treatment column.	***For increased clarity and completeness.***
Section 4.4 Toxicity management/dose delay and modifications	Previous table	Replaced by new table: Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy With Tremelimumab or Tremelimumab Monotherapy) 1 November 2017 Version	***Updated table with latest toxicity management guidelines sent by Astrazenaca***

Section 5.1 Study procedures for Pre-surgery and surgery	The first column heading was blank	The heading of "Assessment/Activity" has been inserted.	***For increased clarity and completeness.***
Section 5.2 Study procedures table for Post-Surgery/Adjuvant Therapy	CBC and differential was required to be done weekly while on adjuvant treatment.	CBC and differential is now required to be done every other week while on adjuvant treatment.	***For convenience, and to avoid unnecessary testing on patients.***
Section 6.1 Primary Endpoint	Evaluable patient for primary endpoint defined as **"**Only patients who have undergone surgery will be evaluable for this endpoint."	Reworded as "Only patients who have had pre-treatment blood sampling, have undergone surgery with pre-surgical blood sampling, and are able to continue to post-operative drug treatment with blood sampling prior to the first post-surgical dose will be evaluable for this endpoint."	***For increased clarity.***
Section 6.4 Table showing comparison of RANO and iRANO criteria	Malignant glioma and low-grade glioma were listed together under one column heading.	Low grade glioma has been deleted and is paced correctly in the next column.	***Correction of error***
Throughout	Previous information	Some minor administrative updates have been made and references to sections and appendices have been corrected.	***For clarity and consistency.***
Section 10.3 and Study Summary	Previous statistical language. Timepoints were stated as "Immunologic measures will be summarized over the three or more time points (pre-treatment, treatment, post-treatment)."	Language has been updated to align with the new accrual numbers as stated above. The time points have been reworded as *"Immunologic measures will be summarized over the three or more time points (pre-treatment, following first treatment/pre-surgery, post-surgery."* for better clarity.	***For consistency and accuracy.***

Section 11	Previous language Janssen Scientific Affairs was listed as funding sponsor	Language updated to align with current CTO template and policy. Updated to AstraZeneca/MedImmune	***Administrative.*** ***Correction of error.***
Appendix B Effective methods of contraception	Previous list	List has been updated and formatted.	***For clarity.***
Amendment 6 8.29.18			
Section(s) Affected	**Prior Version**	**Amendment 4 changes**	**Rationale**
Title page	Dr.Orin Bloch is listed as the Principal Investigator	PI name updated to Dr.Karan Dixit with contact information.	***Dr Orin Bloch is leaving Northwestern University and has handed over the study to Dr.Karan Dixit as the new Principal Investigator.***
Section 4.4 Toxicity management and Dose delays/Modifications	Previous table (version November 2017) CTCAE v.4.03	Updated: • Management of immune-mediated hepatitis • Regarding Cardiac toxicities the major modification is: drug is to be discontinued permanently upon diagnosis, regardless of biopsy as opposed to previous requirement of proof of biopsy.	***Based on Durvalumab Action letter dated 8.6.18.*** ***(Note: The modifications align with the CTCAEv5.0 as stated in the action letter]***