



A Phase II Study of MEDI4736 (Durvalumab) in Patients with Brain Metastasis from Epithelial-derived Tumors

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SUMMARY

Eligible patients will be enrolled and receive MEDI4736 at a fixed dose of 750 mg every two weeks until progression. Cohort A will enroll patients with metastatic non-small cell lung cancer (NSCLC) with at least one measurable brain lesion that does not require corticosteroids for symptomatic control. Cohort B will enroll patients with metastatic solid tumors of epithelial origin (excluding NSCLC) with at least one measurable brain lesion that does not require corticosteroids for symptomatic control. Cohort C will enroll patients with metastatic solid tumors of epithelial origin (including NSCLC) with at least one measurable brain lesion that requires corticosteroids for symptomatic control.

Glossary of Abbreviations

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
ANC	Absolute neutrophil count
aPTT	Active partial thromboplastin time
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
B-HCG	Beta human chorionic gonadotropin
CBC	Complete blood count
CFR	Code of Federal Regulations
CMP	Complete metabolic panel
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DCR	Disease control rate
DLT	Dose limiting toxicity
DMSO	Dimethyl sulfoxide
DNA	deoxyribonucleic acid
DSM	Data and Safety Monitoring
ECG (or EKG)	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
HCC	Hepatocellular carcinoma
HIV	Human Immunodeficiency Virus
HRPO	Human Research Protection Office (IRB)
IHC	Immunohistochemistry
ILD	Interstitial lung disease
IM	Intramuscular
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
irAE	Immune-related adverse event
irRC	Immune-related response criteria
IULN	Institutional upper limit of normal
IV	Intravenous
LCM	Laser capture microdissection

LFT	Liver function tests
LLN	Lower limit of normal
LTP	Laboratory for Translational Pathology
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NIH	National Institutes of Health
NSCLC	Non-small cell lung cancer
OCT	Optimum cutting temperature
OHRP	Office of Human Research Protections
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PFT	Pulmonary function tests
PI	Principal investigator
PK	Pharmacokinetics
PR	Partial response
PT	Prothrombin time
QASMC	Quality Assurance and Safety Monitoring Committee
QTc	QT interval (corrected)
RANO	Response Assessment in Neuro-Oncology
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors (Committee)
RNA	Ribonucleic acid
SAE	Serious adverse event
SCC	Siteman Cancer Center
SCCHN	Squamous cell carcinoma of the head & neck
SD	Stable disease
TIL	Tumor infiltrating lymphocyte
TSH	Thyroid stimulating hormone
UPN	Unique patient number

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1.0 BACKGROUND AND RATIONALE

1.1 Metastatic Brain Lesions

Metastatic brain lesions are the most common intracranial malignancy, arising in 20-40% of all cancer patients and representing over 200,000 new cases per year in the United States alone.¹ The presence of brain lesions represents a significant source of morbidity and mortality associated with debilitating neurologic deficits and shortened survival. Unfortunately, the frequency of brain metastases has increased recently, largely attributed to better diagnostic modalities such as MRI and more effective systemic therapy resulting in longer overall survival. In adults, the most common sources of metastatic brain lesions are lung, breast, and skin (melanoma) cancers.¹ Together, lung and breast cancer represent approximately two-thirds of all cases, and melanoma, the tumor that has the highest neurotropism, where 20-45% of patients will develop brain lesions, accounts for an additional 5-20% of all cases.

Current treatment for brain lesions involves a combinatorial approach including surgery, radiosurgery, and/or whole brain radiation.² Despite the fact that these therapies are often effective initially, patients eventually suffer from progression of their disease either locally or distantly. Further limitations of current therapeutic modalities include the treatment of patients with multiple lesions, which occurs in 50-75% of cases of brain metastasis. In these cases, surgery and radiosurgery may have less utility, though their role in the treatment of such lesions in conjunction with contemporary systemic treatments is incompletely understood and remains an area of active investigation.³ Moreover, many tumors that metastasize to the brain such as melanoma and renal cell carcinoma are relatively radioresistant, which further demonstrates the limitations of these therapies. As such, current treatment of brain metastases is largely palliative and focused on limiting neurologic compromise. Therefore, there is a dire need to expand the available therapeutic armament and identify alternate modalities that can be used to enhance response rates, extend remission duration, target multiple lesions, and effectively treat both systemic and CNS disease simultaneously.

1.2 Immunotherapy

1.2.1 Immunosurveillance

Immunosurveillance is a term used to describe the role of the immune response in controlling tumor development. The role of immunosurveillance in the control and/or development of tumors has been described in three steps termed the three E's: Elimination, Equilibrium, and Escape.⁴ During the elimination phase, the immune system is able to recognize aberrantly expressed antigens or molecules that signal to the immune system that the cell has undergone a transformative event and should be eliminated. Unfortunately, transformed cells eventually adopt evasive properties that allow it to subvert detection or destruction by the immune system (Equilibrium) permitting its eventual outgrowth into a clinically evident tumor

(Escape).⁵ Thus, immunotherapy refers to strategies that attempt to re-establish an effective immunosurveillance mechanism to control tumor growth through manipulation of the immune response. Another benefit of cancer immunity is that the immune system represents a relatively tumor-specific effector mechanism that can simultaneously target multiple disease sites including the CNS, and the response can be long-lived often persisting for years.⁶

One mechanism by which tumors are able to evade immunologic detection is through the upregulation of inhibitory signals. For example, PD-L1 and PD-L2 are molecules frequently upregulated on many tumor types. Their cognate receptor, PD-1, is expressed on the surface of many activated immune cell populations, including tumor-infiltrating T lymphocytes, and binding of PD-1 to either of these inhibitory ligands results in an “exhausted” or suppressed effector phenotype of infiltrating T cells permitting tumor escape.⁷ Under normal conditions, these inhibitory molecules serve to control chronic immune activation representing a “checkpoint” mechanism to prevent unregulated inflammatory responses that may be potentially detrimental to the host.⁸ In the context of cancer immunity, however, the tumor microenvironment has coopted this checkpoint pathway to permit immune escape.^{7,8} Therefore, one approach to bypass this immunosuppressive environment to reestablish immunosurveillance is through the use of monoclonal antibodies specific to these inhibitory molecules to allow for the activation and expansion of endogenous anti-tumor T cells. This approach has been termed “checkpoint blockade” and initial phase I studies using either anti-PD-1 or anti-PD-L1 antibodies have demonstrated significant objective, long-term responses in patients with various tumor types, including NSCLC.⁹⁻¹³

1.2.2 PD-L1 in NSCLC

PD-L1 is overexpressed in 23-83% of NSCLC samples.¹⁴⁻¹⁸ The large discrepancy in frequency of PD-L1 expression among these studies is due to differences in the definition of “positive.” All studies use an arbitrary cut-off that varies between 1%, 5%, and 50% of tumor cells expressing PD-L1 to be considered positive. Despite this variability, there is a general consistency among these various studies that provide an approximate frequency of PD-L1 expression in NSCLC patients. For example, ~80% of samples will be positive if the cut-off is defined as >1% of tumor cells expressing PD-L1 whereas only ~25% of samples will be positive if the cut-off is >50% of tumor cells expressing PD-L1.^{17,19} This has important clinical implications for two reasons: (1) the relatively high frequency of PD-L1 expression in NSCLC makes checkpoint blockade with inhibitory PD-1 or PD-L1 antibodies rational and (2) the level of PD-L1 expression has been used as a predictive biomarker for response to PD-1 or PD-L1 antibody therapy.

Regarding efficacy of anti-PD-1 or anti-PD-L1 antibodies in patients with NSCLC, there are currently at least three different anti-PD-1 and four different anti-PD-L1 agents being evaluated in clinical trials at various stages of disease and various phases of development (phase I, II, and III).¹⁹ Perhaps the most illustrative

examples of the promise of PD-1/PD-L1 checkpoint blockade are the results from two large studies that have recently been published demonstrating efficacy of anti-PD-1 therapy in metastatic NSCLC.^{17,18} Brahmer et al¹⁸ randomly assigned 272 patients with advanced (stage IIIB or IV) squamous-cell NSCLC that had progressed following first-line platinum-containing chemotherapy to either nivolumab or standard of care docetaxel. Impressively, they reported a higher objective response rate with nivolumab compared to docetaxel (20% vs 9%, $p = 0.008$) and a statistically significant improvement in median overall survival (9.2 months vs 6.0 months) resulting in a 41% reduction in risk of death with nivolumab (HR 0.59; $p < 0.0001$). This study led to the FDA approval of nivolumab for treatment of squamous-cell NSCLC as second-line therapy. Garon et al¹⁷ extended these findings in a cohort of 495 patients with metastatic NSCLC (all histologies) that were treated with pembrolizumab. Comparably, they also reported an objective response rate of 19.4%, a progression free survival of 3.7 months, and a median overall survival of 12.5 months. Importantly, they also report that there are no differences in response rate among squamous and adenocarcinoma histology, or in treatment naïve compared to treatment refractory patients, which has been confirmed in a subsequent study²⁰ suggesting a more broad applicability of these results. However, results from randomized phase III studies addressing these questions are pending.

Regarding the correlation between PD-L1 expression and response rate, the results have been inconclusive. There have been several large meta-analyses of evaluable clinical trials assessing response rate and PD-L1 expression in patients with NSCLC that have suggested an overall higher response rate associated with higher PD-L1 expression.^{14,16,21} In PD-L1 “positive” patients, the combined overall response rate was 23.2% compared to 14.5% in the PD-L1 “negative” group. Unfortunately, as different definitions of positive were used (>1% versus >5%), direct comparisons cannot be made. However, if all studies using a cutoff of >5% PD-L1 expression on tumor cells is applied, the overall response rate remains 22% for PD-L1 positive patients and 15.5% for PD-L1 negative patients consistent with the above findings. Expanding upon this point, there is likely a linear relationship between the level of PD-L1 expression and response rate as demonstrated by Garon et al where the objective response rate to pembrolizumab in patients with metastatic NSCLC with <1%, 1-24%, 25-49%, 50-74%, and >75% was 8.1%, 12.9%, 19.4%, 29.6%, and 45.4%, respectively.¹⁷ Additionally, it is of further note that there remains an 8-15% objective response rate in patients with negative PD-L1 expression suggesting PD-L1 expression is not an ideal biomarker to predict response or survival. As such, there are routinely an additional 10-30% of patients in these studies who have stable disease for months to years suggesting that the overall effect of these antibodies on overall survival is also not directly related to level of PD-L1 expression or an objective response.¹⁴⁻¹⁶

1.2.3 Checkpoint Blockade in Brain Metastasis

The effect of checkpoint blockade on the treatment of brain metastasis remains

unclear because this patient population is largely excluded from most clinical trials to date. However, there is a number of anecdotal reports suggesting that checkpoint blockade may be efficacious in brain lesions as well as systemic disease. These reports have predominantly been in patients with metastatic melanoma who are being treated with ipilimumab, a checkpoint inhibitor that blocks the activity of CTLA-4, another co-inhibitory molecule. For example, one case reports a durable complete remission in a patient with progressive brain lesions following treatment with ipilimumab as part of a compassionate use program.²² In another case report, a young female with melanoma and symptomatic brain and spine metastases refractory to stereotactic radiosurgery was treated with ipilimumab followed by resolution of her neurologic symptoms and stabilization of her disease progression.²³ Subsequently, several retrospective analyses of phase II and III clinical trials of ipilimumab in the treatment of metastatic melanoma have reported a disease control rate (stable disease, partial response, or complete response) of 16 to 27% in patients with stable CNS disease at time of enrollment²⁴⁻²⁶, which is comparable to the disease control rate of non-CNS disease. This led to a prospective phase II study examining the efficacy of ipilimumab in melanoma with asymptomatic and symptomatic brain mets.²⁷ Cohort A enrolled 51 patients with asymptomatic CNS disease while cohort B enrolled 21 patients with symptomatic CNS disease requiring glucocorticoid treatment. Cohort A had disease control rate (CR+PR+SD) of 24% (12/51) in CNS disease compared to 28% (14/51) in non-CNS disease. The median overall survival was 7 months which is comparable to the phase III studies of ipilimumab in metastatic melanoma where CNS disease was excluded. Cohort B had a disease control rate of 10% (2/21) in the CNS compared to 5% (1/21) in non-CNS disease with a median overall survival of 3.7 months. Overall, the objective response rate and survival were comparable to those reported in prior studies with patients without CNS disease.

Similarly, there have also been several cases reported that support a similar effect of PD-1 checkpoint blockade therapy in having a protective effect in CNS disease as well. For example, 5 patients with untreated brain metastases were enrolled in the phase II study evaluating nivolumab in patients with metastatic melanoma with or without prior ipilimumab therapy.²⁸ While the text states these patients had an objective response, there are no further details provided regarding the extent or duration of the response. Furthermore, 2 patients with refractory metastatic squamous cell NSCLC had stable, asymptomatic CNS disease and were treated with nivolumab as part of a phase II study.²⁹ Both patients reportedly had continued stable disease of the CNS lesions though further details are also not provided.

In summary, these studies provide some suggestion that checkpoint inhibition may have efficacy in CNS disease. However, the data for the effect of PD-1 checkpoint blockade is less robust than that for CTLA-4 blockade, and more trials are needed to draw any meaningful conclusions.

1.3 MEDI4736 (Durvalumab)

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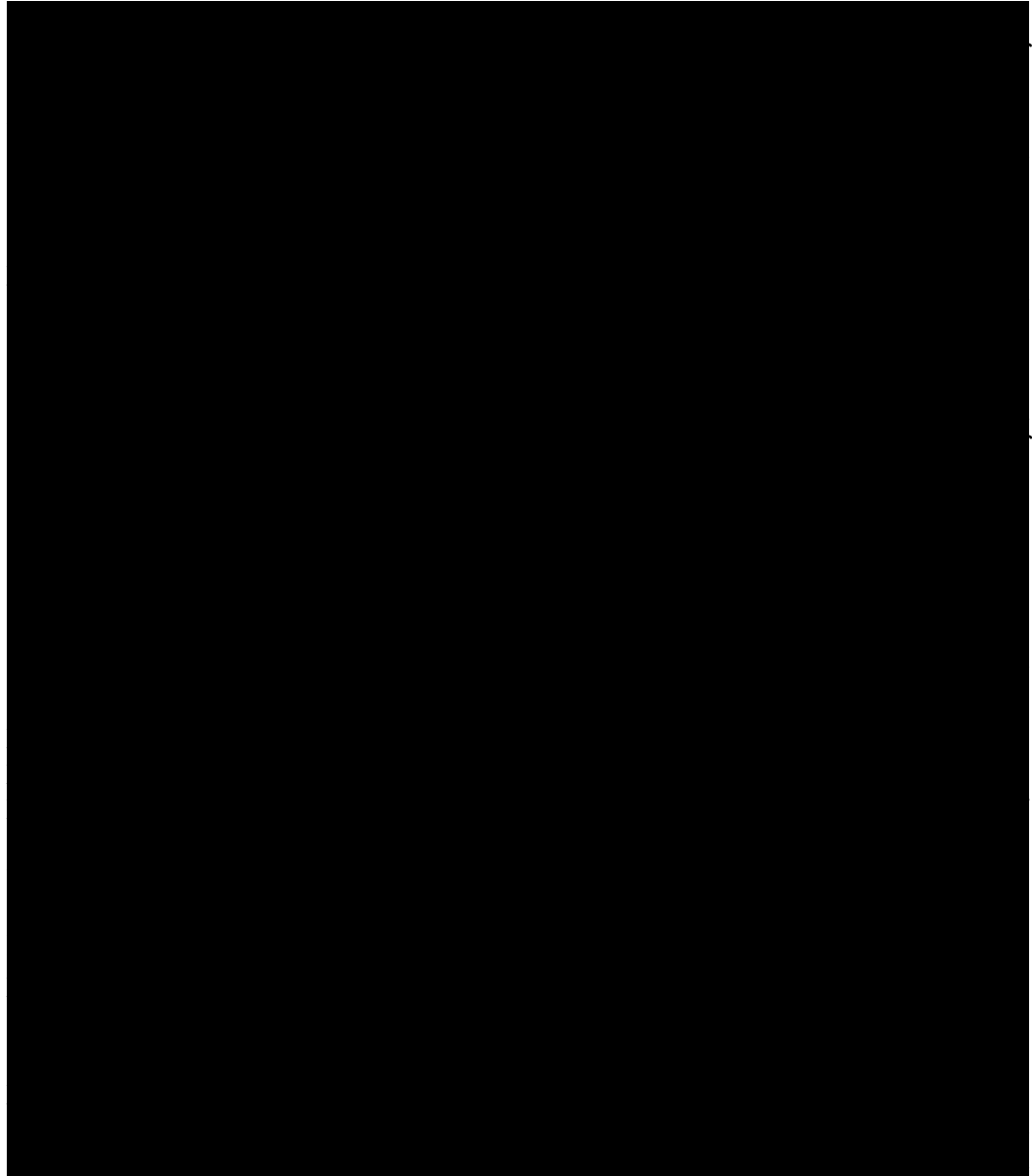
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1.4 Study Rationale

Brain metastases are the most common intracranial malignancy occurring in 20-40% of all cancers, and the presence of CNS metastases is associated with a poor prognosis. As such, the median overall survival of patients with symptomatic brain lesions is a dismal 2-3 months regardless of tumor type. Because standard chemotherapy largely does not cross the blood brain barrier at a meaningful concentration, standard treatment is limited and usually involves surgical resection and/or stereotactic radiosurgery for isolated lesions and whole brain radiation for multiple lesions. Unfortunately, the median overall survival is only improved by about 6 months with this multimodality approach², and there is a paucity of second-line therapies to treat recurrence. Furthermore, re-resection and re-radiation are often not feasible options due to concern for increasing complications or neurotoxicity, respectively. Thus, there is a dire clinical need for additional treatment options for this patient population.

Checkpoint blockade therapy, in particular PD-1 and PD-L1 inhibition, has recently shown clinical efficacy in multiple types of solid tumors.⁷ Nivolumab and pembrolizumab are PD-1 checkpoint inhibitors that have been FDA approved for first line therapy in metastatic melanoma, while nivolumab has been approved for second line therapy in metastatic squamous-cell NSCLC. Moreover, several large phase III studies are pending with promising results that will likely lead to the expansion of the number of indications where these agents (and others) will be approved [www.clinicaltrials.gov].³⁰ Lastly, there is data suggesting that checkpoint inhibitors may also be equally efficacious in treating patients with CNS disease (see Section 1.2.3).

Therefore, we propose to study the efficacy of checkpoint blockade therapy in patients with solid tumors and refractory/recurrent brain metastases. However, as there has already been a phase II study evaluating CTLA-4 checkpoint blockade in patients with melanoma and CNS disease²⁷ as well as several clinical trials utilizing PD-1 or PD-L1 checkpoint blockade specifically in the same patient population [www.clinicaltrials.gov], we will specifically exclude patients with melanoma from our analysis. Additionally, given the rare occurrence of CNS disease in patients with sarcoma, we will limit our study to solid tumors of epithelial origin, and will predominantly focus on patients with NSCLC as it is the most common cause of brain metastasis plus has been shown to be responsive to checkpoint blockade. An expansion, basket cohort will include other epithelial malignancies.

While CTLA-4 checkpoint inhibition has proven to be an effective treatment for melanoma, results in other solid tumor types has been poor. Thus, we will focus our study on the PD-1/PD-L1 pathway as it has been shown to be upregulated in various solid tumors and has been associated with an overall poor prognosis.^{14-16,31,32} Furthermore, inhibiting this pathway has been shown to be effective, specifically NSCLC. To date, there are no studies that directly compare PD-1 vs PD-L1 checkpoint inhibitors head-to-head. Though while there are similar mechanisms between the two approaches, there are distinct differences as well. PD-1 is expressed on immune cells, particularly T cells, and exerts its immunosuppressive effects when it recognizes PD-L1 or PD-L2 expressed by the tumor cells and/or other infiltrating immune cells such as B cells, dendritic cells or macrophages/monocytes. Conversely, PD-L1 is expressed on both tumor cells as well as activated immune cells including T cells, and can inhibit T cells directly when it recognizes either PD-L1 or PD-L2 as well as the activation molecule, CD80, which is expressed on activated antigen presenting cells. Therefore, we hypothesize that inhibition of PD-L1 will result in more robust T cell activation than PD-1 inhibition by releasing the inhibitory signal on T cells in two ways: (1) directly blocking suppression from the tumor microenvironment (i.e. PD-L1 and PD-L2) as well as (2) indirectly leading to more efficient priming of tumor-specific T cells by permitting costimulatory molecules on activated T cells (i.e. CD28) to freely recognize activation molecules on antigen-presenting cells (i.e. CD80).

Therefore, we will assess the efficacy of MEDI4736, a novel PD-L1 inhibitory monoclonal antibody, in this study.

1.5 Correlative Studies Background

The clinical correlates of this study will have two aims:

- Aim 1: Identify CNS and systemic biomarkers that predict response to MEDI4736.
- Aim 2: Characterize the immune response at baseline and post-MEDI4736 to identify immune parameters associated with protection.

Peripheral blood samples and, when available, paired tissue biopsies from primary and CNS lesions will be collected. Peripheral blood samples will be drawn at time of enrollment and at day 8, day 15, day 29, 3 months, 6 months, 12 months, and at time of progression (no further blood samples will be drawn after progression).

1.5.1 Aim 1: Biomarker assessment

PD-L1 expression on tumor cells is thought to serve as a clinical biomarker that is correlated with response to PD-1 checkpoint blockade. However, there remains debate regarding an appropriate cut-off to define positivity. Moreover, there remains a substantial percentage of patients who benefit from therapy who are considered negative for PD-L1 expression. Furthermore, it is not clear if a similar association between PD-L1 positivity and response OR what an appropriate definition of positivity should be with PD-L1 checkpoint inhibitors. Lastly, there have been no studies to date that have demonstrated concordance/discordance in checkpoint inhibitor expression between primary and CNS metastases. Therefore, Aim 1 will address three goals:

- Quantify expression of PD-1 and PD-L1 by IHC on tumor cells and tumor infiltrating lymphocytes to determine if there is a correlation with response and if so, to determine the level of PD-L1 expression on either tumor and/or TIL that adequately defines positivity to predict patients that would most likely benefit from MEDI4736 therapy.
- Quantify expression of PD-L2, and CTLA-4 to identify biomarkers associated resistance to therapy. Because PD-L1 blockade does not block the interaction between PD-L2 and PD-1, it is possible that high expression of either of these two molecules may lead to resistance to PD-L1 checkpoint inhibition as it provides a bypass mechanism of immunosuppression. Additionally, since PD-L1 interacts with PD-1 on T cells, if the immune infiltrate does not express high levels of PD-1, there may be no effect of PD-L1 inhibition despite high levels of PD-L1 present. Alternatively, CTLA-4 serves as a potential source of resistance that is not affected by PD-1/PD-L1 blockade.
- Compare checkpoint inhibitor expression levels of PD-1, PD-L1, PD-L2, and CTLA-4 in paired primary and CNS biopsies. This data will allow determination of frequency of concordant or discrepant expression of various mechanisms of checkpoint inhibition between primary and metastatic disease sites. For example, if there is high concordance between primary and CNS sites, the expression levels from the primary tissue can be used to predict a potentially responding individual rather than having to obtain tissue from the CNS, which is difficult and relatively more morbid than systemic tissue acquisition. Alternatively, if there is high discordance, then obtaining biopsies from the CNS would be recommended. Furthermore, a high discordance between primary and CNS disease locations may explain the basis of mixed responses.

1.5.2 Aim 2: Immune characterization

The tumor infiltrating lymphocytes (TIL) have been studied in various tumor tissue and generally felt to be associated with good prognosis.³³⁻³⁶ The presence of TILs has been used as justification for the presence of immunosurveillance and thus the basis for the efficacy of immunotherapy. While the presence of CD8+ cytotoxic T cells within the TIL have predominantly been associated with protection, there is

often the presence of immunosuppressive subsets such as regulatory T cells (Tregs) and myeloid derived suppressor cells (MDSCs) that are associated with poor prognosis.^{37,38} The interplay between these effector and suppressive subsets in determining the response to checkpoint inhibitor therapy has yet to be elucidated. Therefore, Aim 2 will characterize the tumor immune infiltrate and circulating immune cells using the following approaches:

- TCR profiling by spectrotyping and flow cytometry to assess changes in relative frequency of TCR gene utilization as a surrogate of clonal expansion and selection of the CD4 and CD8 T cell repertoire (i.e. tumor-specific T cell response) following MEDI4736.
- Flow cytometry and CyTOF to identify and quantify the immunophenotype of various effector immune subsets to determine changes in immune profile between baseline and post-MEDI4736. Correlations between treatment response and resistance will be determined to predict potential patients that will benefit from MEDI4736 therapy. The following immune subsets will be assessed:
 - T cell: CD3, CD8, CD4, Foxp3 (Tregs), t-bet (Th1), ROR-g (Th2), effector memory T cells (Tem), central memory T cells (Tcm); intracellular staining for IFN-g, TNF-a, IL-2, IL-17, IL-4, IL-10 will be determined to assess functional capacity of T cells before and after MEDI4736.
 - NK cell: CD56, CD16
 - MDSC: CD14, HLA-DR
 - Activation markers: ICOS, OX40, CD137, CD25, GITR
 - Inhibitory markers: PD-1, PD-L1, PD-L2, CTLA-4, TIM-3, LAG-3
- Multiplex analysis and QPCR to assess changes in cytokine profile: IFN-a, IFN-b, IFN-g, IL-2, TNF-a, IL-2, IL-4, IL-5, IL-13, IL-10, IL-6, TGF-b.
- Tumor cells will be microdissected from tissue biopsies and sent for whole exome sequencing and RNAseq to quantify the mutational landscape as a surrogate of antigenic burden. As antigenic burden has been correlated with response to checkpoint inhibitor therapy, we will determine if response to MEDI4736 is associated with mutational burden.³⁹⁻⁴¹

2.0 OBJECTIVES

2.1 Primary Objective

To determine the overall response rate of intracranial disease following treatment with MEDI4736.

2.2 Secondary Objectives

1. To determine safety of MEDI4736 in advanced solid epithelial-derived tumor patients with brain metastases
2. To determine the overall disease control rate of intracranial disease.

3. To determine the overall response rate and disease control rate of extracranial disease.
4. To determine the overall response rate and disease control rate considering both intracranial and extracranial disease.
5. To evaluate the duration of response for intracranial disease, extracranial disease, and both considered together.
6. To determine the progression-free survival.
7. To determine the overall survival
8. To determine the safety of MEDI4736 in patients with intracranial epithelial-derived tumor metastases
9. To evaluate the influence of concomitant corticosteroid therapy on treatment outcomes

2.3 Exploratory Objective

To determine the correlation of iRANO criteria with overall response rate and overall disease control rate of intracranial disease.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Cohort A: Histologically confirmed metastatic non-small cell lung cancer (all histologic subtypes allowed) with radiographic evidence by MRI of at least one measurable brain lesion as defined by RANO criteria that does not require corticosteroids for symptomatic control.

Cohort B: Histologically confirmed metastatic solid tumor of epithelial origin, excluding NSCLC, including but not limited to ovarian cancer, colorectal cancer, pancreatic cancer, gastric cancer, renal cancer, bladder cancer, or breast cancer with radiographic evidence by MRI of at least one measurable brain lesion as defined by RANO criteria that does not require corticosteroids for symptomatic control.

Cohort C: Histologically confirmed metastatic solid tumor of epithelial origin, including both NSCLC and non-NSCLC, with radiographic evidence by MRI of at least one measurable brain lesion as defined by RANO criteria that requires corticosteroids for symptomatic control.

2. At least one prior treatment to a CNS-based lesion is required. Prior therapy must be completed > 2 weeks prior to enrollment. A previously treated lesion must be demonstrated by MRI to have progressed following treatment in order to be eligible. The subsequent development of a new CNS lesion that was not previously treated will be permitted and does not require treatment followed by progression prior to enrollment. Treatment of a single CNS lesion with local therapy in the context of multifocal disease is permitted as long as at least one untreated lesion meets criteria for measurable disease. Patients should have received minimum of one line of systemic therapy.

3. At least 18 years of age.
4. ECOG performance status of 0 to 2 (Appendix A).
5. Adequate bone marrow and organ function as defined below:
 - a. Absolute neutrophil count $\geq 1,500/\text{mcL}$
 - b. Platelets $\geq 100,000/\text{mcL}$
 - c. Hemoglobin $\geq 8.0 \text{ g/dL}$
 - d. Serum bilirubin $\leq 1.5 \times \text{IULN}$
 - e. AST(SGOT)/ALT(SGPT) $\leq 2.5 \times \text{IULN}$
 - f. Creatinine clearance $\geq 40 \text{ mL/min/1.73 m}^2$ by the Cockcroft-Gault formula (Appendix B) or by 24-hour urine collection for determination of creatinine clearance
6. Negative antiviral serology:
 - a. Negative human immunodeficiency virus (HIV) antibody.
 - b. Negative hepatitis B surface antigen (HBsAg) and negative hepatitis B core (HBc) antibody or undetectable hepatitis B (HBV) DNA by quantitative polymerase chain reaction (PCR) testing.
 - c. Negative hepatitis C virus (HCV) antibody or negative HCV ribonucleic acid (RNA) by quantitative PCR.
7. Mean QT interval corrected for heart rate (QTc) $< 470 \text{ msec}$ calculated from 3 ECGs performed at least 2 minutes apart using Frediricia's Correction.
8. Female subjects must either be of non-reproductive potential (i.e., post-menopausal by history: ≥ 60 years old and no menses for ≥ 1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative serum pregnancy test upon study entry.
9. Ability to understand and willingness to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

3.2 Exclusion Criteria

1. Diagnosis of leptomeningeal carcinomatosis.
2. Diagnosis of melanoma or other non-epithelial based malignancy such as sarcoma, neuroendocrine tumor, small cell lung cancer.
3. Presence of unstable systemic disease (e.g., visceral crisis or rapid progression) in the judgment of the investigator.

4. A history of other malignancy ≤ 5 years previous with the exception of basal cell or squamous cell carcinoma of the skin which were treated with local resection only or carcinoma *in situ* of the cervix.
5. Currently receiving any other investigational agents.
6. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to MEDI4736 or other agents used in the study.
7. Previous treatment with a PD-1 or PD-L1 inhibitor, including MEDI4736, or a CTLA-4 inhibitory agent.
8. Current or prior use of immunosuppressive medication within 28 days before the first dose of MEDI4736 with the exceptions of intranasal and inhaled corticosteroids, or systemic corticosteroids in Cohort C.
9. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) 21 days prior to the first dose of study drug.
10. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension ($>180/110$), 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.
11. Active or prior documented 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).
12. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis).
13. History of prior immunodeficiency.
14. History of allogeneic organ transplant.
15. Known history of previous clinical diagnosis of tuberculosis.
16. Receipt of live attenuated vaccination within 30 days prior to first dose of MEDI4736.
17. Pregnant and/or breastfeeding or female patients of reproductive potential who are not employing an effective method of birth control.
18. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center Database

All patients must be registered through the Siteman Cancer Center database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

5.0 TREATMENT PLAN

5.1 Premedication Administration

There are no required premedications.

5.2 Agent Administration

MEDI4736 will be given to all patients > 30 kg actual body weight intravenously at a fixed dose 750 mg every 2 weeks over the course of 60 minutes on an outpatient basis on Days 1 and 15 of each 28-day cycle. Patients < 30 kg actual body weight will be dosed at 10 mg/kg every 2 weeks. Subjects will be monitored during and after the infusion with assessment of vital signs.

5.3 Evaluability

All patients who receive any study treatment are evaluable for toxicity. Patients are evaluated from first receiving study treatment until a 30-day follow up after the conclusion of treatment or death.

All patients are evaluable for disease response unless they discontinue treatment due to treatment related adverse events(s) prior to completion of Cycle 2 and have not had any disease assessment.

5.4 General Concomitant Medication and Supportive Care Guidelines

In the event of a \leq 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 \leq 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.

5.4.1 Excluded Concomitant Medications

The following medications are considered exclusionary during the study:

- Any investigational anticancer therapy.
- Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for noncancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.
- Immunosuppressive medications including, but not limited to systemic

corticosteroids at doses exceeding 4 mg/day of dexamethasone or equivalent, methotrexate, azathioprine, and TNF- α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs (see section 6.0) or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted.

- Live attenuated vaccines within 30 days of MEDI4736 dosing (i.e., 30 days prior to the first dose, during treatment with MEDI4736, and for 30 days post discontinuation of MEDI4736). Inactivated viruses, such as those in the influenza vaccine, are permitted.

5.4.2 Corticosteroids

One of the expected side effects of immunotherapy in general is increased inflammation at the site of disease due to immune cell infiltration. As such, subjects may experience CNS-related adverse effects related to increased vasogenic edema and inflammation. The standard treatment is a short course of corticosteroids such as dexamethasone. While subjects in Cohorts A and B must not require dexamethasone at time of enrollment or first dose of MEDI4736, a course of dexamethasone is permitted in the setting of a flare. Given the immunosuppressive effects of corticosteroids, all subsequent doses of MEDI4736 will be held until patients are able to be tapered to at least 4 mg daily of dexamethasone or equivalent before reinitiating therapy. Alternatively, if patients in Cohorts A or B develop evidence of progression requiring immediate treatment while on corticosteroids, they will be removed from the study. There will be no maximum time limit MEDI4736 can be held before subjects must be withdrawn for study protocol as long as there is no evidence of disease progression that requires alternative treatment options.

5.5 Women of Childbearing Potential

Females of childbearing potential who are sexually active with a non-sterilized male partner must use 2 methods of effective contraception from screening, and must agree to continue using such precautions for 90 days following the last infusion of MEDI4736; 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).
- Subjects must use 2 acceptable methods of effective contraception as described in the table below.
- Non-sterilized males who are sexually active with a female partner of childbearing potential must use 2 acceptable methods of effective contraception (see table below) from Day 1 and for 90 days after receipt of the final dose of investigational product.

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.

5.6 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

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

- Documented and confirmed CNS disease progression by RANO criteria
- Documented and confirmed non-CNS disease progression by Immune-related Response Criteria (irRC)
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unable to receive further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious non-compliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will be followed as indicated in the study calendar.

5.6.1 Permanent Discontinuation of MEDI4736

An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

1. Withdrawal of consent or lost to follow-up
2. Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing
3. 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

4. Pregnancy or intent to become pregnant
5. Grade \geq 3 infusion reaction
6. Initiation of alternative anticancer therapy including another investigational agent

5.6.2 Withdrawal of consent

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

5.7 Duration of Follow-up

Patients will be followed every 6 months for 2 years after completion of treatment or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6.0 DOSE DELAYS/DOSE MODIFICATIONS

For adverse events (AEs) that are considered at least partly due to administration of MEDI4736 the following dose adjustment guidance may be applied:

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity where required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of MEDI4736 along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted for MEDI4736 (see below).
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

In addition, there are certain circumstances in which MEDI4736 should be permanently discontinued. Following the first dose of MEDI4736, subsequent administration of MEDI4736 can be modified based on toxicities observed (see the tables below).

Based on the mechanism of action of MEDI4736 leading to T-cell activation and proliferation, there is the possibility of observing immune-related adverse events (irAEs) during the conduct of this study. Potential irAEs include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or progressive disease) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.

Dose modification recommendations and toxicity management guidelines for immune-mediated reactions, for infusion-related reactions, and for non-immune-mediated reactions are detailed in the tables below. In addition, management guidelines for adverse events of special interest (AESIs) are detailed in Section 7.9. All toxicities will be graded according to NCI CTCAE v4.03.

Immune-Mediated Reactions			
Event	Dose Modifications	Toxicity Management	
Immune-related Adverse Events (overall management for toxicities not noted below)	Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03. In addition to the criteria for permanent discontinuation of study drug/regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: <ul style="list-style-type: none"> • 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/regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing. 	It is recommended that management of irAEs follow the guidelines presented in this table <ul style="list-style-type: none"> - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, infections, etc.) - In the absence of a clear alternative etiology, all events should be considered potentially immune related. - Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events - For persistent (greater than 3 to 5 days) low-grade (Grade 2) or severe (Grade ≥ 3) events promptly start prednisone PO 1-2mg/kg/day or IV equivalent - If symptoms recur or worsen during corticosteroid tapering 28 days of taper), increase the corticosteroid dose (prednisone dose [e.g. up to 2-4mg/kg/day or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (≥ 28 days of taper) - More potent immunosuppressives such as TNF inhibitors (e.g. infliximab) – (also refer to the individual sections of the immune related adverse event for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. - Discontinuation of study drug is not mandated for Grade 3 / Grade 4 inflammatory reactions attributed to local tumour response (e.g. inflammatory reaction at sites of metastatic disease, lymph nodes etc.). Continuation of study drug in this situation should be based upon a benefit/risk analysis for that patient 	
	Grade 1		No dose modification
	Grade 2		Hold study drug/study regimen dose until grade 2 resolution to \leq Grade 1 <ul style="list-style-type: none"> • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date Study drug/study treatment can be resumed at the next scheduled dose once event stabilizes to grade ≤ 1 and 5-7 days have passed after completion of steroid taper Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled, 2) the patient is clinically stable as per Investigator or treating physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent.
	Grade 3		Depending on the individual toxicity, may permanently discontinue study drug/study regimen. Please refer to guidelines below
	Grade 4		Permanently discontinue study drug/study regimen Note: For Grade 3 and above asymptomatic amylase or lipase levels hold study drug/regimen and if complete work up shows no evidence of pancreatitis, may continue or resume study drug/regimen

Event	Grade	Dose Modifications	Toxicity Management
Pneumonitis / ILD	Any Grade	N/A	<ul style="list-style-type: none"> - Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests including other diagnostic procedures as described below - Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan.
	Grade 1 (Asymptomatic, clinical or diagnostic observations only, intervention not indicated)	No dose modification required. However, consider holding study drug/study regimen dosing as clinically appropriate and during diagnostic work-up for other etiologies	<p>For Grade 1 (Radiographic Changes Only)</p> <ul style="list-style-type: none"> - Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated - Consider pulmonary and infectious disease consult
	Grade 2 (Symptomatic, medical intervention indicated, limiting instrumental ADL)	<p>Hold study drug/study regimen dose until grade 2 resolution to \leq Grade 1</p> <ul style="list-style-type: none"> • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then the decision to reinstate study drug/regimen at next scheduled treatment date will be based upon treating physician's clinical judgment. Study drug/study treatment can be resumed at the next scheduled dose once event stabilizes to grade \leq1 and 5-7 days have passed after completion of steroid taper 	<p>For Grade 2 (Mild to Moderate New Symptoms)</p> <ul style="list-style-type: none"> - Monitor symptoms daily and consider hospitalization - Promptly start systemic steroids (e.g., prednisone 1-2mg/kg/day or IV equivalent) - Reimaging as clinically indicated - If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started - If still no improvement within 3-5 days despite IV methylprednisone at 2-4/g/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg every 2 weeks). Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab - Once improving, gradually taper steroids over \geq4 weeks and consider prophylactic antibiotics, antifungal or anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation) - 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;	Permanently discontinue study drug/study regimen	<p>For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life threatening)</p> <ul style="list-style-type: none"> - Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent - Obtain pulmonary and infectious disease consult - Hospitalize the patient

Event	Grade	Dose Modifications	Toxicity Management
	Grade 4: life threatening respiratory compromise, urgent intervention indicated [e.g. tracheostomy or intubation])		<ul style="list-style-type: none"> - Supportive Care (oxygen, etc.) - If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab - Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and in particular, anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation))
Diarrhea/ Enterocolitis	Any Grade	N/A	<ul style="list-style-type: none"> - Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs and ileus) - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, infections including testing for clostridium difficile toxin, etc.) - Steroids should be considered in the absence of clear alternative etiology, even for low grade events, in order to prevent potential progression to higher grade event - Use analgesics carefully; they can mask symptoms of perforation and peritonitis
	Grade 1 diarrhea (stool frequency of <4 over baseline per day)	No dose modification	For Grade 1 diarrhea : <ul style="list-style-type: none"> - Close monitoring for worsening symptoms - Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use of probiotics as per treating physician’s clinical judgment.
	Grade 2 diarrhea (stool frequency of 4-6 over baseline per day)	Hold study drug/study regimen until resolution to \leq Grade 1 <ul style="list-style-type: none"> • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade ≤ 1 and 5-7	For Grade 2 diarrhea: <ul style="list-style-type: none"> - 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 or IV equivalent - If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, GI consult should be obtained for consideration of further workup such as imaging and/or colonoscopy to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. - If still no improvement within 3-5 days despite 2-4mg/kg IV

Event	Grade	Dose Modifications	Toxicity Management
		days have passed after completion of steroid taper	<p>methylprednisolone, promptly start immunosuppressives such as (infliximab at 5mg/kg once every 2 weeks). Caution: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab</p> <ul style="list-style-type: none"> - Consult study physician if no resolution to \leq Grade 1 in 3-4 days - Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
	<p>Grade 3 or 4 diarrhea</p> <p>(Grade 3: stool frequency of ≥ 7 over baseline per day;</p> <p>Grade 4: life threatening consequences)</p>	Permanently discontinue study drug/study regimen	<p>For Grade 3 or 4 diarrhea:</p> <ul style="list-style-type: none"> - Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent - Monitor stool frequency and volume and maintain hydration - Urgent GI consult and imaging and/or colonoscopy as appropriate - If still no improvement within 3-5 days of IV methylprednisolone 2 to 4mg/kg/day or equivalent, promptly start further immunosuppressives (e.g. infliximab at 5mg/kg once every 2 weeks). - Caution: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. - Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
Hepatitis (Elevated LFTs)	Any Grade	Infliximab should not be used for management of Immune Related Hepatitis	<ul style="list-style-type: none"> - Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin - Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications)
	Grade 1 (AST or ALT > ULN to 3 times ULN and/or TB > ULN to 1.5 times ULN)	<p>No dose modification</p> <p>If it worsens, treat as Grade 2 event</p>	<p>For Grade 1 AST or ALT and/or TB elevation</p> <ul style="list-style-type: none"> - Continue LFT monitoring per protocol
	Grade 2 (AST or ALT > 3 to 5 times ULN and/or TB > 1.5-3.0 times ULN)	<p>Hold Study drug/study regimen dose until grade 2 resolution to \leq Grade 1</p> <ul style="list-style-type: none"> • If toxicity worsens then treat as Grade 3 or Grade 4 • If improves to baseline then 	<p>For Grade 2 AST or ALT and or TB elevation :</p> <ul style="list-style-type: none"> - Regular and frequent checking of LFTs (e.g. every 1-2 days) until elevations of these are improving or resolved. - If no resolution to \leq Grade 1 in 1-2 days, discuss with study physician. - If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2mg/kg/day or IV equivalent.

Event	Grade	Dose Modifications	Toxicity Management
		<p>treat at next scheduled treatment date</p> <p>Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade ≤ 1 and 5-7 days have passed after completion of steroid taper</p>	<ul style="list-style-type: none"> - If still no improvement within 3-5 days despite 1-2mg/kg/day of prednisone or IV equivalent, consider additional workup and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. - If still no improvement within 3-5 days despite 2-4mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil). Discuss with study physician if mycophenolate mofetil is not available. Infliximab should NOT be used. - Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
	<p>Grade 3 (AST or ALT > 5-20 times ULN and/or TB > 3.0-10 times ULN)</p>	<p>For elevations in transaminases $\leq 8 \times$ ULN, or elevations in bilirubin $\leq 5 \times$ ULN</p> <ul style="list-style-type: none"> -Hold study drug/study regimen dose until resolution to \leq Grade 1 or baseline -Resume study drug/study regimen administration at the next scheduled dose if elevations downgrade \leq Grade 1 or baseline within 14 days <p>Permanently discontinue study drug/study regimen if the elevations do not downgrade to \leq Grade 1 or baseline within 14 days</p> <p>For elevations in transaminases $> 8 \times$ ULN or elevations in bilirubin $> 5 \times$ ULN, discontinue study drug/study regimen</p> <p>Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (ALT $> 3x$ ULN + bilirubin $> 2x$ ULN without initial findings of cholestasis (i.e.</p>	<p>For Grade 3 or 4 AST or ALT and/or TB elevation:</p> <ul style="list-style-type: none"> - Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent - If still no improvement within 3-5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (mycophenolate mofetil) Discuss with study physician if mycophenolate is not available. Infliximab should NOT be used. - Hepatology consult, abdominal workup, and imaging as appropriate. - Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])

Event	Grade	Dose Modifications	Toxicity Management
		elevated alkaline P04) and in the absence of any alternative cause ⁱ	
	Grade 4 (AST or ALT > 20 times ULN and/or TB > 10 times ULN)	Permanently discontinue study drug/study regimen	
Nephritis or Renal Dysfunction (Elevated Serum Creatinine)	Any Grade	N/A	<ul style="list-style-type: none"> - Consult with Nephrologist - Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc.) - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections etc.) - Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2) , in order to prevent potential progression to higher grade event
	Grade 1 [Serum Creatinine > 1-1.5X baseline; > ULN to 1.5X ULN]	No dose modification	<p>For Grade 1 elevated creatinine:</p> <ul style="list-style-type: none"> - Monitor serum creatinine weekly and any accompanying symptom <ul style="list-style-type: none"> • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If it worsens, depending on the severity , treat as Grade 2 or 3 or 4 - Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc.
	Grade 2 [Serum Creatinine>1.5-3.0X baseline; >1.5X-3.0XULN]	<p>Hold study drug/study regimen until resolution to ≤ Grade 1</p> <ul style="list-style-type: none"> • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date <p>Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade ≤1 for 5-7 days have passed after completion of steroid taper</p>	<p>For Grade 2 elevated creatinine:</p> <ul style="list-style-type: none"> - Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc. - Carefully monitor serum creatinine every 2-3 days and as clinically warranted - Consult Nephrologist and consider renal biopsy if clinically indicated - If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day or IV equivalent - If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4mg/kg/day started. - Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections

Event	Grade	Dose Modifications	Toxicity Management
			[Category 2B recommendation]). - When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: Serum Creatinine > 3.0 X baseline; >3.0-6.0 X ULN Grade 4: Serum Creatinine > 6.0 X ULN)	Permanently discontinue study drug/study regimen	- Carefully monitor serum creatinine on daily basis - Consult Nephrologist and consider renal biopsy if clinically indicated - Promptly start prednisone 1 to 2 mg/kg/day or IV equivalent - If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
Rash (excluding Bullous skin formations)	Any Grade	N/A	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 modification	For Grade 1: - Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream)
	Grade 2	For persistent (> 1- 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to ≤ Grade 1 or baseline <ul style="list-style-type: none"> • If toxicity worsens then treat as Grade 3 • If toxicity improves then resume administration at next scheduled dose • Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper 	For Grade 2 : - Obtain dermatology consult - Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream) - Consider moderate-strength topical steroid - If no improvement of rash/skin lesions occurs within 3-5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, discuss with study physician and promptly start systemic steroids prednisone 1-2 mg/kg/day or IV equivalent - Consider skin biopsy if persistent for >1-2 weeks or recurs

Event	Grade	Dose Modifications	Toxicity Management
	Grade 3	Hold study drug/study regimen until resolution to \leq Grade 1 or baseline If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to \leq Grade 1 or baseline within 30 days, then permanently discontinue Study drug/study regimen	For Grade 3 or 4: <ul style="list-style-type: none"> - 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 improving, gradually taper steroids over \geq28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) - Discuss with Study Physician
Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, hypopituitarism, adrenal insufficiency, etc.)	Any Grade	N/A	<ul style="list-style-type: none"> - Consult Endocrinologist - 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, hypotension and weakness. - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infections, etc.) - Monitor and evaluate thyroid function tests: TSH, free T₃ and free T₄ and other relevant endocrine labs depending on suspected endocrinopathy. - If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing
	Grade 1 (Depending on the type of endocrinopathy, refer to CTCAE v 4.03 for definition)	No dose modification	For Grade 1: (including those with asymptomatic TSH elevation) <ul style="list-style-type: none"> - Monitor patient with appropriate endocrine function tests - If TSH $<$ 0.5X LLN, or TSH $>$2X ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider endocrinology consult.
	Grade 2 (Depending on the type of endocrinopathy, refer to CTCAE v 4.03 for definition)	For Grade 2 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until subject is clinically stable <ul style="list-style-type: none"> • If toxicity worsens then treat as Grade 3 or Grade 4 	For Grade 2: (including those with symptomatic endocrinopathy) <ul style="list-style-type: none"> - Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids - Initiate hormone replacement as needed for management - Evaluate endocrine function, and as clinically indicated, consider pituitary scan

Event	Grade	Dose Modifications	Toxicity Management
		<ul style="list-style-type: none"> • If toxicity improves to baseline then treat at next scheduled treatment date <p>Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade ≤ 1 and 5-7 days have passed after completion of steroid taper</p> <p>Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled, 2) the patient is clinically stable as per Investigator or treating physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent.</p>	<ul style="list-style-type: none"> - For patients with abnormal endocrine work up, except for those with isolated hypothyroidism, consider short-term, corticosteroids (e.g., 1-2mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g. Levothyroxine, hydrocortisone, or sex hormones). - - Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) - For patients with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated.
	Grade 3 or 4 (Depending on the type of endocrinopathy, refer to CTCAE v 4.03 for definition)	<p>For Grade 3 or 4 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled</p> <p>Resume study drug/study regimen administration if controlled at the next scheduled dose</p> <p>Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade ≤ 1 and 5-7 days have passed after completion of steroid taper</p>	<p>For Grade 3 or 4:</p> <ul style="list-style-type: none"> - Consult endocrinologist - Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids - Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent - Administer hormone replacement therapy as necessary. - For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity - Once improving, gradually taper immunosuppressive steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) - Discuss with study physician
Immune mediated	Any Grade	N/A	<ul style="list-style-type: none"> - Patients should be evaluated to rule out any alternative etiology (e.g.,

Event	Grade	Dose Modifications	Toxicity Management
Neurotoxicity (to include but not limited to limbic encephalitis . autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)			disease progression, infections, metabolic syndromes and medications, etc.) <ul style="list-style-type: none"> - Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness) - Consider appropriate diagnostic testing (e.g. electromyogram and nerve conduction investigations) - Symptomatic treatment with neurological consult as appropriate
	Grade 1	No dose modifications	See "Any Grade" recommendations above.
	Grade 2	<ul style="list-style-type: none"> • For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to \leq Grade 1 • For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to \leq Grade 1. <ul style="list-style-type: none"> ○ If toxicity worsens then treat as Grade 3 or Grade 4 ○ If toxicity improves to baseline then treat at next scheduled treatment date • Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade \leq 1 and 5-7 days have passed after completion of steroid taper 	<ul style="list-style-type: none"> - Discuss with the study physician - Obtain Neurology Consult - Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.) - Promptly start systemic steroids prednisone 1-2mg/kg/day or IV equivalent - If no improvement within 3-5 days despite 1-2mg/kg/day prednisone or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (e.g. IVIG)
	Grade 3	<ul style="list-style-type: none"> • Hold Study drug/study regimen dose until resolution to \leq Grade 1 • Permanently discontinue Study drug/study regimen if Grade 3 irAE does not resolve to \leq Grade 1 within 30 days. 	For Grade 3 or 4: <ul style="list-style-type: none"> - Discuss with study physician - Obtain Neurology Consult - Consider hospitalization - Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent - If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g. IVIG) - Once stable, gradually taper steroids over \geq4 weeks
	Grade 4	Permanently discontinue study drug/study regimen	
Immune-	Any Grade	N/A	<ul style="list-style-type: none"> - The prompt diagnosis of immune-mediated peripheral neuromotor

Event	Grade	Dose Modifications	Toxicity Management
mediated peripheral neuromotor syndromes, such as Guillain-Barre and Myasthenia Gravis			<p>syndromes is important, since certain patients may unpredictably experience acute decompensations which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability</p> <ul style="list-style-type: none"> - Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult - Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and “repetitive stimulation” if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation <p>Important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG</p>
	Grade 1	No dose modification	<ul style="list-style-type: none"> - Discuss with the study physician - Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above - Obtain a neurology consult unless the symptoms are very minor and stable
	Grade 2	<p>Hold study drug/study regimen dose until resolution to \leq Grade 1</p> <p>Permanently discontinue study drug/study regimen if it does not resolve to \leq Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability</p>	<p>Grade 2</p> <ul style="list-style-type: none"> - Discuss with the study physician - Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above - Obtain a Neurology Consult - Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.) <p><i>MYASTHENIA GRAVIS</i></p> <ul style="list-style-type: none"> o Steroids may be successfully used to treat Myasthenia Gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a

Event	Grade	Dose Modifications	Toxicity Management
			<p>consulting neurologist.</p> <ul style="list-style-type: none"> ○ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. ○ If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. <p><i>GUILLAIN-BARRE:</i> Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.</p>
	Grade 3	<p>Hold study drug/study regimen dose until resolution to ≤ Grade 1</p> <p>Permanently discontinue Study drug/study regimen if Grade 3 irAE does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability</p>	<p>For severe or life threatening (Grade 3 or 4) events:</p> <ul style="list-style-type: none"> - Discuss with study physician - Recommend hospitalization - Monitor symptoms and obtain neurological consult <p><i>MYASTHENIA GRAVIS</i></p> <ul style="list-style-type: none"> ○ Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist. ○ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. ○ If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. <p><i>GUILLAIN-BARRE:</i> Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG</p>
	Grade 4	Permanently discontinue study drug/study regimen	<p><i>GUILLAIN-BARRE:</i> Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG</p>

Infusion-Related Reactions		
Grade	Dose Modifications	Toxicity Management
Any Grade		<ul style="list-style-type: none"> - Management per institutional standard at the discretion of investigator - Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes etc.) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, tachycardia, etc.)
Grade 1	The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event	For Grade 1 or Grade 2: <ul style="list-style-type: none"> - Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator - Consider premedication per institutional standard prior to subsequent doses
Grade 2	The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event Subsequent infusions may be given at 50% of the initial infusion rate	
Grade 3/4	Permanently discontinue study drug/study regimen	For Grade 3 or 4: Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid)

Non-immune Mediated Reactions		
Grade	Dose Modification	Toxicity Management
Any Grade	Note: dose modifications are not required for adverse events not deemed to be related to study treatment (i.e. events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly as per institutional standard
1	No dose adjustment	Treat accordingly as per institutional standard
2	Hold study drug/study regimen until resolution to \leq Grade 1 or baseline	Treat accordingly as per institutional standard
3	Hold study drug/study regimen until resolution to \leq Grade 1 or baseline For AEs that downgrade to \leq Grade 2 within 7 days or resolve to \leq Grade 1 or baseline within 14 days, resume study drug/study regimen administration at next scheduled dose. Otherwise, discontinue study drug/study regimen	Treat accordingly as per institutional standard
4	Discontinue Study drug/study regimen (Note for Grade 4 labs, decision to discontinue would be based on accompanying clinical signs/symptoms and as per Investigator's clinical judgment and in consultation with the sponsor)	Treat accordingly as per institutional standard

7.0 REGULATORY AND REPORTING REQUIREMENTS

7.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.03 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:

<http://www.hhs.gov/ohrp/policy/advevntguid.html>

7.2 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.3 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

7.4 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

7.5 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Pre-approval of all protocol exceptions must be obtained prior to the event.

7.6 Reporting to the Human Research Protection Office (HRPO) and the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

7.7 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the investigator to report any unanticipated problem to the FDA as follows:

- Report any unexpected fatal or life-threatening adverse experiences associated with use of the drug (i.e., there is a reasonable possibility that the experience may have been caused by the drug) by telephone or fax no later than **7 calendar days** after initial receipt of the information. A life-threatening adverse experience is defined as any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Report any serious, unexpected adverse experiences, as well as results from animal studies that suggest significant clinical risk within **15 calendar days** after initial receipt of this information. A serious adverse drug experience is defined as any

adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

An unexpected adverse drug experience is defined as any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

All MedWatch forms will be sent by the investigator or investigator's team to the FDA at the following address or by fax:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products
5901-B Ammendale Rd.
Beltsville, MD 20705-1266
FAX: 1-800-FDA-0178

7.8 Reporting to Astra Zeneca

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.

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

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

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

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

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

7.9 Definition of adverse events of special interest (AESI)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product. AESIs for MEDI4736 include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with MEDI4736 monotherapy and combination therapy. An immune-related adverse event (irAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

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

AESIs observed with MEDI4736 include:

- Colitis
- Pneumonitis
- ALT/AST increases / hepatitis / hepatotoxicity
- Neuropathy / neuromuscular toxicity (i.e. events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)
- Endocrinopathy (i.e. events of hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism)

- Dermatitis
- Nephritis
- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase , increased serum amylase)

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the MEDI4736 Investigator Brochure.

7.9.1 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 Section 6.

7.9.2 Hypersensitivity Reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy (Brahmer et al 2012). As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of MAbs can be caused by various mechanisms, including acute anaphylactic (immunoglobulin E-mediated) and anaphylactoid reactions against the MAb, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness.

Guidelines for management of subjects with hypersensitivity (including anaphylactic reaction) and infusion-related reactions are outlined in Section 6.

7.9.3 Hepatic function abnormalities (hepatotoxicity)

Increased transaminases have been reported during treatment with anti-PD-L1/anti-PD-1 antibodies (Brahmer et al 2012). Inflammatory hepatitis has been reported in 3% to 9% of subjects treated with anti-CTLA-4 monoclonal antibodies (e.g., ipilimumab). The clinical manifestations of ipilimumab-treated subjects included general weakness, fatigue, nausea and/or mild fever and increased liver function tests such as AST, ALT, alkaline phosphatase, and/or total bilirubin.

Hepatic function abnormality is defined as any increase in ALT or AST to greater than $3 \times$ ULN and concurrent increase in total bilirubin to be greater than $2 \times$ 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 Section 6.

Cases where a subject shows an AST **or** ALT $\geq 3x$ ULN **or** total bilirubin $\geq 2x$ 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.

7.9.4 Gastrointestinal disorders

Diarrhea/colitis is the most commonly observed treatment emergent SAE when tremelimumab is used as monotherapy. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome if not properly managed. Guidelines on management of diarrhea and colitis in patients receiving durvalumab are provided in Section 6.0.

7.9.5 Endocrine disorders

Immune-mediated endocrinopathies include hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism. Guidelines for the management of patients with immune-mediated endocrine events are provided in Section 6.0.

7.9.6 Pancreatic disorders

Immune-mediated pancreatitis includes autoimmune pancreatitis, and lipase and amylase elevation. Guidelines for the management of patients with immune-mediated pancreatic disorders are provided in Section 6.0.

7.9.7 Neurotoxicity

Immune-mediated nervous system events include encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Section 6.0.

7.9.8 Nephritis

Consult with Nephrologist. Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc)

Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections etc.)

Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to higher grade event. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Section 6.0.

7.10 Other events requiring reporting

7.10.1 Overdose

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

Any overdose of a study subject with MEDI4736, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the sponsor and AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox. If the overdose results in an AE, the AE must also be recorded as an AE. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE. There is currently no specific treatment in the event of an overdose of MEDI4736.

The investigator will use clinical judgment to treat any overdose.

7.10.2 Hepatic function abnormality

Hepatic function abnormality (as defined in Section 7.9.3) in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" *within 24 hours of knowledge of the event* to the sponsor and AstraZeneca/MedImmune Patient Safety using the designated Safety e-mailbox,

unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study subject will be based on the clinical judgment of the investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

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

7.10.3 Pregnancy

Maternal exposure

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

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

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

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

The same timelines apply when outcome information is available.

Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of durvalumab monotherapy.

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

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

7.11 Timeframe for Reporting Required Events

Reportable adverse events will be tracked for 30 days following the last day of study treatment.

8.0 PHARMACEUTICAL INFORMATION

8.1 MEDI4736

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9.0 CORRELATIVE STUDIES

The basis for the proposed correlative studies is to gain further mechanistic insight into the immunologic parameters that dictate response versus resistance to MEDI4736. The first aim, biomarker analysis (see Section 1.5.1), will characterize the expression of inhibitory molecules, PD-1, PD-L1, PD-L2, CTLA-4, in paired primary and CNS biopsies to identify clinical correlates of protection and resistance following MEDI4736. The second study aim, immune characterization (see Section 1.5.2), is to annotate the immune response before and after MEDI4736 to identify

mediators of response and protection to MEDI4736. Overall, these data will provide greater understanding of the immunologic basis for MEDI4736 therapy that can be used to design more rational trials in the future.

9.1 Sample Collection Plan

After trial enrollment, patients will undergo their first research blood draw at baseline according to standard procedures. Additional blood samples will be obtained on Days 8, 15, 29, 3 months, 6 months and 12 months post-Cycle 1 Day 1 (see study calendar in Section 10.0). Six collection tubes (BD Vacutainer® sodium heparin (green top), REF 367874, 10 mL each for a total of approximately 60 mL) are filled by venipuncture at each time point. Blood samples will be transported to the Dunn laboratory (7th floor BJC Institute of Health) within one hour of collection. PBMC will be obtained by Ficoll-Hypaque gradient centrifugation and cryopreserved in 10% DMSO according to standard procedures.

Exome sequencing of PBMC will be performed to obtain germline sequences for comparison to isolated tumor from tissue biopsies (somatic mutations).

In addition to blood samples, tumor samples will be collected from diagnostic biopsies of the primary tumor site and surgical biopsy/resection of CNS lesion(s) (when available) and will be prioritized for immunohistochemistry and flow cytometry. These samples are obtained under the tumor bank consent for the patient's primary disease site (i.e. lung, breast, GI, GU, gynecologic), which authorizes permission for cellular, molecular, and genomic characterization and return of information. Patients who enroll in this study and are not enrolled in the applicable tumor bank will have archival tissue requested from their diagnostic biopsy. Patients who do not have tissue available from their diagnostic biopsy will be allowed to enroll in the study but will not be able to fully participate in the correlative studies.

Tumor tissue will be transported to the Tissue Procurement Core and to the Dunn laboratory.

OCT embedding: Will be performed according to pre-existing institutional tissue banking protocols. Briefly, approximately 10-50 mg of tissue, sectioned into pieces no larger than 0.5 cm x 0.5 cm, will be prepared. Cryomold will be filled slowly to the top with OCT compound. Tissue will be gently submerged into the OCT compound in the cryomold. OCT will be hardened by cooling. This will be achieved by placing the cryomold in the vapor phase of liquid nitrogen or on dry ice. After the OCT has hardened, the mold will be placed in a container and transferred to a -80°C freezer for storage. The frozen tissue will be transferred to the Laboratory of Translational Pathology (LTP, BJC-Institute of Health, Room 5110) for sectioning, H&E staining, and pathology evaluation.

Nucleic acid isolation: DNA will be isolated from PBMC by the LTP or Dunn laboratory personnel for exome sequencing at The Genome Institute. To identify somatic mutations, DNA and RNA will be extracted from OCT-embedded banked tissue. The OCT block will

be delivered to the LTP where the block will be sectioned and stained in order to confirm the presence of tumor, determine tumor/normal ratio, and guide isolation of tumor cells by, for instance, laser capture microdissection (LCM). All tissue selected for sequencing will be processed into a single-cell suspension by mechanical and enzymatic digestion, and used to extract nucleic acids. Tumor DNA + RNA will then undergo tumor exome and tumor cDNA-capture sequencing, respectively at The Genome Institute.

Serum separation: PBMC will undergo centrifugation with Ficoll to separate the serum and cellular layer (buffy coat) from RBC. While the buffy coat will be used for cellular studies discussed below, the serum will be frozen at -80°C to be stored for further studies.

9.2 Immune Monitoring

9.2.1 Immune profiling

Patient-derived PBMC will be used to quantify and characterize the immunologic landscape at baseline and at various time points post-MEDI4736. Single cell suspensions will be isolated as described above. All correlative studies will be performed in the laboratory of Dr. Dunn, Dr. Schreiber, or in the Immune Monitoring Laboratory at the Center of Human Immunology and Immunotherapy Programs at Washington University.

The T cell repertoire pre- and post- MEDI4736 will be further characterized by analyzing the TCR gene utilization of circulating PBMCs. This will be done by multi-parametric flow cytometry, spectratyping, and sequencing. MHC class I and II tetramers will be generated either in the Dunn laboratory, the Immune Monitoring Laboratory at the Center of Human Immunology and Immunotherapy Programs at Washington University, or the NIH Tetramer Core Facility.

Phenotypic and polyfunctional characterization of tumor-specific T cells will be performed by ELISPOT, multi-parametric flow cytometry, and mass cytometry (CyTOF). Ex vivo cytotoxicity assays will be performed to determine the cytolytic activity of circulating and tumor infiltrating T cells pre- and post-MEDI4736.

Serum will be analyzed for changes in cytokine expression following MEDI4736. Cytokine levels will be quantified using ELISA, QPCR, and multiplex analysis.

9.2.2 Microenvironment characterization

Tumor samples obtained from resection or initial biopsy at diagnosis will be analyzed for biomarkers that are associated with response to MEDI4736 to identify individuals who may benefit most from this therapeutic approach.

IHC staining of OCT embedded tissue will characterize the location of various infiltrating lymphocytes relative to tumor. Furthermore, single cell suspensions can be made from fresh frozen tissue to characterize the phenotype of various

populations of infiltrating leukocytes (T cells, B cells, NK cells, monocytes/macrophages, dendritic cells) by multi-parametric flow cytometry and mass cytometry. Expression of various activation and inhibitory markers within the tumor microenvironment will also be assessed.

TIL cultures will be generated by microdissection or magnetic bead-based isolation of single lymphocytes from tumor tissue. A baseline (pre-MEDI4736) assessment of the phenotype and functionality of these cells will be performed in a similar fashion as described above for PBMCs. Consideration will be given for T cell receptor sequencing of these TIL as well.

10.0 STUDY CALENDAR

Screening/baseline evaluations are to be conducted within 28 days prior to start of protocol therapy.

	Baseline / Screening	Day 1 of Each Cycle	Day 15 of Each Cycle	End of Every Even-Numbered Cycle	End of Treatment (Time of progression)	Follow-Up ³
Informed consent and review of eligibility criteria	X					
H&P, ECOG PS	X	X			X	
VS, wt, ht	X					
VS pre-, during, and post-infusion		X	X			
CBC	X	X				
CMP	X	X				
LFTs			X			
TSH, T3, T4	X	X				
PT, aPTT, INR	X					
β-hCG ¹	X					
Urinalysis	X					
12-lead ECG ⁴	X ⁴	X ²				
PFTs	X					
Transthoracic echocardiogram	X					
Brain MRI	X			X	X	
CT C/A/P	X			X	X	
MEDI4736		X	X			
Blood for correlatives		Please refer to Section 9.0				
Acquisition of diagnostic tumor specimens from applicable bank or archival tissue		Please refer to Section 9.0				
AE assessment	X ----- X					

1. Women of childbearing potential only
2. Cycle 5 only; should be taken within an hour prior to the start of infusion and 0-3 hours after the end of infusion
3. Follow for survival every 6 months for 2 years after end of treatment
4. In triplicate at baseline/screening and if abnormal results are discovered if an ECG is administered clinically

11.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
Registration Form Eligibility Form On-Study Form	Prior to starting treatment
Treatment Form	Every cycle
Toxicity Form	Continuous
Treatment Summary Form	Completion of treatment
Correlatives Form	Refer to Section 9.4
Follow Up Form	Every 6 months for 2 years after end of treatment
Tumor Measurement Form	Baseline, end of every even numbered cycles, and end of treatment
MedWatch Form	See Section 7.0 for reporting requirements

12.0 MEASUREMENT OF EFFECT – CNS DISEASE

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients will be re-evaluated for recurrence or progression every 8 (+/- 1) weeks. Response and progression will be evaluated in this study using the updated response assessment criteria for high-grade gliomas: Response Assessment in Neuro-Oncology (RANO) working group guideline ⁴².

Criteria for Response Assessment Incorporating MRI and Clinical Factors (Adapted from ⁴²)

Response	Criteria
Complete response	<ul style="list-style-type: none"> Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks. No new lesions; stable or improved nonenhancing (T2/FLAIR) lesions. Patients must be off corticosteroids (or on physiologic replacement doses only) and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease.
Partial response	<p>Requires all of the following:</p> <ul style="list-style-type: none"> ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained

Response	Criteria
	<p>for at least 4 weeks.</p> <ul style="list-style-type: none"> • No progression of nonmeasurable disease. • Stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan. • Stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease.
Stable disease	<p>Requires all of the following:</p> <ul style="list-style-type: none"> • Does not qualify for complete response, partial response, or progression. • Stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
Progression	<p>Defined by any of the following:</p> <ul style="list-style-type: none"> • $\geq 25\%$ increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids*. The absolute increase in any dimension must be at least 5mm when calculating the products. • Significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy* not caused by comorbid events (e.g. radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects). • Any new measurable lesion. • Clear clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose. • Failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.

- NOTE. All measurable and nonmeasurable lesions must be assessed using the same techniques as at baseline.
- Abbreviations: MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery.
- Stable doses of corticosteroids include patients not on corticosteroids.

iRANO criteria for progression: Confirmation of progression on follow-up imaging 3 months after initial radiographic progression if:

1. No new or significantly worsened neurologic deficits not due to co-morbid event or concurrent medication
2. ≤ 6 months from initiation of immunotherapy

If follow-up imaging confirms progression, the date of actual progression should be back-dated to the date of initial radiographic progression.

Otherwise, progressive disease will be defined as radiographic evidence of progression with significant clinical decline that is felt to be unrelated to co-morbid event or concurrent medication, or if there is radiographic evidence of progression > 6 months after initiation of immunotherapy.

12.2 Disease Parameters

Measurable disease: Bi-dimensionally measurable lesions with clearly defined margins by MRI scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable or evaluable disease: Uni-dimensionally measurable lesions or lesions with margins not clearly defined such as areas of T2/FLAIR signal abnormality or poorly defined enhancing abnormality.

Note: For cystic lesions, the only measurable part is any enhancement area around the cyst that is clearly defined and bi-dimensionally measurable. The cyst itself should not be considered measurable or non-measurable disease.

Target lesions: All measurable lesions that are residual of the lesion treated with MLA should be identified as target lesions and recorded and measured. Target lesions should be selected on the basis of their size (lesions with the longest diameter), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly should be selected. When there are too many measurable lesions, choose the largest 3 lesions as target lesions to follow. The other measurable lesions should be considered evaluable for the purpose of objective status determination.

Non-target lesions: All non-measurable lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 2 weeks before the beginning of the treatment.

Clinical lesions: Clinical lesions will only be considered measurable on brain MRI when they are ≥ 5 mm diameter as assessed using a ruler.

Histology: This technique can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases when biopsy or surgical resection of a measurable lesion is clinically indicated.

Perfusion/CBV: This advanced brain MRI technique can be used as an adjunct test to determine treatment response or disease status. However, it should not be used as the primary or sole method to determine response or disease status.

Brain FDG-PET coupled with head CT or brain MRI: This advanced metabolic imaging technique can be used as an adjunct test to determine response or disease status. However it should be used as the primary or sole method of determining response or disease status.

12.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): $\geq 50\%$ decrease compared with baseline in the sum of products of perpendicular diameters of all target lesions sustained for at least 4 weeks.

Progressive Disease (PD): At least a 25% increase in the sum of products of perpendicular diameters of at least 1 target lesion, taking as reference the smallest sum of products of perpendicular diameters on study (this includes the baseline sum if that is the smallest on study). The absolute increase in any dimension must be at least 5mm when calculating the products of perpendicular diameters.

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

12.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s).

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy* not caused by comorbid events (e.g. radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects). Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

12.3.3 Evaluation of Best Overall Response

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

Summary of the RANO Response Criteria (Adapted from ⁴²)

Criterion	CR	PR	SD	PD
T1 gadolinium enhancing disease	None	≥ 50% ↓	< 50% ↓ but < 25% ↑	≥ 25% ↑*
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑*
New lesion	None	None	None	Present*
Corticosteroids	None	Stable or ↓	Stable or ↓	NA†
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓*
Requirement for response	All	All	All	Any*

Abbreviations: RANO, Response Assessment in Neuro-Oncology; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; FLAIR, fluid-attenuated inversion recovery; NA, not applicable.

* Progression occurs when this criterion is present.

† Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

12.3.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented

(taking as reference for progressive disease the smallest measurements recorded since the treatment started).

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

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

12.3.5 Neurological Exam and Performance Status

Patients will be graded using the Karnofsky Performance Status scale and their neurological function evaluated as improved, stable or deteriorated in addition to objective measurement of tumor size. These parameters will be used to determine the overall response assessment.

12.3.6 Progression-Free Survival

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

13.0 MEASUREMENT OF EFFECT – NON-CNS DISEASE

13.1 RECIST Guidelines

For the purposes of this study, patients should be re-evaluated for response/progression every 8 weeks. A confirmatory scan should also be obtained not less than 4 weeks following initial documentation of objective response.

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

13.1.1 Disease Parameters

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

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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

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

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

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

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

13.1.2 Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

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

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

introduces additional data which may bias an investigator if it is not routinely or serially performed.

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

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

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

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

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

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

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

13.1.3 Response Criteria

13.1.3.1 Evaluation of Target Lesions

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

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

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

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

13.1.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and

normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

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

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

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

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

13.1.3.3 Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once >4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	
<p>* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion. ** Only for non-randomized trials with response as primary endpoint. *** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration.” Every effort should be made to document the objective progression even after discontinuation of treatment.</p>				

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
<p>* ‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised</p>		

13.1.3.4 Duration of Response

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

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

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

13.1.3.5 Progression-Free Survival

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

13.2 Immune-Related Response Criteria⁴³

For the immune-related response criteria, only index and measurable new lesions are taken into account. At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters of all index lesions (5 lesions per organ, up to 10 visceral lesions and 5 cutaneous index lesions) is calculated. At each subsequent tumor assessment, the sum of the products of the two largest perpendicular diameters of the index lesions and of new, measurable lesions ($\geq 5 \times 5$ mm; up to 5 new lesions per organ: 5 cutaneous lesions and 10 visceral lesions) are added together to provide the total tumor burden.

Percentage changes in tumor burden per assessment time point describe the size and growth kinetics of both conventional and new, measurable lesions as they appear. At each tumor assessment, the response in index and new, measurable lesions is defined based on the change in tumor burden (after ruling out immune-related progressive disease). Decreases in tumor burden must be assessed relative to baseline measurements. The immune-related response criteria were derived from WHO criteria and, therefore, the thresholds of response remain the same.

The overall response according to the immune-related response criteria is derived from time-point response assessments (based on tumor burden) as follows:

- irCR, complete disappearance of all lesions (whether measurable or not, and no new lesions) – confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented
- irPR, decrease in tumor burden $\geq 50\%$ relative to baseline – confirmed by a consecutive assessment at least 4 weeks after first documentation
- irSD, not meeting criteria for irCR or irPR, in absence of irPD
- irPD, increase in tumor burden $\geq 25\%$ relative to nadir (minimum recorded tumor burden) – confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented

14.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date and accrual by cohort
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities separated by cohorts with the number of dose-limiting toxicities indicated
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

15.0 STATISTICAL CONSIDERATIONS

15.1 Study Design

This is an open-label, single center, phase II study evaluating MEDI4736 (durvalumab), a PD-L1 checkpoint inhibitor, in patients with advanced epithelial-based malignancies and CNS metastasis.

15.2 Study Population

In total, three cohorts of patients will be enrolled. Because NSCLC is the most frequent source of brain metastasis and PD-1/PD-L1 pathway inhibition has been shown to be effective in this patient population, Cohort A will enroll only patients with NSCLC but will include all histologies and PD-L1 status. Cohort B will enroll all other non-NSCLC solid tumors of epithelial origin. This will include breast, gastroesophageal, pancreatic, colorectal, renal, bladder, and ovarian cancers. Melanoma, sarcoma, neuroendocrine tumors, and small cell lung cancers will be excluded as they are not of epithelial origin. Both Cohorts A and B will enroll patients not on corticosteroids at time of enrollment. Cohort C will enroll NSCLC or non-NSCLC patients requiring corticosteroid use.

15.3 Sample Size/Power Analysis

Because this study will only enroll patients with previously treated metastatic CNS disease, we assume a null hypothesis of 5% ORR in this setting. We further hypothesize that an ORR of 20% or higher warrants further investigation. A power analysis was performed for three primary cohorts (A: NSCLC without corticosteroids; B: non-NSCLC without corticosteroids; C: NSCLC or non-NSCLC requiring corticosteroid use) separately. Using Chen and NG's flexible design (an extension of Simon 2-stage Optimal design), a total of N=46 subjects will be enrolled in each cohort. Specifically, 21 subjects will be enrolled in the 1st stage in each cohort. If no more than 1 out of 21 subjects (<5%) were to have an objective tumor response, then we would conclude insufficient evidence for preliminary efficacy and enrollment to that cohort would be stopped. Otherwise, 25 additional subjects would be accrued for a total of 46 subjects in each cohort. At the completion of study, we expect that at least 41 out of 46 subjects would be evaluable for efficacy. The null hypothesis would be rejected if ≥ 5 objective intracranial responses were observed in the total of 41–46 evaluable subjects. This design would yield 90% power at a 1-sided significance level of 0.05 to detect the hypothesized improvement in ORR. At the end of Stage 1, the probability of erroneously proceeding with the study would be 0.27 under the null hypothesis and the probability of erroneously discontinuing the study would be 0.05 under the alternative hypothesis.

If the required Stage 1 intracranial ORR is seen, accrual can proceed in Stage 2 without interruption. If the required total number of patients are accrued to Stage 1 but follow-up is not sufficiently mature (ie, through the Week 12 radiographic evaluation) in all Stage 1 patients to reasonably assess the Stage 1 ORR, accrual to Stage 2 may proceed while the Stage 1 data are being collated. All available tumor response and progression data will be considered at the time of the assessment. At the latest, the interim analysis will occur when the last of the Stage 1 subjects has been enrolled and has completed the 12-week tumor assessment and these data are available for review.

15.4 Primary Endpoint

Overall intracranial response rate defined as the proportion of subjects who achieve a CR or PR based on assessment of brain lesions using RANO criteria.

15.5 Secondary Endpoints

- Overall intracranial disease control rate, defined as the proportion of subjects who achieve a CR, PR, or SD based on assessment of brain lesions using RANO criteria
- Overall extracranial response rate defined as the proportion of subjects who achieve a CR or PR based on assessment of systemic lesions using irRC
- Overall extracranial disease control rate, defined as the proportion of subjects who achieve a CR, PR, or SD based on assessment of systemic lesions using irRC
- Overall response rate defined as the proportion of subjects who achieve a CR or PR based on assessment of brain and systemic lesions using RANO criteria and irRC, respectively
- Overall disease control rate, defined as the proportion of subjects who achieve a CR, PR, or SD based on assessment of brain and systemic lesions using RANO criteria and irRC, respectively
- Time to response (TTR), defined as the interval from the start of study therapy to the first documentation of an objective response
- Duration of response (DOR), defined as the interval from the first documentation of objective response to the earlier of the first documentation of disease progression or death from any cause
- Progression-free survival (PFS), defined as the interval from the start of study therapy to the earlier of the first documentation of disease progression or death from any cause
- Overall survival (OS), defined as the interval from the start of study therapy to death from any cause

15.6 Exploratory Endpoints

Correlation of iRANO criteria with overall response rate and overall disease control rate of intracranial disease.

15.7 Accrual

There are currently no competing clinical trials for this patient population at Siteman Cancer Center. As such, it will have top priority for recruitment. We anticipate enrolling 1-2 patients per month into each cohort with completion of enrollment by 2 years from beginning of accrual.

15.8 Data Analysis

15.8.1 General Considerations

All data will be evaluated as observed, and no imputation method for missing values will be used. All data will be presented in a descriptive manner. Each cohort will be analyzed separately, and no multiplicity adjustment across cohorts will be

performed. All other analyses are considered as exploratory, even if statistical tests are used.

Descriptive statistics will be used to summarize the trial results, i.e., statistics for continuous variables may include means, medians, ranges and appropriate measures of variability. Qualitative variables will be summarized by counts and percentages. The uncertainty of estimates will be assessed by confidence intervals. Unless otherwise specified, the calculation of proportions will be based on the sample size of the population of interest. Counts of missing observations will be included in the denominator and presented as a separate category if not otherwise specified in the statistical analysis plan (SAP).

15.8.2 Primary Efficacy Endpoint Analysis

The primary endpoint is the overall intracranial response rate defined as the proportion of subjects who achieve a CR or PR based on assessment of brain lesions. Overall intracranial response rate per investigator assessment will be determined according to RANO criteria for CNS disease. Confirmation of the response will be required no sooner than 4 weeks after the initial documentation of CR or PR. Incidences of ORR and the corresponding 90% confidence intervals will be calculated in the primary cohorts separately.

15.8.3 Secondary Efficacy Endpoint Analyses

Incidences of categorical secondary endpoints (overall intracranial disease control rate, overall extracranial response rate, etc., as defined in Section 15.5) and the corresponding 90% confidence intervals will be calculated in the primary cohorts separately.

Duration of response, according to modified irRC, RECIST 1.1, and RANO, will be calculated for each subject and will be analyzed using the Kaplan-Meier method in the primary cohorts separately.

PFS time, irPFS time, and OS time will be presented in subject listings and analyzed using the Kaplan-Meier method in the primary cohorts separately.

Subgroup analyses of efficacy parameters will be performed according to tumor PD-L1 expression status. Subjects will be divided based on PD-L1 expression defined by the percentage of the tumor cells showing PD-L1 membrane staining at the following predefined cutoffs for positivity: >1% (<1% negative), >5% (<5% negative), >20% (<20% negative), and >50% (<50% negative). The percentage positive and negative for each cut-off as well as the associated BOR/iBOR and DCR/iDCR will be displayed in a histogram and PFS/iPFS and OS will be analyzed using the Kaplan-Meier method. The association between PD-L1 expression status (positive, negative) and response (according to RANO, RECIST 1.1, and modified irRC) will be assessed using Fisher's exact test. Further exploratory analyses may

be performed to investigate the association of PD-L1 expression level as a continuous variable and efficacy parameters. Other subgroup analyses of efficacy will also be performed as applicable in the given cohort, e.g., with respect to demography, histology, number of prior anti-cancer therapy lines, other biomarkers, immunologic parameter. Furthermore, paired t-test or paired-sample Wilcoxon Signed Rank test will be used to compare the gene expression of TIL and immune response in blood as measured before and after treatment.

15.8.4 Safety

15.8.4.1 Adverse Events

All AEs will be listed. The focus of AE summarization will be on treatment-emergent adverse events (TEAEs).

AEs will be classified using MedDRA with descriptions by System Organ Class and Preferred Term. The severity of AEs will be graded by the investigator according to the CTCAE, Version 4.03, whenever possible. If a CTCAE criterion does not exist for a specific type of AE, the grade corresponding to the appropriate adjective will be used by the investigator to describe the maximum intensity of the AE: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), or Grade 5 (fatal). The relationship of the AE to the study drugs will be categorized as related or unrelated.

Summary tables will be presented to show the number of subjects reporting TEAEs by severity grade and corresponding percentages. A subject who reports multiple TEAEs within the same Preferred Term (or System Organ Class) is counted only once for that Preferred Term (or System Organ Class) using the worst severity grade. AE descriptions will be presented in order of decreasing frequency for System Organ Class, and by decreasing frequency in the overall or total column for a given Preferred Term.

Separate listings and summaries will be prepared for the following types of AEs:

- Study-drug-related AEs
- AEs that are Grade ≥ 3 , 4, or 5 in severity
- AEs leading to study drug interruption and/or dose modification
- AEs leading to study drug discontinuation
- SAEs (with categorization of the primary reason that the AE is considered serious, eg, life-threatening, hospitalization)

15.8.4.2 Laboratory Evaluations

All laboratory data will be listed. Summaries of laboratory data will be based on observed data and will be reported using conventional units. The

focus of laboratory data summarization will be on treatment-emergent laboratory abnormalities. A treatment-emergent laboratory abnormality is defined as an abnormality that, compared to baseline, worsens by ≥ 1 grade in the period from the first study drug administration to 30 days after the last study drug administration. If baseline data are missing, then any graded abnormality (i.e., an abnormality that is Grade ≥ 1 in severity) will be considered treatment-emergent.

Test data will be programmatically graded according to CTCAE severity grade, when applicable. For parameters for which a CTCAE scale does not exist, reference ranges from the laboratory will be used to determine programmatically if a laboratory parameter is below, within, or above the normal range for the subject's age, sex, etc.

Test data will be summarized in tables and may be summarized in figures showing values over time, if informative. Summary tables will be presented for each relevant assay to show the number of subjects by CTCAE severity grade with corresponding percentages. For parameters for which a CTCAE scale does not exist, the frequency of subjects with values below, within, and above the normal ranges will be summarized. Subjects will be characterized only once for a given assay, based on their worst severity grade observed during a period of interest (eg, during the study or during a cycle).

Shift tables for hematology and serum biochemistry will also be presented by showing change in CTCAE severity grade from baseline to each time point. For parameters for which a CTCAE scale does not exist, shift tables will be presented showing change in results from baseline (normal, low and high [or abnormal]) to each time point (normal, low and high [or abnormal]). For selected variables of interest, tables may be prepared to show frequencies adjusted for baseline values; for these frequencies, subjects with the same or worse grade at baseline are not considered.

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APPENDIX A: ECOG Performance Status Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: Cockcroft-Gault Formula

Males:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age}) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$
